PERIODIC SAFETY UPDATE REPORT #4
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (nucleoside modified) (BNT162b2)[1]

BNT162b2 Original – BNT162b2 Bivalent (Original and Omicron BA.1) – BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)

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AUTHORISATION PROCEDURE in the EU: Centralised

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19 JUNE 2022 through 18 DECEMBER 2022

DATE OF THIS REPORT: 17 FEBRUARY 2023

SIGNATURE: _____**Date**: **17 February 2023**

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Please note that this report may contain unblinded clinical trial information.

[1] Change of the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran in EU (EMEA/H/C/005735/X/0044/G).

[2] Earliest conditional approval date.

EXECUTIVE SUMMARY

This is the 4th Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (nucleoside modified) (Coronavirus disease 2019 [COVID-19] mRNA Vaccine, COMIRNATY®, also referred to as BNT162b2 Original,[3] BNT162b2 (Original and Omicron BA.1) or BNT162b2 (Original and Omicron BA.4/BA.5),[4] covering the reporting interval 19 June 2022 through 18 December 2022.

COMIRNATY® presentations include:

Original (BNT162b2)

- PBS/Sucrose 30 micrograms/dose – for age 12 years and older [Purple cap]
- Tris/Sucrose 30 micrograms/dose – for age 12 years and older [Grey cap]
- Tris/Sucrose 10 micrograms/dose – for age 5 years to <12 years [Orange cap]
- Tris/Sucrose 3 micrograms/dose – for age 6 months to <5 years [Maroon cap]

Bivalent (Original + Omicron)

Original +

- Tris/Sucrose BA.1 15/15 micrograms/ dose – for age 12 years and older [Grey cap]
- Tris/Sucrose BA.4/BA.5 15/15 micrograms/ dose – for age 12 years and older [Grey cap]
- Tris/Sucrose BA.4/BA.5 5/5 micrograms/ dose – for age 5 years to <12 years [Orange cap]

The active substance of each of the COVID-19 mRNA vaccine presentations is a highly purified single-stranded, 5'-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the viral spike (S) protein of SARS-CoV-2 (Original).

The nucleoside-modified mRNA in Original BNT162b2 and Bivalent BNT162b2 is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralising antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

COMIRNATY® is indicated for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 6 months of age and older.

[3] Also referred to as Pfizer-BioNTech COVID-19 vaccine in other Company's documents.

[4] BNT162b2 (Original and Omicron BA.1) or BNT162b2 (Original and Omicron BA.4/BA.5) were also referred individually as Bivalent Omi BA.1 and Bivalent Omi BA.4/BA.5, or together as Bivalent in this document.

Age group		**12 years and older**				**5 through 11 years**		**6 months through 4 years**
Formulation		PBS sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose
Name		Comirnaty	Comirnaty	Comirnaty Original/ Omicron BA.1	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty
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 colour		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
Route of Administration		intramuscularly		intramuscularly	intramuscularly	intramuscularly	intramuscularly	intramuscularly
Posology	**Primary vaccination course**	2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.		Not applicable	Not applicable	2 doses (0.2 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.	Not applicable	3 doses (0.2 mL each). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.[a]
	Booster	May be administered at least 5 months after the second dose in individuals 12 years of age and older. Subsequent doses may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of the same formulation. Purple cap, concentrate for dispersion for injection (30 micrograms/dose) or grey cap, dispersion for injection (30 micrograms/dose) vaccine are considered interchangeable.		A booster dose of Bivalent vaccine, grey cap, may be administered at least 5 months after completing the primary series of COMIRNATY. Subsequent doses of Bivalent vaccine grey cap, may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of COMIRNATY or COMIRNATY Bivalent grey cap.		May be administered at least 6 months after the second dose	May be administered at least 4 months after the last prior dose in individuals 5 years through <12 years of age.	Not applicable

a. Individuals who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.

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

Cumulatively, it is estimated that 68,997[5] participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with:

- 57,505[6] participants exposed to BNT162b2;
- 7306 participants exposed to clinical candidates developed as variant and variant-adapted vaccines based on BNT162b2 (BNT162b2 [B.1.351], BNT162b2 [B.1.1.7 + B.1.617.2], BNT162b2 [B.1.617.2], BNT162b2 [B.1.1.529], BNT162b2 [B.1.1.7], BNT162b2/ BNT162b2 Omi [1774], BNT162b2 original/ BNT162b2 Omi BA.1 [102], BNT162b2 original/ BNT162b2 Omi BA.2 [104], and BNT162b2 original/ BNT162b2 Omi BA.4/BA.5 [1572[7]]);
- 633 participants exposed to other early development candidates (including BNT162a1 [30], BNT162b1 [411], BNT162b3 and BNT162c2 [96 participants each]).

There were 8958 participants exposed to blinded therapy, 4018 to placebo, and 7 to seasonal inactivated influenza vaccine (SIIV)/placebo.

BNT162b2 is also being utilised in 2 other Pfizer clinical development programs: 372 participants received BNT162b2 as a study vaccine or as a comparator in the clinical study B7471026[8] and 124 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine or as a comparator in the clinical study C5261001.[9]

From the receipt of the first temporary authorisation for emergency supply on 01 December 2020[10] through 18 December 2022, approximately 4,369,782,515 doses of BNT162b2 (original and bivalent) were shipped from BioNTech and Pfizer worldwide. Considering the current status of the vaccination schedule and the availability of only partial data published on the ECDC websites for doses of BNT162b2 vaccines (original and

[5] Participants to more than one clinical trial (e.g., extension study) are counted once when receiving the same treatment in the parent study.

[6] The number of participants who had received BNT162b2 is lower compared to the number reported in the previous PSUR (reporting period 19 December 2021 through 18 June 2022), since in the current PSUR the treatment for the group 6 months to <5 years and the 5-11 years troponin cohort of study C4591007 is reported as blinded, because there were still some participants in the age group 6 months to <5 years not reaching the protocol defined unblinding milestone and in the 5-11 years troponin cohort, although all participants reached unblinding milestone, randomisation code has not been released to study team for any reporting event yet.

[7] Exposure data for the 15 subjects who are either randomised in the BNT162b4+ BNT162b2 Bivalent arm and /or the BNT162b2 bivalent arm.

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

[9] A phase 1 randomized study to evaluate the safety, tolerability, and immunogenicity of combined modified RNA vaccine candidates against COVID-19 and influenza in healthy individuals.

[10] BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK on this date.

bivalent) administered in the EU-EEA countries, it is no longer applicable to estimate the number of doses administered from those shipped. Out of the cumulative number of shipped doses, 3,974,026,615 were original and bivalent adult[11] presentations (including PBS and Tris/Sucrose); 395,755,900 were original and bivalent paediatric[12] presentations; 515,859,600 were bivalent vaccines of which 10,963,900 were for paediatric presentations; 2,274,181,295 doses of BNT162b2 (original and bivalent) were shipped to ROW.[13]

During the current reporting interval (19 June 2022 through 18 December 2022), approximately 813,783,710 doses of BNT162b2 original and bivalent vaccines were shipped worldwide during the current reporting interval from 19 June 2022 through 18 December 2022. Out of the doses shipped during the reporting period, 142,687,310 were original and bivalent adult[11] presentations (including PBS and Tris/Sucrose); 155,236,800 were original and bivalent paediatric[12] presentations; 515,859,600 were bivalent vaccines of which 10,963,900 were for paediatric presentations; 232,907,810 doses of BNT162b2 (original and bivalent) were shipped to ROW.[14]

Additionally, as per data provided by license partner (LP) in Hong Kong, Macau, and Taiwan, 30,170,177 doses of original BNT162b2 and bivalent Omi BA.4/BA.5 were administered cumulatively through the DLP, and 2,855,293 doses were administered from 19 June 2022 through the DLP.

BNT162b2 Original is approved for the following formulations:

- PBS/Sucrose 30 µg formulation for individuals aged 16 years and older in 103[15] countries for primary series and in 50 countries for booster.
- PBS/Sucrose 30 µg formulation for individuals aged 12 years and older in 81[16] countries for primary series and in 36 countries for booster.
- Tris/Sucrose 30 µg formulation for individuals aged 12 years and older in 77 countries for primary series and in 48 countries for booster.
- Tris/Sucrose 10 µg formulation for individuals aged 5 years to <12 years in 83 countries for primary series and in 50 countries for booster.
- Tris/Sucrose 3 µg formulation for individuals aged 6 months to <5 years in 61 countries for primary series.

[11] Approved for 12 years of age and older.

[12] Six (6) months through <12 years.

[13] Non-EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa.

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

[15] For this population, both full and EUA approvals were granted in Canada, Singapore, UK and the US.

[16] Both conditional and EUA approvals for this population were granted in the UK.

BNT162b2 Bivalent (BNT162b2 Original/Omicron BA.1 and BNT162b2 Original/ Omicron BA.4/BA.5) is approved for the following formulations:

- BNT162b2 Original/Omicron BA.1 Tris/Sucrose 15/15 µg formulation for individuals aged 12 years and older in 44 countries for booster;
- BNT162b2 Original/Omicron BA.4/BA.5 Tris/Sucrose 15/15 µg formulation for individuals aged 12 years and older in 63 countries for booster;
- BNT162b2 Original/Omicron BA.4/BA.5 Tris/Sucrose 5/5 µg formulation for individuals aged 5 years to <12 years in 40 countries for booster.

The marketing authorisation holders (MAHs) of BNT162b2 Original and Bivalent vaccines (BNT162b2 Original/Omicron BA.1 and BNT162b2 Original/Omicron BA.4/BA.5) in different countries/regions are the following: BioNTech, Pfizer, the local Ministry of Health (MoH), the local Government, the LP Fosun Pharma, and the LP Hemas.

In addition, World Health Organization **(**WHO) had approved the Emergency Use Listing (EUL) of BNT162b2.

There were no marketing authorisation withdrawals for safety reasons during the reporting interval.

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 18.0 dated 05 December 2022, in effect at the end of the reporting period. Five (5) previous CDS versions (version 13.0 dated 10 May 2022, version 14.0 dated 26 July 2022, version 15.0 dated 31 August 2022, version 16.0 dated 08 September 2022, version 17.0 dated 06 October 2022) were also in effect during the reporting period. Safety-related changes included updates of the following Sections: 2 Qualitative and quantitative composition (CDS version 16.0), 4.1 Therapeutic indications (CDS version 14.0), 4.2 Posology and method of administration (CDS version 14.0), 4.4 Special warnings and precautions for use (CDS version 14.0), 4.6 Fertility, pregnancy and lactation (CDS version 15.0), 4.8 Undesirable effects (CDS versions 14.0, 15.0 and 17.0), 5.1 Pharmacodynamic properties (CDS versions 14.0 and 15.0), Appendix A and Appendix B (CDS versions 14.0, 15.0 and 17.0).

During the reporting period, the following signals were evaluated:

- Signals determined not to be risks: Haemophagocytic lymphohistiocytosis (HLH), Dermatomyositis, Histiocytic necrotizing lymphadenitis (HNL), Genital (Vulvovaginal) ulceration, IgA nephropathy, Acquired hemophilia, Hearing loss.
- Signal determined to be an identified risk (not important): Dizziness.
- Ongoing signal: Pemphigus and Pemphigoid.

Requests to be addressed in this PSUR were received from European Medicines Agency (EMA), World Health Organization (WHO), and 4 Health Authorities (HA) (Health Canada,

Medsafe [New Zealand Medicines and Medical Devices Safety Authority], MFDS [Ministry of Food and Drug Safety, South Korea] and TGA [Therapeutic Goods Administration, Australia]). The Pharmacovigilance Risk Assessment Committee (PRAC) requests were included in the AR (Assessment Report) of PSUR #3 and in signals' AR (Assessment Report). The WHO requests were included in the EUL Procedure. Topics covered in these requests are summarised in the table below.

Source	Request(s)
EMA PSUR#3 AR	Report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases is below 99%.
	Continue to closely monitor multisystem inflammatory syndrome in children/adults (MIS-C/-A) and all new cases of MIS-C/-A should be reported in the future PSURs.
	Analysis of myocarditis/pericarditis cases focus on information concerning the course, outcome, and possible risk factors of the myocarditis/pericarditis cases following Comirnaty exposure.
	For future PSURs the evaluation of cardiovascular adverse events of special interest (AESIs), haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity, should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	The vaccination stress/anxiety related ADRs are considered well documented and can be removed from 'Evaluation of other risks (not categorised as important).
	For future PSURs the evaluation of overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs the evaluation of the use in frail patients with co-morbidities, and/or interactions with other vaccines should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	In the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine.
	Cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase.
	Concerning hearing loss, the MAH is requested in future reviews of cases reporting hearing loss to conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss, if applicable.
	Cumulative review on the association between Comirnaty and post orthostatic tachycardia syndrome.
	Estimate of the exposure of "third doses" in European economic area (EEA) countries, per country and by age group.
	Presentation of all relevant literature concerning the safety of Comirnaty (also besides the database Medline and Embase) during the reporting period.
EU-RMP	Critically appraise if the wealth of safety data accumulated during the product use can inform rationalising the safety concerns in the RMP.
Signals' AR	Cumulative review of all cases of histiocytic necrotizing lymphadenitis.
	Cumulative updated analysis of amenorrhoea.
	Review of vulval ulceration cases received since 16 August 2022.
Type II variations AR	Monitoring of medication errors due to the availability of bivalent vaccines.
	Close monitoring of the risk of myocarditis and pericarditis in the 5-11 years of age group and following the booster dose(s)
WHO	Pregnancy outcome in clinical trials.
	Data on low- and middle-income countries (LMICs) populations with HIV, malnutrition and tuberculosis and other infectious diseases.

Source	Request(s)
Health Canada	Cumulative review of histiocytic necrotizing lymphadenitis and vulval ulceration.
	Review of incremental reports of Guillain-Barre Syndrome
	Review of incremental reports of "Poor quality product administered"
	Data stratification by vaccine variants.
	Presentation and discussion of interim reports of the studies C4591010, C4591021 and C4591022.
Medsafe	Adverse events reported in <5-year-old should be split by dose 1, 2 and 3.
	Differentiate between ADRs reported in <5-year-old following the 3 mcg maroon cap formulation vs given another product not approved for this age group.
	Include global usage data of the bivalent vaccines and present data, where available, on race and ethnicity, including Māori and Pacific peoples.
MFDS	Safety evaluation for the second booster vaccination in AESI and VAED including VAERD.
TGA	Cumulative review of subacute thyroiditis.

According to the European Risk Management Plan (EU-RMP) version 5.0 dated 02 February 2022 (EMEA/H/C/005735/II/0087) approved on 10 March 2022, in effect at the beginning of the reporting period, safety concerns for BNT162b2 are:

- Important identified risks: Anaphylaxis,[17] Myocarditis and Pericarditis.
- Important potential risk: 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 (eg, 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.

The EU-RMP versions and associated procedures, submitted during the PSUR reporting period, are summarised in the table below. Version number of the EU-RMPs was agreed with EMA.

[17] The important identified risk of anaphylaxis was removed from the list of safety concerns in RMP version 5.1 (procedure EMEA/H/C/005735/X/0138). Additionally, the Rapporteur agreed to remove the important identified risk of anaphylaxis from the list of safety concerns for the PSUR #4 reporting period, because anaphylaxis is a known risk of vaccines that is adequately being managed by HCPs who administer vaccines and the vaccinees in daily practice.

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
Reporting period			
EMEA/H/C/005735/X/0138 Line extension – WT (original) in 6 months to 4yo	08 July 2022	RMP v5.1: 08 July 2022 (Gateway) Consol. RMP v7.3 = var0138 v5.1 + var0143 v7.1): 04 October 2022 (Eudralink) Upversioned RMP v8.0 (content wise similar to upd. Consol. RMP v7.3 = var0138 v5.1 + var0143 v7.1): 07 October 2022 (Eudralink), 02 November 2022 (Gateway)	Approved CHMP Opinion: 19 October 2022 EC decision: 20 October 2022
EMEA/H/C/005735/II/0140 PI update regarding Original/Omicron BA.1 in patients 12yo+	Roll 1 CMC: 09 June 2022 Roll 2 clinical: 20 June 2022 Roll 2 clinical corr: 24 June 2022 Roll 3 CMC: 07 July 2022 Roll 4 clinical: 19 July 2022	RMP v6.0: 19 July 2022 (Gateway) RMP v6.1: 24 August 2022 (Eudralink)	Approved CHMP Opinion: 01 September 2022 EC decision: 01 September 2022
EMEA/H/C/005735/II/0143 PI update regarding Original/Omicron BA.4-5 in patients 12yo+	Roll 1 non-clinical, CMC and administrative: 08 August 2022 Roll 2 clinical, non-clinical and administrative: 15 August 2022 Roll 3 CMC and clinical: 26 August 2022	RMP v7.0: 15 August 2022 (Gateway) RMP v7.1: 12 September 2022 (Eudralink) Revised RMP v7.1 (without confidential footnote): 23 September 2022 (Eudralink), 27 September 2022 (Gateway)	Approved CHMP Opinion: 12 September 2022 EC decision: 12 September 2022
EMEA/H/C/005735/X/0147 PI update regarding Original/Omicron BA.4-5 in 5-11yo	28 September 2022	Consol. RMP v7.2 = X-0147 v7.1 based on var0143 v7.1: 28 September 2022 (Gateway) Consol. RMP v8.1 = X-0147 v7.2 + X-0138 v8.0: 03 November 2022 (Eudralink) Upversioned RMP v9.0 (content-wise similar to upd. Consol. RMP v8.1 = X-0147 v7.2 + X-0138 v8.0): 04 November 2022 (Eudralink)	Approved CHMP Opinion: 10 November 2022 EC decision: 10 November 2022

Based on the clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, no new significant safety information has

been identified that substantiates retaining VAED/VAERD as an important potential risk in the PSUR for BNT162b2. The MAH proposes to remove the important potential risk of VAED/VAERD from the PSUR on the basis that accumulated scientific and clinical data are not supportive of the initial theoretical supposition that VAED/VAERD may be a risk of vaccination with the COVID-19 mRNA vaccine.

After the DLP,

- an updated CDS (version 19.0) was made effective on 22 December 2022; main changes included:
  - Section 4.8 *Undesirable effects*: updated clinical data after 2 doses for children 5 to <12 years of age was added; Diarrhea was added as adverse drug reaction in children 5 to <12 years of age;
  - Section 5.1 *Pharmacodynamic properties*: addition of efficacy and immunogenicity data after 3 doses in 6 months through <5 years of age and efficacy data after 2 doses in 5 through <12 years of age; deletion of efficacy data in infants and in children after 3 doses.
  - updated frequency values in 5 through <12 years of age (Appendix A, Table A-3); addition of Angioedema and Night sweats as rare ADR and reclassification of Diarrhea from "Common" to "Very Common" ADR in 5 through <12 years of age (Appendix B, Table B-3).
- a new signal (Myositis) was opened based upon a signal assessment report EMA PRAC.
- The following action was taken for safety reasons. In Switzerland the bivalent Omi BA.1 is not approved for individuals 12 to less than 18 years because there was no clinical data available for that population. As country-specific packaging is not yet available, Switzerland is receiving EU packaging that has the age on the carton (12+ as per EU MA). Therefore, an information Letter (in English) explaining the discrepancy between information on the carton and indication approved by Swissmedic is provided with each shipment. In addition, the MAH provides electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

The literature article "Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023" (Hause et al.) including important safety information about the use of bivalent vaccines and young children has been included in Section 11 *Literature.*

The following 2 requests will be addressed in a separate supplemental document:

- In the preliminary AR for variation EMEA/H/C/005735/II/0139, EMA requested the MAH to present a cumulative review of all myocarditis and pericarditis cases with

fatal outcome that have been reported with the vaccine. The MAH is requested to evaluate whether a further update of the SmPC section 4.4 and/or 4.8 is warranted.

- The PRAC Rapporteur requested a review on the outcome of myocarditis/pericarditis cases following Comirnaty exposure. The review should include not only case reports, but also any data from (observational) studies and published literature. Furthermore, please provide the MAH's position on whether the current PI wording remains appropriate or if an update of the PI is warranted.

Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2 original and bivalent vaccines (Omi BA.1 and Omi BA.4/BA.5), the overall benefit-risk profile of BNT162b2 remains favourable. No further changes to the BNT162b2 RSI or additional risk minimisation activities are warranted in addition to those above mentioned.

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Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADEM	acute disseminated encephalomyelitis
ADR	adverse drug reaction
AE	adverse event
AERP	adverse event reporting proportion
AESI	adverse event of special interest
AR	assessment report
ARDS	acute respiratory distress syndrome
AT	Austria
ATC	anatomical therapeutic chemical
AV	atrioventricular
BC	Brighton Collaboration
BE	Belgium
BG	Bulgaria
BLA	biologics license application
BMI	body mass index
BT	blinded therapy
CDC	Centres for Disease Control and Prevention
CDS	core data sheet
CET	Central European Time
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	confidence interval
CK	creatine kinase
cMA	conditional marketing authorisation
CMC	Chemistry, Manufacturing, and Control
CMI	Charlson comorbidity index
CMR	cardiac magnetic resonance
CONJ	conjugate
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	coronavirus disease 2019
COVID-19 vaccine INACT (VERO) CZ02	Vero Cell, Sinovac Life Sciences Co COVID-19 vaccine
COVID-19 vaccine NRVV MVA	modified vaccinia virus Ankara COVID-19 vaccine
COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19)	Vaxzevria, AstraZeneca COVID-19 vaccine
COVID-19 vaccine NRVV AD26 (JNJ 78436735)	Jcovden, Janssen COVID-19 vaccine

Abbreviation	Term
COVID-19 vaccine prot. Subunit (NVX COV 2373)	Novavax COVID-19 vaccine
CPR	cardiopulmonary resuscitation
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial/computed tomography
CVST	cerebral venous sinus thrombosis
CY	Cyprus
CZ	Czechia
DK	Denmark
DLP	data lock point
DNA	deoxyribonucleic acid
DPT	Diphtheria, Tetanus and Polio
EBV	Epstein-Barr virus
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EE	Estonia
EEA	European economic area
EHR	electronic health record
EL	Greece
EMA	European Medicines Agency
EPITT	European pharmacovigilance issues tracking tool
ES	Spain
EU	European Union
EUA	emergency use authorization
EUL	emergency use listing
EURD	European Union reference dates
F	female
FDA	Food and Drug Administration
FFRNT	fluorescent focus reduction neutralization test
FI	Finland
FR	France
GBS	Guillain-Barrè syndrome
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
GVP	Good pharmacovigilance practices
HA	Health Authority
HCP	healthcare professional
HBV	hepatitis B virus

Abbreviation	Term
HCV	hepatitis C virus
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HHV	human herpesvirus
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HLGT	high level group term
HLT	high level term
HNL	histiocytic necrotizing lymphadenitis
HPV	human papilloma virus
HR	Croatia/ hazard ratio
HU	Hungary
IB	Investigator's brochure
IBD	International Birth Date
ICH	International Council for Harmonisation; intracerebral haemorrhage
ICU	Intensive care unit
IE	Ireland
Ig	immunoglobulin
IMP	investigational medicinal product
INACT 4V	inactivated quadrivalent
IR	incident rate
IRR	incidence rate ratio
IS	Iceland
IT	Italy
IVY	Investigating Respiratory Viruses in the Acutely Ill
JCVI	Joint Committee on Vaccination and Immunisation
JNJ	Johnson & Johnson
JST	Japan Standard Time
LC-FAOD	long-chain fatty acid oxidation disorder
LGE	late gadolinium enhancement
LI	Liechtenstein
LLOQ	lower limit of quantitation
LLT	lower level term
LMIC	low- and middle-income country
LNP	lipid nanoparticles
LOE	lack of efficacy
LP	license partner
LT	Lithuania
LU	Luxembourg
LV	Latvia/ left ventricular
M	male
MA	marketing authorisation
MAA	marketing authorisation application
MAH	marketing authorisation holder

Abbreviation	Term
MC	medically confirmed
MDV	multidose vial
ME	medication error
Medsafe	Medicines and Medical Devices Safety Authority
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MHPD	Marketed Health Products Directorate
MHRA	Medicines and Healthcare products Regulatory Agency
MAX	maximum
MIN	minimum
MIS	multisystem inflammatory syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MoH	ministry of health
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MS	multiple sclerosis
MT	Malta
N/A	not applicable
NAAT	nucleic acid amplification test
NEC	not elsewhere classified
NIS	Non interventional study
NL	Netherlands
NMC	non-medically confirmed
NO	Norway
NOS	not otherwise specified
NT50	50% neutralising titer
O/E	observed versus expected
Omi	Omicron
OR	odds ratio
PASS	post-authorisation safety study
PBRER	periodic benefit-risk evaluation report
PBS	phosphate buffered saline
PC	product complaint
PCR	polymerase chain reaction
PI	product information
PL	Poland
PM	post-marketing
PMDA	Pharmaceuticals and Medical Devices Agency
PBS	phosphate buffered saline
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PSUSA	periodic safety update report single assessment
PT	Preferred Term, Portugal

Abbreviation	Term
PVP	pharmacovigilance plan
QPPV	qualified person for pharmacovigilance
RD	risk difference
RGE	recombinant glycoprotein E
RMP	risk management plan
RO	Romania
ROW	rest of world
RNA	ribonucleic acid
RSI	reference safety information
RT-PCR	reverse transcription-polymerase chain reaction
RTU	ready-to-use
RVE	relative vaccine efficacy
RWD	real-world data
S	spike
SAE	serious adverse event
SAG	surface antigen
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBSR	summary bimonthly safety report
SDV	single dose vial
SE	Sweden
SI	Slovenia
SIIV	seasonal inactivated influenza vaccine
SK	Slovakia
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SMSR	summary monthly safety report
SOC	system organ class
SPEAC	Safety Platform for Emergency vACcines
SRC	Scientific Review Committee
SSR	summary safety report
TET TOX	tetanus toxoid
TGA	Therapeutic Goods Administration
TME	targeted medical event
Tris	tromethamine
TTO	time to onset
U	unknown
UK	United Kingdom
UMC	Uppsala Monitoring Centre
Unk	Unknown
US	United States
USG	United States Government
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System

Abbreviation	Term
VE	vaccine efficacy
YO	year old
WHO	World Health Organization
WT	wild type

1. INTRODUCTION

This is the 4th PSUR for the COVID-19 mRNA vaccine (nucleoside modified), COMIRNATY®, also referred to as BNT162b2,[3] covering the reporting interval 19 June 2022 through 18 December 2022.

The format and content of this PSUR is in accordance with the Guideline on GVP Module VII—Periodic safety update report (EMA/816292/2011 [December 2013]), with ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, January 2013]), corePSUR19 guidance (EMA/362988/2021 [08 July 2021]), and Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance v. 3.0 (EMA/PRAC/73244/2022 [08 February 2022]).

BNT162b2 is highly purified single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral S protein of SARS-CoV-2. The nucleoside-modified mRNA is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralising antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19.

Indication: Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 6 months of age and older. It is administered intramuscularly.

Please refer to the table below for formulations, presentations and posology in the approved populations.

Age group		12 years and older				5 through 11 years		6 months through 4 years
Formulation		PBS sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose
Name		Comirnaty	Comirnaty	Comirnaty Original/ Omicron BA.1	Comirnaty Original/ Omicron BA.4/BA. 5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty
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 colour		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
Route of Administration		intramuscularly		intramuscularly	intramuscularly	intramuscularly	intramuscularly	intramuscularly
Posology	Primary vaccination course	2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.		Not applicable	Not applicable	2 doses (0.2 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.	Not applicable	3 doses (0.2 mL each). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose. [a]
	Booster	May be administered at least 5 months after the second dose in individuals 12 years of age and older. Subsequent doses may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of the same formulation. Purple cap, concentrate for dispersion for injection (30 micrograms/dose) or Grey cap, dispersion for injection (30 micrograms/dose) vaccine are considered interchangeable.		A booster dose of Bivalent vaccine, Grey cap, may be administered at least 5 months after completing the primary series of COMIRNATY. Subsequent doses of Bivalent vaccine Grey cap, may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of COMIRNATY or COMIRNATY Bivalent Grey cap.		May be administered at least 6 months after the second dose	May be administered at least 4 months after the last prior dose in individuals 5 years through <12 years of age.	Not applicable

a. Individuals who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.

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

The list of the PSURs previously prepared for BNT162b2 is presented in Table 1.

Table 1. List of PSURs

PSUR Number	Reporting Period
1	19 December 2020 through 18 June 2021
2	19 June 2021 through 18 December 2021
3	19 December 2021 through 18 June 2022

Pfizer is responsible for the preparation of the PSUR on behalf of license partners according to the Pharmacovigilance Agreement(s) in place. Data from respective license partner(s) are included in the report when applicable.

2. WORLDWIDE MARKETING APPROVAL STATUS

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK[18] on 01 December 2020.

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020. In the European Union, conditional marketing authorisation was granted on 21 December 2020; this was switched to a standard marketing authorisation on 10 October 2022.

BNT162b2 Original is authorised for the following formulations:

- PBS/Sucrose – Purple cap 30 µg formulation:
  - in individuals aged 16 years and older in 103[15] countries for primary series and in 50 countries for booster;
  - in individuals aged between 12 and 15 years in 81[16] countries for primary series and in 36 countries for booster.
- Tris/Sucrose formulation:
  - Grey cap: at the dosage of 30 µg formulation in individuals aged 12 years and older in 77 countries for primary series and in 48 countries for booster.
  - Orange cap: at the dosage of 10 µg formulation in individuals aged 5 years to <12 years in 83 countries for primary series and in 50 countries for booster.
  - Maroon cap: at the dosage of 3 µg formulation in individuals aged 6 months to <5 years in 61 countries for primary series.

[18] On 01 January 2021, conditional marketing authorisation approval was also granted in the UK and the approval is currently active.

BNT162b2 Bivalent (BNT162b2 Original/Omicron BA.1 and BNT162b2 Original/Omicron BA.4/BA.5) is authorised for the following formulations:

- Grey cap Original/Omicron BA.1: at the dosage of 15/15 µg (Tris/Sucrose formulation) in individuals aged 12 years and older in 44 countries for booster.
- Grey cap Original/Omicron BA.4/BA.5: at the dosage of 15/15 µg (Tris/Sucrose formulation) in individuals aged 12 years and older in 63 countries for booster.
- Orange cap Original/Omicron BA.4/BA.5: at the dosage of 5/5 µg (Tris/Sucrose formulation) in individuals aged 5 years to <12 years in 40 countries for booster.

Overall, BNT162b2 Original received marketing authorisation approval in 104 countries/regions and BNT162b2 Bivalent BNT162b2 Original/Omicron BA.1 and BNT162b2 Original/Omicron BA.4/BA.5 received marketing authorisation approval in 43 and 63 countries/regions, respectively. The MAHs and the number of countries where the different MAHs hold the authorisation are presented in Table 2.

Table 2. Marketing Authorisation Holders of BNT162b2 Original and BNT162b2 Bivalent Vaccines

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held		
	BNT162b2 Original	BNT162b2 Bivalent (Original and Omicron BA.1)	BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)
BioNTech	56	35	43
Pfizer	40	7	17
Fosun Pharma	2	0	2
Local MoH	3	0	0
Local Government	3	1	1
Hemas (LP)	1	0	0
All	**104[a]**	**43**	**63**

a. The sum of the number of the countries where the authorisation is held does not coincide with the total number of countries where BNT162b2 is authorised, because in the UK there are 2 different authorisations: the UK Government is the MAH of the EUA and BioNTech is the MAH of the conditional authorisation.

In addition, WHO had approved the EUL of BNT162b2.

There were no marketing authorisation withdrawals for safety reasons during the reporting interval.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, no actions have been taken with respect to BNT162b2 for safety reasons, either by a HA or by the MAH.

After the DLP, the following action was taken with respect to BNT162b2 for safety reasons. In Switzerland the approval for bivalent Omi BA.1 was not obtained for individuals 12 to less than 18 years because there is no clinical data available for that population. As

country-specific packaging is not yet available, Switzerland is receiving EU packaging that has the age on the carton (12+ as per EU MA). Therefore, an information Letter (in English) explaining the discrepancy between information on the carton and indication approved by Swissmedic is provided with each shipment. In addition, the MAH provides electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID-19 mRNA vaccine CDS version 18.0 dated 05 December 2022, in effect at the end of the reporting period and included in Appendix 1.

The 5 previous CDS versions (version 13.0 dated 10 May 2022, version 14.0 dated 26 July 2022, version 15.0 dated 31 August 2022, version 16.0 dated 08 September 2022, version 17.0 dated 06 October 2022), which were also in effect during the reporting period, are included in Appendix 1.2 through Appendix 1.6.

Safety-related changes included updates of the following sections:

- 2 Qualitative and quantitative composition (version 16.0),
- 4.1 Therapeutic indications (version 14.0),
- 4.2 Posology and method of administration (version 14.0),
- 4.4 Special warnings and precautions for use (version 14.0),
- 4.6 Fertility, pregnancy and lactation (version 15.0),
- 4.8 Undesirable effects (versions 14.0, 15.0 and 17.0),
- 5.1 Pharmacodynamic properties (versions 14.0 and 15.0),
- Appendix A and Appendix B versions 14.0, 15.0 and 17.0).

Safety-related changes to the RSI are presented in Appendix 1.1.

After the DLP, an updated CDS (version 19.0) was made effective on 22 December 2022; the safety-related changes are summarised in Table 3.

Table 3. Safety-Related Changes Made to the RSI After the DLP

Version 19.0 dated 22 December 2022		
Section	**Revision Type**	**Revision**
4.8 *Undesirable effects*	Addition	• Clinical data after 2 doses for children 5 to <12 years of age. • Diarrhoea as ADR in children 5 to <12 years of age.
5.1 *Pharmacodynamic properties*	Addition	• Efficacy data after 2 doses in children 5 to <12 years of age without evidence of prior infection. • Efficacy and immunogenicity data in 6 months through <5 years of age after 3 doses.
	Deletion	• Efficacy in infants 6 through 23 months of age after 3 doses. • Efficacy in children 2 through 4 years of age after 3 doses.
Appendices A and B	Addition	• Frequency values updated at the data cut-off of 20 May 2022 in 5 through <12 years of age (Appendix A, Table A-3). • Addition of Angioedema and Night sweats as "Rare" ADR and reclassification of Diarrhea from "Common" to "Very Common" in 5 through <12 years of age (Appendix B, Table B-3).

5. ESTIMATED EXPOSURE AND USE PATTERNS

In the current PSUR, the following regulatory requests about the exposure and number of third doses administered are addressed:

EMEA/H/C/005735/MEA/002.8 (9th SMSR), *The MAH should provide an estimate of the exposure of "third doses" in future PSURs separately (reporting period and cumulatively), if applicable*.

Response

Please refer to Section 5.2. *Cumulative and Interval Patient Exposure from Marketing Experience*, where the total number of the third doses administered of BNT162b2 and bivalent vaccines, is provided cumulatively in Table 9 through Table 11 for the EU/EEA countries and in Table 13 and Table 14 for Japan; Table 19 displays the incremental number of third doses of BNT162b2 administered in the EU/EEA countries (for bivalent vaccines, cumulative values are overlapping).

In the Medsafe assessment of the Comirnaty EU-RMP version 8, the following request was made: *Please commit to include global usage data of the bivalent vaccines in the abbreviated SSRs and PSURs that are submitted to Medsafe*.

Response

Please refer to Section 5.2. *Cumulative and Interval Patient Exposure from Marketing Experience*, where the following estimated cumulative and incremental data is provided: the number of shipped doses (Table 5 and Table 16); the number of administered doses by the LP (Table 7 and Table 17), the number of administered doses downloaded from the HA's websites (EMA [Table 9, Table 10, Table 11 and Table 18]; PMDA [Table 12 through Table 14] and FDA[Table 15]).

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 68,997[5] participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

BNT162b2: 57,505[6] participants of which

- 30,221 had received BNT162b2;
- 25,204 had received BNT162b2 post-unblinding and had received placebo before;
- 959 had received BNT162b2/placebo;
- 2 had received BNT162b2/ SIIV[19];
- 1119 had received BNT162b2/ SIIV/ placebo.

Variant and variant-adapted vaccines based on BNT162b2: 7306 participants of which

- 753 had received BNT162b2 (B.1.351)[20];
- 372 had received BNT162b2 (B.1.617.2);
- 768 had received BNT162b2 (B.1.1.7 + B.1.617.2);
- 20 had received BNT162b2 (B.1.1.7);
- 71 had received BNT162b2 (B.1.1.529)[21];
- 1770 had received BNT162b2 Omi;
- 1774 had received BNT162b2/ BNT162b2 Omi ;
- 102 had received BNT162b2 original/ BNT162b2 Omi BA.1;
- 104 had received BNT162b2 original/ BNT162b2 Omi BA.2;
- 1572[7] had received BNT162b2 original/ BNT162b2 Omi I BA.4/BA.5.

Early development candidates: 633 participants of which

- 30 had received BNT162a1;
- 411 had received BNT162b1;
- 96 had received BNT162b3;
- 96 had received BNT162c2.

[19] Seasonal inactivated influenza vaccine.

[20] BNT162b2 (B.1.351), which is also referred to as BNT162b2s01 and BNT162b2$_{SA}$.

[21] BNT162b2 (B.1.1.529) is a monovalent vaccine, which is also referred to as BNT162b2 Omi BA.1.

Blinded therapy: 8958 participants.

Placebo: 4018 participants.

SIIV/placebo: 7 participants.

Participant demographics data (e.g., age, gender, race) for 'C459' CTs is presented by treatment group in Appendix 2.3. Cumulative CT exposures with demographic data from BioNTech and Fosun CTs is presented in Appendix 2.3B and Appendix 2.3C.

Of note, BNT162b2 is also being utilised in 2 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine or as a comparator in the clinical study B7471026;[8]
- C526: 124 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine or as a comparator in the clinical study C5261001.[9]

Participant demographics data (e.g., age, gender, race) by treatment groups are presented in Appendix 2.3.1.

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1. Cumulative Exposure

5.2.1.1. MAH and License Partner Data – Cumulative Exposure

MAH Data

The number of doses cumulatively administered (as per public available data for the EU-EEA countries,[22] the US,[23] and Japan[24]) is currently updated on a bi-weekly base. Considering the current status of the vaccination schedule and the availability of only partial data published on the ECDC websites for doses of BNT162b2 vaccines (original and bivalent) administered in the EU-EEA countries,[25] it is no longer applicable to estimate the number of doses administered from those shipped. Estimated administered doses were provided separately, as available on the public source data.

[22] https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea, Accessed on 14 December 2022.

[23] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5, Accessed on 17 December 2022.

[24] https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html, Accessed on 22 December 2022, 6:00 p.m. [JST].

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

Approximately a total of 4,369,782,515[26] doses of BNT162b2 (original and bivalent) were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 December 2022. The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group based on data provided in the shipment tracker (Order Book)[27] through 18 December 2022 is showed in Table 4 through Table 6. Out of the cumulative number of shipped doses, 3,974,026,615 were original and bivalent adult[11] presentations (including PBS and Tris/Sucrose); 395,755,900 were original and bivalent paediatric[12] presentations; 515,859,600 were bivalent vaccines of which 10,963,900 were for paediatric presentations; 2,274,181,295 doses of BNT162b2 (original and bivalent) were shipped to ROW.[13]

Table 4. Cumulative Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years[b]	All
Europe	31.4	**3264000**	**69816000**	**1137544035**	**1210624035**
European Union (27)	22.9	3259200	57400800	820816440	881476440
European Economic Area Countries (3)	0.3	4800	452400	12007185	12464385
Switzerland	0.3	0	600000	11397330	11997330
UK	3.3	0	10993200	117557895	128551095
Other Countries	3.3	0	52800	126778635	126831435
Commonwealth of Independent States	1.3	0	316800	48986550	49303350
North America	15.0	**12799100**	**67996900**	**495832835**	**576628835**
US	13.0	11089100	61446900	428169455	500705455
Canada	2.0	1710000	6550000	67663380	75923380
Central and South America	14.8	**1842000**	**67805600**	**501670755**	**571318355**
Asia	30.4	**12946800**	**132292600**	**1024905840**	**1170145240**
Japan	7.2	8803200	16016400	252909540	277729140
Other Countries	23.2	4143600	116276200	771996300	892416100
Oceania	2.3	**806400**	**12045000**	**74335590**	**87186990**
Australia/New Zealand	2.2	806400	11976000	73120680	85903080
Other Countries	0.0	0	69000	1214910	1283910
Africa	6.2	**0**	**3177600**	**234841860**	**238019460**
Total	100.0	**31658300**	**353133700**	**3469130915**	**3853922915**

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

[26] The total includes doses shipped for COVAX, USG Donation and EC Donation programs; it does not include License Partner data.

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

Table 5. Cumulative and Incremental Estimated Shipped Doses of BNT162b2 Bivalent Omi BA.1 by Region Worldwide and Age Group

Region/Country	≥12 years	All
Europe	**76181760**	**76181760**
European Union (27)	47076480	47076480
European Economic Area Countries (3)	1016640	1016640
Switzerland	3084480	3084480
UK	25004160	25004160
Other Countries	0	0
Commonwealth of Independent States	0	0
North America	**0**	**0**
US	0	0
Canada	0	0
Central and South America	**9997200**	**9997200**
Asia	**37004670**	**37004670**
Japan	28088190	28088190
Other Countries	8916480	8916480
Oceania	**4700160**	**4700160**
Australia/New Zealand	4700160	4700160
Other Countries	0	0
Africa	**0**	**0**
Total	**127883790**	**127883790**

Table 6. Cumulative and Interval Estimated Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**46.6**	**0**	**1785600**	**178877520**	**180663120**
European Union (27)	45.7	0	1780800	175579920	177360720
European Economic Area Countries (3)	0.7	0	4800	2554560	2559360
Switzerland	0.0	0	0	0	0
UK	0.0	0	0	0	0
Other Countries	0.2	0	0	743040	743040
Commonwealth of Independent States	0.0	0	0	0	0
North America	**21.0**	**974200**	**8199300**	**72366680**	**81540180**
US	17.6	974200	7747700	59739920	68461820
Canada	3.4	0	451600	12626760	13078360
Central and South America	**0.9**	**0**	**0**	**3456000**	**3456000**
Asia	**31.5**	**0**	**4800**	**122311710**	**122316510**
Japan	25.4	0	0	98662590	98662590
Other Countries	6.1	0	4800	23649120	23653920
Oceania	0.0	**0**	**0**	**0**	**0**
Australia/New Zealand	0.0	0	0	0	0
Other Countries	0.0	0	0	0	0
Africa	**0.0**	**0**	**0**	**0**	**0**
Total	**100.0**	**974200**	**9989700**	**377011910**	**387975810**

LP Data

Cumulative LP (Fosun) data on the number of original BNT162b2 and bivalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 7.

Table 7. Cumulative Administered Doses of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Vaccine – License Partner Data

Region **Country** ***-Vaccine Presentation***	**Number of Administered Doses**
Asia	**30170177**
Hong Kong	11152111
- BNT162b2 (Original)	*10951051*
- Original + BNT162b2 Omi BA.4/BA.5, 15/15 µg	*201060*
Macau [a]	326905
Taiwan	18691161
- BNT162b2 (Original)	*18691161*

a. For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) is possible.

5.2.1.2. Health Authority Public Data – Cumulative Exposure

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

Table 8 below displays the EU/EEA published data with number of doses administered for each age group and by vaccine type.

Data downloaded for the EU/EEA countries were reported considering that

- the BNT162b2 original was approved in the 6 months through 4 years age population on 20 October 2022 (week 42),
- the BNT162b2 bivalent Omi BA.1 was approved in 12 years of age and older on 01 September 2022 (week 35),
- the BNT162b2 bivalent Omi BA.4/BA.5 was approved in 12 years of age and older on 12 September 2022 (week 37), and
- the BNT162b2 bivalent Omi BA.4/BA.5 was approved in 5 years through less than 12 years of age on 10 November 2022 (week 45).

Therefore, for the above age groups and for the bivalent vaccines type cumulative and interval values are the same ones.

Table 8. EU/EEA – Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[g]	TOTAL
< 18 years	27055219	19720	41298	8534	27124771
0 – 4 years	2259[d]	NA[e]	NA[e]	0	2259
5 – 9 years	4168125	NA[e]	698[f]	0	4168823
10 – 14 years	9712260	1721	9982	2881	9726844
15 – 17 years	8231535	1765	9149	5490	8247939
18 – 24 years	30475986	124738	112145	44471	30757340
25 – 49 years	138654494	919186	921085	462911	140957676
50 – 59 years	67548429	941198	1385100	469205	70343932
60 – 69 years	55578415	1408422	2012499	2054088	61053424
70 – 79 years	54188335	1754125	1612965	2328964	59884389
≥ 80 years	40436126	1115612	884832	1963926	44400496
Age Unknown	192712	5	1	0	192718
All	497721500	6263273	9512259	7323565	520820597

a. Cumulative period: 2020 week 50 through 2022 week 50 (up to 14 December 2022).
b. Cumulative period: 2022 week 35 through 50.
c. Cumulative period: 2022 week 37 through 50.
d. BNT162b2 Original for 6 months through <5 years was approved in EU/EEA on 20 October 2022; correspondent data for BNT162b2 original evaluated for 2022 week 42 through 50.
e. Not approved.
f. BNT162b2 Bivalent Omi BA.4/BA.5 for 5 through <12 years was approved in EU/EEA on 10 November 2022; correspondent data for evaluated BNT162b2 Bivalent Omi BA.4/BA.5 for 2022 week 45 through 50.
g. Not specified if BA.1 or BA.4/BA.5.

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

Table 9 through Table 11 provide the cumulative total number of administered Comirnaty dose 3 for both BNT162b2 original and bivalent Omi (dose additional 1 in the ECDC webpage) in EU/EEA, per country, and by age group. The tables contain also data about dose 4 (reported as dose additional 2).

Table 9. EU/EEA – Cumulative Number of BNT162b2 Original Administered 3rd and 4th Doses by Age Group and Country

	Age Group																	
	<18 years		18 - 24 years		25 – 49 years		50 – 59 years		60 – 69 years		70 – 79 years		≥80 years		Age Unknown		ALL	
	Dose																	
Countries ↓	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
AT	195863	4425	378033	18327	1637191	108693	886546	101618	765023	180516	565808	212299	425774	181719	0	0	4658375	803172
BE	147922	968	221886	10288	1016544	69330	676858	70501	887390	94945	804216	115965	567108	344064	0	0	4174002	705093
BG	2029	36	17159	600	164102	10651	119417	11046	177350	27575	165677	37665	51312	13137	0	0	695017	100674
CY	0	0	22928	17	150449	431	64435	586	64671	8583	54277	14695	28346	9609	0	0	385106	33921
CZ	72589	123	152416	1672	1155334	21904	633749	22724	747057	68177	693021	102007	290447	55394	0	0	3672024	271878
DK	0	0	273990	1115	881640	13854	646667	10925	565807	17922	532460	25572	238902	15372	0	0	3139466	84760
EE	5612	220	21904	1739	127552	12401	65896	8033	76483	15114	64325	15962	42319	11110	31	5	398479	64359
EL	4489	6	304118	154	1697052	23353	953726	34284	952643	133598	784737	185004	563939	147466	0	0	5256215	523859
ES	33255	533	623109	7647	2861856	53849	1695742	42856	1894561	40945	2740171	28028	2150019	15500	0	0	11965458	188825
FI	16927	183	120696	1724	635541	23444	354950	36820	427152	224832	424257	308531	251371	192788	0	0	2213967	788139
FR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	28009862	6144839
HR	1122	0	17096	113	167190	2011	139511	2604	223343	9776	184787	13467	90986	8850	14	0	822913	36828
HU	55201	110	165117	2480	1021026	30716	527501	23245	707260	84478	582210	118682	249359	52336	0	0	3252473	311937
IE	95676	1214	234020	6873	798240	77164	364215	174044	360915	186189	342152	132375	193848	79980	7	1	2293390	656625
IS	0	0	20603	97	83658	1165	29789	1665	23869	5687	22140	9538	10959	9636	0	0	191018	27788
IT	1844724	947	1837659	4740	6659571	57829	3763960	91393	3192606	654402	2662329	920248	3038137	1249713	0	0	21154262	2978325
LI	0	0	1144	1	2181	0	1017	1	1109	3	1233	32	654	235	0	0	7358	272
LT	1945	12	50871	262	262104	4108	141909	2397	168857	5941	131492	7971	74602	5410	3	0	829835	26089
LU	0	0	26404	994	40027	1279	11982	493	19668	4604	13438	5423	18933	5503	0	0	130452	18296
LV	2872	60	25247	663	110541	5679	41640	2929	36936	5129	20232	5378	10415	3656	3	0	244957	23385
MT	257	10	10362	178	56009	2088	22326	1583	31578	4620	29453	6612	14733	7678	11	549	163472	23537
NL	0	0	653330	5125	2364040	18893	620458	33447	474237	223069	333993	226851	287594	156663	0	0	4863574	664048
NO	0	0	209096	688	710208	8149	387227	11576	408935	85996	386692	206204	207860	125262	0	0	2310018	437875
PL	0	0	483605	28891	3519663	291938	1856566	205961	2772434	820527	2007278	839762	857460	325201	23136	1268	11497006	2512280
PT	0	0	284034	1586	1679225	14644	1003141	10006	913952	10844	836013	19215	629851	421352	275	263	5346216	477647
RO	14162	79	90653	426	546787	4941	303816	3052	334048	5595	201406	5831	67231	2574	0	0	1544468	22491
SE	0	0	330387	28505	1127127	301846	596835	307110	698038	492300	731027	572756	404718	311218	0	0	3888132	2013735
SI	1383	4	25781	68	152553	729	114437	765	143084	2352	108753	3565	64332	4500	0	0	608940	11979
SK	0	0	74690	732	498105	12389	246933	8963	347616	17141	242534	16817	88341	7990	45	1	1498219	64032

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

Table 10. EU/EEA – Cumulative Number of Bivalent Omi BA.1 Administered 3rd and 4th Doses by Age Group and Country

	Age Groups																	
	<18 years		18 - 24 years		25 – 49 years		50 – 59 years		60 – 69 years		70 – 79 years		≥80 years		Age Unknown		ALL	
	Dose																	
Countries ↓	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
AT	1165	553	401	1450	1575	11732	683	11185	617	15091	384	13228	419	9731	0	0	4079	62417
BE	2928	7252	1455	91427	7756	630725	3362	561245	2794	700167	1989	541470	1532	96276	0	0	18888	2621310
CY	0	0	164	10	230	26	14	128	4	106	0	144	0	31	0	0	412	445
CZ	494	102	646	621	4315	10541	1507	10194	1630	27002	1406	37789	717	18752	0	0	10221	104899
DK	0	0	440	1454	1680	21765	1563	84015	1262	142605	1153	220743	1219	139859	0	0	7317	610441
EE	53	5	58	75	328	1024	118	816	159	2065	91	1789	103	1103	0	0	857	6872
EL	150	0	926	13	3724	4827	1038	5266	656	11711	471	12522	687	7800	0	0	7502	42139
FI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HU	218	68	314	633	1374	10144	514	6450	663	14195	606	15267	609	8760	0	0	4080	55449
IS	0	0	92	316	342	2877	117	2596	277	14228	119	8454	29	977	0	0	976	29447
IT	2641	3290	3611	7584	17824	75588	9834	87794	19572	216353	15063	269328	6899	135168	0	0	72803	791815
LI	0	0	0	16	0	111	1	83	2	134	2	182	0	41	0	0	5	567
LU	0	0	16	18	59	196	17	259	33	1483	33	1025	12	326	0	0	170	3307
LV	24	0	30	26	146	328	75	248	121	535	87	575	70	407	0	0	529	2119
NO	0	0	411	473	1990	6689	708	10549	1353	58285	1105	59131	466	15237	0	0	6033	150364
PT	0	0	4946	3268	14263	50968	4782	91137	2897	97689	4376	445667	5079	115149	1	1	36343	803878

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

Table 11. EU/EEA – Cumulative Number of Bivalent Omi BA.4/BA.5 Administered 3rd and 4th Doses by Age Group and Country

	Age Group																	
	<18 years		18 - 24 years		25 – 49 years		50 – 59 years		60 – 69 years		70 – 79 years		≥80 years		Age Unknown		ALL	
Countries↓	Dose																	
	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
AT	6849	8149	2175	21414	9710	173688	4825	148038	3693	157716	2361	105462	1657	60860	0	0	24421	667178
BE	1667	3150	792	26688	3702	124465	1548	86025	1160	77304	626	53892	581	25006	0	0	8409	393380
CY	0	0	130	45	570	2672	130	3322	124	6046	72	6777	35	2636	0	0	1061	21498
CZ	2014	837	1984	2509	12883	43241	4236	38084	4685	96621	3675	122488	1443	51443	0	0	28906	354386
DK	0	0	888	3863	4461	57823	3612	368901	2207	343746	1104	253276	709	94547	0	0	12981	1122156
EE	149	24	209	449	965	4113	322	2540	295	4496	183	4324	146	2625	1	0	2120	18547
EL	678	10	2904	208	11289	38806	4242	50270	3097	99029	2227	93769	3239	54530	0	0	26998	336612
FI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	112202	1760800
IS	0	0	0	1	0	17	0	25	0	78	0	38	0	7	0	0	0	166
IT	6115	10817	6665	25407	34218	243669	24013	249589	40151	419750	29615	481761	13122	301561	0	0	147784	1721737
LU	0	0	76	190	543	2996	142	3078	156	5238	103	3087	35	1014	0	0	1055	15603
LV	28	4	54	52	225	477	79	301	105	499	79	523	72	310	0	0	614	2162
NO	0	0	938	1082	4160	16257	1524	23932	1706	53357	857	36716	405	11519	0	0	9590	142863
PT	0	0	5014	5211	16808	90614	11861	329101	11139	594059	5342	283341	2374	36669	0	0	52538	1338995

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

Table 12 through Table 14 show the cumulative number of BNT162b2 original and bivalent vaccines doses administered in Japan, respectively.

Table 12. Japan - Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Administered Doses (1st and 2nd)

Population(s)	Number of Doses	
	1st Dose	2nd Dose
General population[a]	81607513	81060827
Elderly[c]	32204636	32124036
Child (5 to < 12 years)	1720140	1642717
Infant only (6 months – 4 years)	83869	28123
Medical workers[b]	6378205	5709228
All	**87985718**	**86770055**

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers (1st and 2nd dose) ended on 30 July 2021.
c. This reported value is smaller respect the one reported in PSUR #3. Administration data corrected between PSUR #3 and PSUR #4.

Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed on: 22 December 2022, 6:00 p.m. [JST].

Table 13. Japan - Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Administered Doses (3rd through 5th)

Population(s)	Number of Doses		
	3rd Dose	4th Dose	5th Dose[a]
General population[b]	51282451	37967980	18337675
Elderly	20724545	19697780	15262175
Child (5 to < 12 years)	510928	N/A	N/A
Infant only (6 months – 4 years)	0	N/A	N/A
All	**51282451**	**37967980**	**18337675**

a. Only bivalent vaccines.
b. Including elderly, children and infants.

Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html Accessed on: 22 December 2022, 6:00 p.m. [JST].

Table 14. Japan - Cumulative Number of BNT162b2 Bivalent Omi BA.1 and BNT162b2 Bivalent Omi BA.4/BA.5 Administered Doses (3rd through 5th)

Population(s)	Number of Doses		
	3rd Dose	4th Dose	5th Dose
Bivalent (Original + BNT162b2 Omi BA.1) 15/15 µg	688106	5971770	1160875
Elderly	48199	1138100	1026108
Child (5 to < 12 years)	N/A	N/A	N/A
Infant only (6 months – 4 years)	N/A	N/A	N/A
Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	1074078	9571999	17176800
Elderly	60296	944327	14236067
Child (5 to < 12 years)	N/A	N/A	N/A
Infant only (6 months – 4 years)	N/A	N/A	N/A

Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed on: 22 December 2022, 6:00 p.m. [JST]

Table 15 shows the cumulative number of BNT162b2 original and Bivalent (Original + Omi BA.4/BA.5) doses administered in the US.

Table 15. US - Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Administered Doses

Population	No. of Doses
All	421572855
Original	393271419
Bivalent Omi BA.4/BA.5[a]	28301436

a. Reported as Pfizer-BioNTech updated booster.
Source: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5. Accessed on: 17 December 2022, 7:42 p.m. [CET].

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

5.2.2. Interval Exposure

5.2.2.1. MAH and License Partner Data

Approximately 813,783,710 doses of BNT162b2 original and bivalent vaccines were shipped worldwide during the current reporting interval from 19 June 2022 through 18 December 2022. Out of the doses shipped during the reporting period, 142,687,310 were original adult[11] presentations (including PBS and Tris/Sucrose); 155,236,800 were original paediatric[12] presentations; 515,859,600 were bivalent vaccines (Table 5 and Table 6) of which 10,963,900 were for paediatric presentations; 232,907,810 doses of BNT162b2 (original and bivalent) were shipped to ROW.[13]

The worldwide estimated interval number of shipped doses BNT162b2 original, by region and countries and by age group, based on data provided in the shipment tracker (Order Book)[27] is displayed in Table 16.

Table 16. Interval Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years[a]	All
Europe	**8.7**	**3264000**	**7257600**	**15311700**	**25833300**
European Union (27)	2.4	3259200	3993600	0	7252800
European Economic Area Countries (3)	0.0	4800	4800	0	9600
Switzerland	0.5	0	96000	1399680	1495680
UK	2.3	0	2793600	4004910	6798510
Other Countries	0.1	0	52800	126720	179520
Commonwealth of Independent States	3.4	0	316800	9780390	10097190
North America	**17.7**	**12513300**	**13592500**	**26654900**	**52760700**
US	16.4	10803300	12842500	25304900	48950700
Canada	1.3	1710000	750000	1350000	3810000
Central and South America	**20.5**	**1842000**	**28208400**	**30902580**	**60952980**

Table 16. Interval Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years[a]	All
Asia	**39.9**	**12946800**	**67965800**	**37940220**	**118852820**
Japan	3.0	8803200	0	0	8803200
Other Countries	36.9	4143600	67965800	37940220	110049620
Oceania	**2.0**	**806400**	**3662400**	**1577970**	**6046770**
Australia/New Zealand	1.9	806400	3600000	1253430	5659830
Other Countries	0.1	0	62400	324540	386940
Africa	**11.2**	**0**	**3177600**	**30299940**	**33477540**
Total	**100.0**	**31372500**	**123864300**	**142687310**	**297924110**

a. Including PBS purple cap and Tris/sucrose grey cap.

LP Data

Interval LP (Fosun) data on the number of BNT162b2 original and bivalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 17 below.

Table 17. Interval Number of Administered Doses of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Vaccine – License Partner Data

Region **Country** ***-Vaccine Presentation***	**Number of Administered Doses**
Asia	**2855293**
Hong Kong	837660
- BNT162b2 (Original), 30 µg	*620100*
- BNT162b2 (Original), 10 µg	*10800*
- BNT162b2 (Original), 3 µg	*5700*
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg[a]	*201060*
Macau [b]	70502
Taiwan	1947131
- BNT162b2 (Original), 30 µg	*824970*
- BNT162b2 (Original), 10 µg	*870461*
- BNT162b2 (Original), 3 µg[c]	*251700*

a. Since November 2022.
b. For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. Since August 2022.

5.2.2.2. Health Authority Public Data – Interval Exposure

Estimated interval data about the number of COMIRNATY® doses administered are published only for the EU/EEA countries. Approximately 39,687,303 doses of BNT162b2 original and bivalent vaccines were administered during the interval reporting period.

Table below displays the interval data with number of doses administered for each age group and by dose number in the EU/EEA countries.

Table 18. EU/EEA – Interval Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi	TOTAL
< 18 years	361730	19720	41298	8534	431282
0 – 4 years	2259[d]	NA[e]	NA[e]	0	2259
5 – 9 years	163705	NA[e]	698[f]	0	164403
10 – 14 years	168654	1721	9982	2881	183238
15 – 17 years	104302	1765	9149	5490	120706
18 – 24 years	469839	124738	112145	44471	751193
25 – 49 years	2162623	919186	921085	462911	4465805
50 – 59 years	1348144	941198	1385100	469205	4143647
60 – 69 years	2980098	1408422	2012499	2054088	8455107
70 – 79 years	3214786	1754125	1612965	2328964	8910840
≥ 80 years	1813291	1115612	884832	1963926	5777661
Age Unknown	16311	5	1	0	16317
All	16588206	6263273	9512259	7323565	39687303

a. Interval period: 2022 week 25 through 50 (up to 14 December 2022).
b. Interval period: 2022 week 35 through 50.
c. Interval period: 2022 week 37 through 50.
d. BNT162b2 Original for 6 months through <5 years was approved in EU/EEA on 20 October 2022; data for BNT162b2 original evaluated for 2022 week 42 through 50.
e. Not approved.
f. BNT162b2 Bivalent Omi BA.4/BA.5 for 5 through <12 years was approved in EU/EEA on 10 November 2022; correspondent data for evaluated BNT162b2 Bivalent Omi BA.4/BA.5 for 2022 week 45 through 50.

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

Table 19 provides for the interval reporting period the total number of administered Comirnaty dose 3 for BNT162b2 original (dose additional 1 in the ECDC webpage) in EU/EEA by country and by age group. The table contains also data about dose 4 (reported as dose additional 2).

Table 19. EU/EEA – Interval Number of BNT162b2 Original Administered 3rd and 4th Doses by Age Group and Country

	Age Group																	
	<18 years		18 - 24 years		25 – 49 years		50 – 59 years		60 – 69 years		70 – 79 years		≥80 years		Age Unknown		ALL	
Countries ↓	Dose																	
	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4	3	4
AT	46018	4082	7660	9772	26148	76200	11139	85063	9482	165279	7548	193683	7010	154798	0	0	68987	684795
BE	8356	307	3920	4476	13265	31224	3249	25199	1890	32861	1319	43787	2100	101355	0	0	25743	238902
BG	1189	36	2743	600	19139	10651	9630	11046	11411	27575	10382	37665	3681	13137	0	0	56986	100674
CY	0	0	695	10	2083	191	355	312	229	4228	160	5009	88	1993	0	0	3610	11743
CZ	8463	123	10035	1672	34583	21903	9336	22724	7686	68176	5779	102002	2884	55394	0	0	70303	271871
DK	0	0	4804	856	8989	10421	1615	5551	904	9570	462	13697	332	10751	0	0	17106	50846
EE	885	121	1410	709	5639	6539	1606	5201	1693	12343	1020	14333	998	9892	6	5	12366	49017
EL	926	3	5425	34	24485	19595	7638	27031	6263	63046	5134	69196	8790	43537	0	0	57735	222439
ES	10373	236	111704	4658	328040	26127	95616	16943	29056	13617	6669	8270	3468	6467	0	0	574553	76082
FI	3249	105	6785	1428	20412	19835	6603	32362	10597	212952	9211	240663	2035	21017	0	0	55643	528257
FR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	492597	3846606
HR	168	0	1002	103	7018	1941	4613	2533	12124	9582	15023	13128	9619	8187	0	0	49399	35481
HU	1750	70	1928	895	4613	9631	1296	5048	935	9256	674	8779	587	5154	0	0	10033	38763
IE	17385	1161	7824	6586	24979	75381	8009	171926	7052	163335	4385	91652	2408	48091	0	1	54657	556971
IS	0	0	218	91	780	1032	187	1485	228	5209	190	8557	112	5133	0	0	1715	21507
IT	36036	685	37179	3063	123272	34160	50045	53582	83564	547535	65272	758688	37646	558835	0	0	396978	1955863
LI	0	0	24	1	38	0	12	1	9	3	6	32	7	235	0	0	116	272
LT	430	12	634	262	3505	4108	1147	2397	1337	5941	859	7971	595	5410	0	0	8077	26089
LU	0	0	531	82	1045	216	158	217	116	4379	80	5237	53	1462	0	0	1983	11593
LV	505	59	1380	661	5180	5665	1758	2920	1754	5109	1163	5369	847	3652	3	0	12029	23327
MT	115	3	377	157	1252	1793	271	1364	119	2612	71	2520	65	1591	7	437	2160	10703
NL	0	0	20765	2377	49339	6900	6702	12470	3773	78749	1933	49538	1085	24542	0	0	83597	174576
NO	0	0	3742	319	10744	4295	2770	7158	2995	80040	4087	199390	3933	112636	0	0	28271	403838
PL	0	0	28786	28619	122027	290499	32369	205433	47670	819799	34676	838566	16029	256447	4667	1233	281557	2439363
PT	0	0	39060	388	114706	2520	24121	2042	7963	3102	3576	5980	3346	76229	1	0	192772	90261
RO	606	73	1560	339	7361	3643	2406	2098	1451	3392	847	3363	437	1517	0	0	14589	14424
SE	0	0	19006	27300	64883	290017	14536	294134	8837	242344	5544	97429	2803	34226	0	0	115609	985450
SI	179	3	713	55	2278	571	774	651	629	2231	490	3431	649	4324	0	0	5533	11263
SK	0	0	1312	710	4975	12192	1393	8855	926	16923	500	16638	356	7904	0	1	9462	63222

Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 17 December 2022.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 25.1 has been used to code adverse events/reactions in summary tabulations.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in Pfizer clinical trial cases received by the MAH. This appendix is organised according to MedDRA SOC. This appendix includes SAEs originated from the following studies: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, C4591024, C4591030, C4591031, C4591044 and C4591048.

Appendix 2.1.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in BioNTech and Fosun clinical trial cases. This appendix includes SAEs originated from the following studies: BNT162-01, BNT162-03, BNT162-04, BNT162-06, BNT162-14, BNT162-17 and BNT162-21.

6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

In the Medsafe assessment of the Comirnaty EU-RMP version 8 the following request was made: *It is acknowledged that the clinical studies (C4591031 Substudy E and D) were conducted outside of New Zealand. Therefore, the race and ethnicity datasets do not provide information on all the ethnicities relevant to New Zealand. The sponsor should commit to present data, where available, information on race and ethnicity, including Māori and Pacific peoples in the PSURs and SSRs that are submitted to Medsafe.*

Response

The Appendix 2.2.5 displays, for the PM dataset, demographic interval data including ethnicity and race, when available.

Appendix 2.2 provides the overall (including original and bivalent vaccines) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. Appendix 2.2.1 through Appendix 2.2.4 provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [BNT162b2 original and BNT162b2 bivalent (Omi BA.1, Omi BA.4/BA.5, Omi)]. These tabulations include serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources. The cumulative data include all data up to 18 December 2022 and the interval data are from 19 June 2022 to 18 December 2022. This appendix is organised according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non-interventional sources.

Please note that adverse event totals presented for safety topic evaluations in Section 16 *Signal and Risk Evaluation*, may differ from Appendix 2.2 through Appendix 2.2.4 totals, due to the fact that Appendix 2.2 only displays the number of serious reactions from

non-interventional studies and solicited sources as described above, whereas the safety topic evaluation includes all reported events. Cases from non-interventional studies and other non-interventional solicited sources must contain at least 1 serious related event to meet PSUR inclusion criteria and may also contain additional events that are considered unrelated, all of which would be evaluated.

Appendix 2.2.5 displays, for the PM dataset, demographic interval data, including ethnicity and race when available.

6.3.1. General Overview

The list of regulatory authority requests to be addressed in the PSUR is detailed below, together with the relevant cross-referenced sections/appendices where responses are provided.

EMA - PSUR#3 AR (Procedure No. EMEA/H/C/PSUSA/00010898/202206) – Appendix 5.2.

Request(s)	Please refer to
Report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases is below 99%.	Section 6.3.1.3
Continue to closely monitor multisystem inflammatory syndrome in children/adults (MIS-C/-A) and all new cases of MIS-C/-A should be reported in the future PSURs.	Section 16.3.3.1.4, Appendix 5.6.1.
Analysis of myocarditis/pericarditis cases focus on information concerning the course, outcome, and possible risk factors of the myocarditis/pericarditis cases following Comirnaty exposure.	Section 16.3.1.1.1, Section 16.3.1.1.2
For future PSURs the evaluation of cardiovascular adverse events of special interest (AESIs), haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity, should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.	Section 16.3.3.1
The vaccination stress/anxiety related ADRs are considered well documented and can be removed from 'Evaluation of other risks (not categorised as important).	Appendix 5.2.
For future PSURs the evaluation of overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.	Section 16.3.4
For future PSURs the evaluation of the use in frail patients with co-morbidities, and/or interactions with other vaccines should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.	Section 16.3.5
In the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine.	Section 6.3.1.3.2.2 and in any safety section
Cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase.	Section 15, Appendix 5.6.2.
Concerning hearing loss, the MAH is requested in future reviews of cases reporting hearing loss to conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss, if applicable.	Appendix 5.2.
Cumulative review on the association between Comirnaty and post orthostatic tachycardia syndrome.	Appendix 5.2.

EMA – 9th SMSR AR (Procedure No. EMEA/H/C/005735/MEA/002.8) – Appendix 5.4.3.

Estimate of the exposure of "third doses" in future PSURs separately (reporting period and cumulatively).	Section 5.2

EMA – 13th SMSR / 2nd SBSR (EMA/PRAC/202255/2022) – Appendix 5.4.3.

Presentation of all relevant literature concerning the safety of Comirnaty (also besides the database Medline and Embase) during the reporting period.	Section 11

EMA – EU-RMP – Appendix 5.4.4.

Critically appraise if the wealth of safety data accumulated during the product use can inform rationalising the safety concerns in the RMP.	Section 16.4

EMA – PRAC EPITT No. 19835 (Histiocytic necrotizing lymphadenitis) – Appendix 5.3.1.

Cumulative review of all cases of histiocytic necrotizing lymphadenitis.	Section 15, Appendix 5.3.1.

EMA – PRAC EPITT No. 19784 (Amenorrhoea) – Appendix 5.3.2.

Signal evaluation and cumulative updated analysis of amenorrhoea.	Appendix 5.3.2. and Appendix 5.3.2.1

EMA – PRAC EPITT No. 19840 (Vulval ulceration) – Appendix 5.3.3.

Review of vulval ulceration cases received since 16 August 2022.	Appendix 5.3.3.

EMA – Procedure No. EMEA/H/C/005735/II/0140 (Second Booster – 4th vaccine dose) – Appendix 5.4.1.

Monitoring of medication errors due to the availability of bivalent vaccines.	Section 9.2

EMA – Procedure No. EMEA/H/C/005735/II/0141 (Myocarditis/Pericarditis) – Appendix 5.4.2.

Close monitoring of the risk of myocarditis and pericarditis in the 5-11 years of age group and following the booster dose(s)	Section 16.3.5.2, Section 16.3.1.1.1, Section 16.3.1.1.2

WHO – EUL – Appendix 5.5.1.

Pregnancy outcome in clinical trials.	Section 16.3.5.3
Data on low- and middle-income countries (LMICs) populations with HIV, malnutrition and tuberculosis and other infectious diseases.	Section 16.3.3.1.12

Health Canada – Appendix 5.5.2.

Cumulative review of histiocytic necrotizing lymphadenitis and vulval ulceration.	Appendix 5.3.1 and Appendix 5.3.3.
Review of incremental reports of Guillain-Barre Syndrome	Section 16.3.3.1.6.1
Review of incremental reports of "Poor quality product administered"	Section 6.3.1.3.5
Data stratification by vaccine variants.	Section 6.3.1.3.2.2, Appendix 2.2.1. through Appendix 2.2.4.
Presentation and discussion of interim reports of the studies C4591010, C4591021 and C4591022.	Appendix 5.5.2.1 through Appendix 5.5.2.3

Medsafe, New Zealand – Appendix 5.5.3.

Adverse events reported in <5-year-old should be split by dose 1, 2 and 3.	Section 16.3.5.2.1
Differentiate between ADRs reported in <5-year-old following the 3 mcg Maroon cap formulation vs given another product not approved for this age group.	Section 9.2.2
Include global usage data of the bivalent vaccines and present data, where available, on race and ethnicity, including Māori and Pacific peoples.	Section 5.2, Section 6.2, Appendix 2.2.5.

MFDS, South Korea (Omicron BA.1 BLA submission) – Appendix 5.5.4.

Safety evaluation for the second booster vaccination in AESI and VAED including VAERD.	Section 16.3.2.1, Section 16.3.3.1

TGA, Australia (Assessment of Bimonthly 16-Feb-2022 to 15-Apr-2022) – Appendix 5.6.3.

Cumulative review of subacute thyroiditis.	Section 16.3.3.1.3.1, Appendix 5.6.3

6.3.1.1. General Overview - All Cases

A total of 283,301 case reports (309 from CT and 282,992 from PM) containing 839,246 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 508,351 case reports retrieved in the PSUR #3. Please refer to Appendix 2.1 and Appendix 2.1.1 for the cumulative summary tabulation of all CT cases and to Appendix 2.2 for the summary tabulation of all PM cases received during the current reporting period and cumulatively.

Demographic information of all cases included in the safety database and received during the reporting interval are shown in Table 20.

Table 20. Demographic Information – All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N= 283,301
MC	Yes	143,910 (50.8%)
	No	139,391 (49.2%)
Country/region of incidence: (*: ≥2% of all cases)	Austria*	61,294 (21.6%)
	Sweden*	35,551 (12.5%)
	Germany*	27,216 (9.6%)
	United States*	22,348 (7.9%)
	France*	18,821 (6.6%)
	Japan*	12,893 (4.6%)
	Portugal*	12,135 (4.3%)
	Norway*	11,845 (4.2%)
	Denmark*	11,346 (4.0%)
	Poland*	7,367 (2.6%)
	Belgium*	6,762 (2.4%)
	Finland*	5,651 (2.0%)
	Other countries	50,072 (17.7%)
Gender	Female	172,685 (61.0%)
	Male	82,995 (29.3%)
	Unknown/No Data	27,621 (9.7%)
Age (years)	N	250,121
	Min-Max	1 Day – 111 Years
	Mean	44.7
	Median	44.0
Age Range	≤ 17 years	12,945 (4.6%) [12,760][c]
	0 to 27 days	62 (0.02%) [6]
	28 days to 23 months	276 (0.1%) [168]
	2-11 years	5526 (2.0%) [5511]
	12-17 years	7081 (2.5%) [7075]
	18-30 years	45,161 (15.9%)
	31-50 years	100,430 (35.4%)
	51-64 years	56,950 (20.1%)
	65-74 years	24,331 (8.6%)
	≥ 75 years	12,821 (4.5%)
	Unknown	30,605 (10.8%)
	N/A[b]	58 (0.02%)
Case Seriousness	Serious	95,725 (33.8%)
	Non-serious	187,576 (66.2%)
Case Outcome	Fatal	1293 (0.5%)
	Not recovered	70,590 (24.9%)
	Recovered/Recovering	74,521 (26.3%)
	Recovered with sequelae	4645 (1.6%)
	Unknown	132,252 (46.7%)
Presence of comorbidities[d]	Yes	24,132 (8.5%)
	No	259,169 (91.5%)

Table 20. Demographic Information – All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N= 283,301
Original	BNT162b2[e]	272,071 (96.0%)
Bivalents	BNT162b2 + BNT162b2 BA.1 Omi	4860 (1.7%)
	BNT162b2 + BNT162b2 BA.4/BA.5 Omi	8802 (3.1%)
Vaccine series	Primary	219,368 (77.4%)
	Boosters	63,933 (22.6%)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Foetus cases: Age range only applies to post-birth subjects.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (foetus/neonates) exposed before or during the mother' pregnancy or babies exposed through breastfeeding. Number of cases reported in this table may not match with number of cases evaluated in individual sections due to case-by-case review that is not possible to implement in the overall dataset.
d. Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, described as special populations in Section 16.3.5.4 and Section 16.3.5.5, respectively, and the Frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis), described as missing information in Section 16.4.2.
e. Includes BNT162b2 (272,070) and BNT162b2s01 (1)
MC = medically confirmed; N = number; Min = minimum; Max = maximum; N/A = not applicable

Data about race and ethnicity are displayed in Appendix 2.2.5.

6.3.1.1.1. Unlocked Cases

A total of 1106 (0.4%) unlocked[28] case reports (7 from CT and 1099 from PM) containing 4014 events fulfilled criteria for inclusion in this PSUR, compared to 2441 (0.5%) case reports retrieved in the PSUR #3.

6.3.1.2. General Overview - Clinical Trial Data

A total of 309 case reports containing 381 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 668 case reports retrieved in the PSUR #3. Demographic information of all CT cases[29] included in the safety database and received during the reporting interval are shown in Table 21. Among these 309 CT cases, 223 cases involved BNT162b2 [including BNT162b2 (222) and BNT162b2s01 (1)], and no cases involved

[28] Unlocked cases are those cases either in the Drug Safety Unit, Primary Review or the Medical Review workflows that are not yet in the Distribution workflow, which locks the cases, and the system automatically runs reporting rules, schedules and subsequently generates expedited reports as appropriate.

[29] Clinical Trial cases include:
- 296 cases originated from 6 interventional trials (C4591001, C4591001-OPENLABEL, C4591007, C4591007-OPENLABEL, C4591024, C4591030, C4591031, C4591031-OPENLABEL, C4591044) for which BioNTech is the Sponsor and Pfizer acts as lead development party; and
- 13 cases from 2 BioNTech interventional trials (BNT162-14 and BNT162-17).

BNT162b2 + Omi BA.1 and BNT162b2 + Omi BA.4/BA.5. In addition, there were 81 cases reported from blinded therapy and 5 cases from placebo.

Table 21. Demographic Information – All CT Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=309	BNT162b2 No. of Cases (%[a]) N=223	Blinded Therapy No. of Cases (%[a]) N=81	Placebo No. of Cases (%[a]) N=5
Country/region of incidence	United States	219 (70.9%)	159 (71.3%)	59 (72.8%)	1 (20.0%)
	Brazil	23 (7.4%)	17 (7.6%)	6 (7.4%)	-
	Poland	18 (5.8%)	11 (4.5%)	8 (9.9%)	-
	South Africa	11 (3.6%)	11 (4.9%)	-	-
	Argentina	9 (2.9%)	9 (4.0%)	-	-
	New Zealand	8 (2.6%)	5 (2.2%)	-	3 (60.0%)
	Other countries	21 (6.8%)	12 (5.4%)	8 (9.9%)	1 (20.0%)
Gender	Female	145 (46.9%)	104 (46.6%)	37 (45.7%)	4 (80.0%)
	Male	162 (52.4%)	117 (52.5%)	44 (54.3%)	1 (20.0%)
	No Data	2 (0.6%)	2 (0.9%)	-	-
Age (years)	N	307	221	81	5
	Min-Max	7 months – 87 years	1 – 87 years	7 months – 82 years	24 – 52 years
	Mean	40.0	43.9	29.4	41.8
	Median	45	51	12	43
Age Range	≤ 17 years	107 (34.6%) [107][c]	62 (27.8%) [62] [c]	45 (55.6%) [45] [c]	-
	0 to 27 days	- [-]	- [-]	- [-]	- [-]
	28 days to 23 months	22 (7.1%) [22]	9 (4.0%) [9]	13 (16.0%) [13]	- [-]
	2-11 years	74 (23.9%) [74]	48 (21.5%) [48]	26 (32.1%) [26]	- [-]
	12-17 years	11 (3.6%) [11]	5 (2.2%) [5]	6 (7.4%) [6]	- [-]
	18-30 years	9 (2.9%)	6 (2.7%)	2 (2.5%)	1 (20.0%)
	31-50 years	51 (16.5%)	40 (17.9%)	8 (9.9%)	3 (60.0%)
	51-64 years	58 (18.8%)	46 (20.6%)	11 (13.6%)	1 (20.0%)
	65-74 years	47 (15.2%)	40 (17.9%)	7 (8.6%)	-
	≥ 75 years	35 (11.3%)	27 (12.1%)	8 (9.9%)	-
	Unknown	-	-	-	-
	N/A[b]	2 (0.6%)	2 (0.9%)	-	-
Case Outcome	Fatal	28 (9.1%)	25 (11.2%)	2 (2.5%)	1 (20.0%)
	Not recovered	42 (13.6%)	30 (13.5%)	12 (14.8%)	-
	Recovered/ Recovering	224 (72.5%)	157 (70.4%)	63 (77.8%)	4 (80.0%)
	Recovered with sequelae	15 (4.9%)	11 (4.9%)	4 (4.9%)	-
	Unknown	-	-	-	-
Presence of comorbidities[d]	Yes	118 (38.2%)	91 (40.8%)	26 (32.1%)	1 (20.0%)
	No	191 (61.8%)	132 (59.2%)	55 (67.9%)	4 (80.0%)

Table 21. Demographic Information – All CT Cases Received during the Reporting Interval

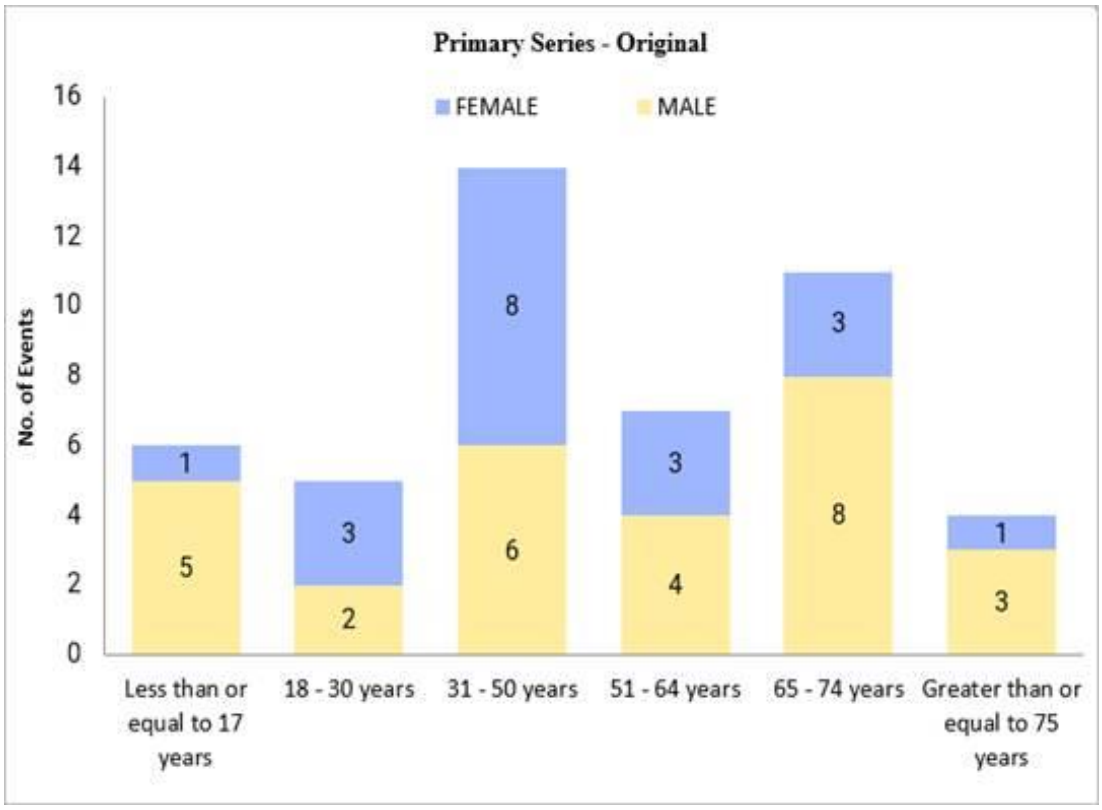
Characteristics		All No. of Cases (%[a]) N=309	BNT162b2 No. of Cases (%[a]) N=223	Blinded Therapy No. of Cases (%[a]) N=81	Placebo No. of Cases (%[a]) N=5
Vaccine series	Primary	85 (27.5%)	36 (16.1%)	44 (54.3%)	5 (100%)
	Booster[30]	224 (72.5%)	187 (83.9%)	37 (45.7%)	-

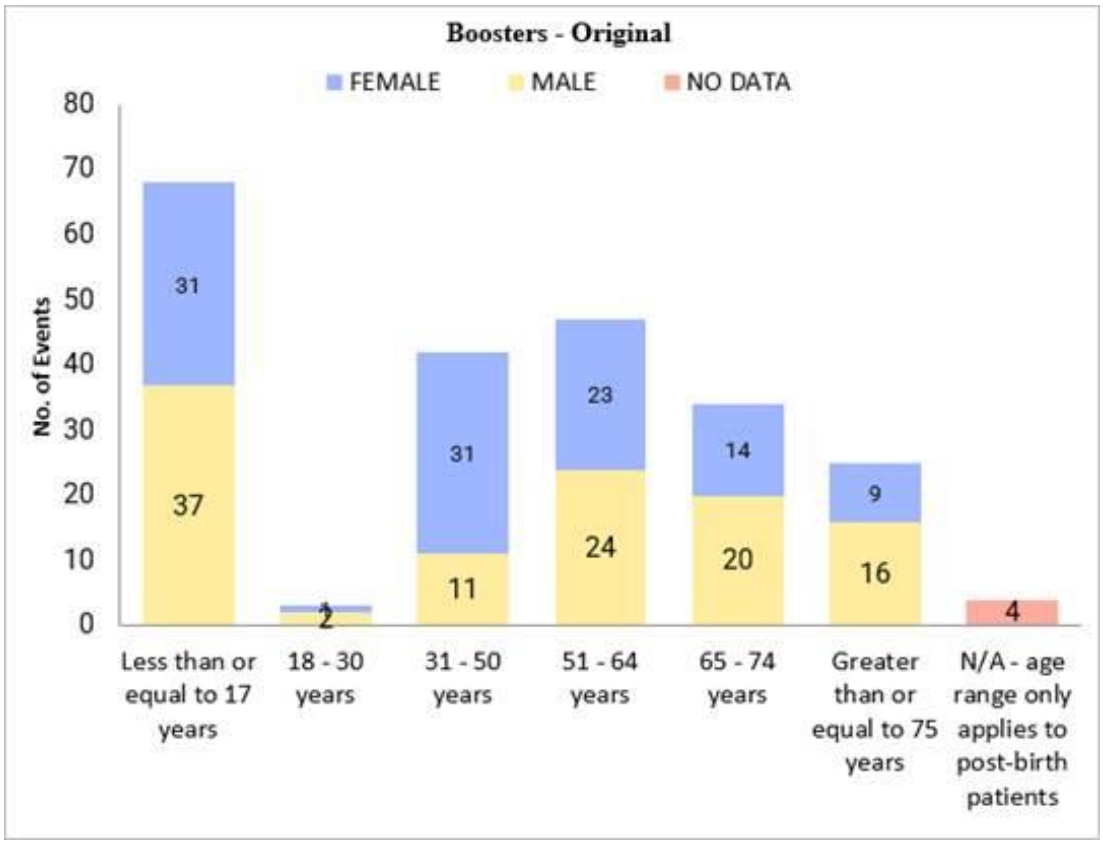
a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Foetus cases: Age range only applies to post-birth subjects.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (foetus/neonates) exposed before or during the mother' pregnancy or babies exposed through breastfeeding. Number of cases reported in this table may not match with number of cases evaluated in individual Sections due to case-by-case review that is not possible to implement in the overall dataset.
d. Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, described as special populations in Section 16.3.5.4 and Section 16.3.5.5, respectively, and the Frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis), described as missing information in Section 16.4.2.
N = number; Min = minimum; Max = maximum

During the reporting period, in the CT dataset, the number of male participants was slightly higher than female (52.4% vs 46.9%); the number of SAEs experienced by male participants is slightly higher than female (199 vs 178). The number of SAEs reported in males was higher than in females through all age groups, except for the 31 – 50 age group, both for primary and booster administration. Data in 18 – 30 years age group was too little to be evaluated in both primary series and boosters (Figure 1).

[30] Search criteria: Age in Years >4 years or Age Group = "CHILD" and Dose number ≥ 3 and Dose Description text including the term "BOOSTER" OR LLT equal to BOOSTER.

Figure 1. Clinical Trial Data: Number of SAEs by Age Group in Primary Series Cases and Boosters Cases by Vaccine Type





The overall of case outcomes, case outcomes by gender and age group in primary series and boosters clinical trial cases are presented in Figure 2 through Figure 4. Overall, the proportion of BNT162b2 boosters cases is higher than cases with primary series, and this is also reflected among the cases with a fatal outcome (Figure 2). A slightly higher number of male participants [primary series (3), boosters (15)] than female participants [primary series (0), boosters (7)] experienced a fatal outcome, and more male than female participants had case outcomes not recovered [primary series (2) and boosters (16) in male vs. primary (0) and boosters (12) in female], and recovered with sequelae [primary series (2) and boosters (5) in male vs. primary (0) and boosters (4) in female]; whereas the numbers of case outcomes with recovered/recovering [primary series (15) and boosters (59) in male vs. primary (14) and boosters (67) in female] in male participants were slightly lower than those in female participants (Figure 3). In addition, the age group 31-50 years is most represented across the case outcomes of recovered/recovering (9) in primary series; while the age group ≤ 17 years is most frequently reported in boosters with the case outcome recovered/recovering. Among the cases with a fatal outcome, most cases were presented in the age groups 51-64 years and 65-74 years. In both primary and boosters, most of the cases had a favourable outcome across all age groups at the time of reporting (Figure 4).

Figure 2. Clinical Trial Data: Overall Case Outcome in Primary Series Cases and Boosters Cases by Vaccine Type

Figure 3. Clinical Trial Data: Overall Case Outcome by Gender in Primary Series Cases and Boosters Cases by Vaccine Type

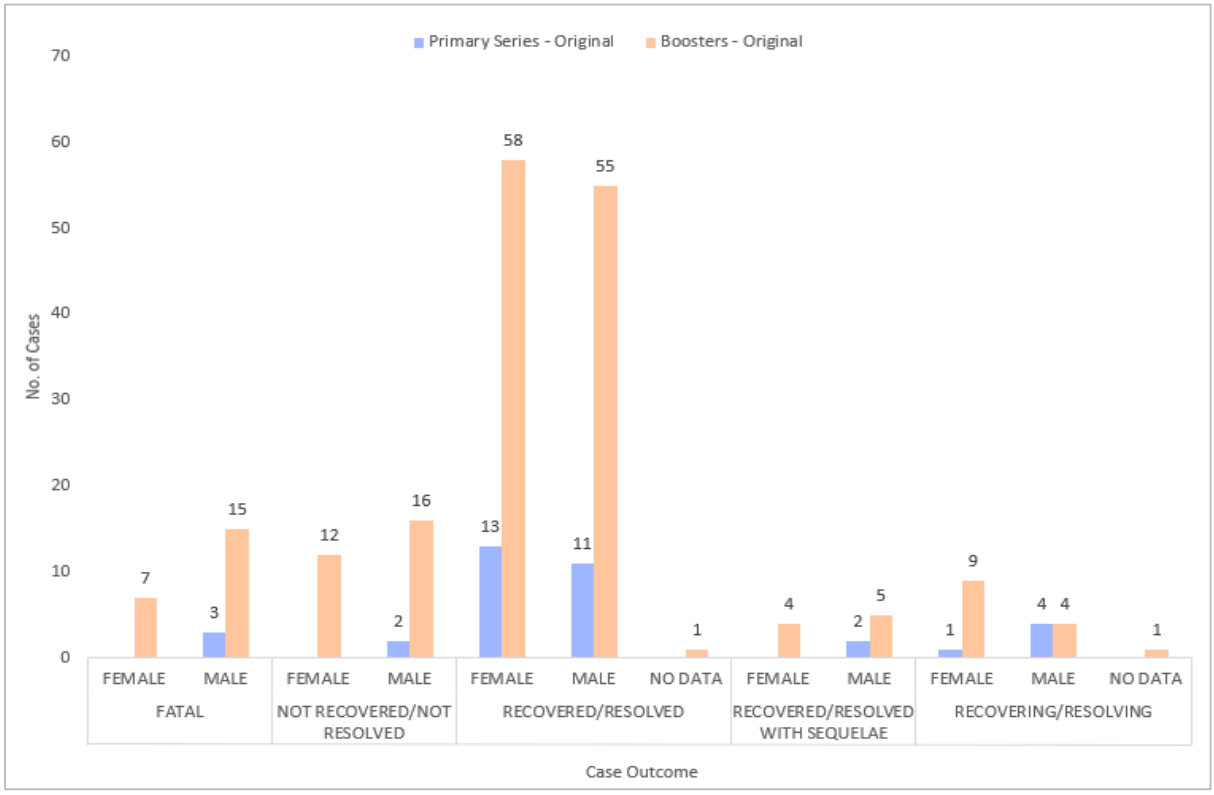
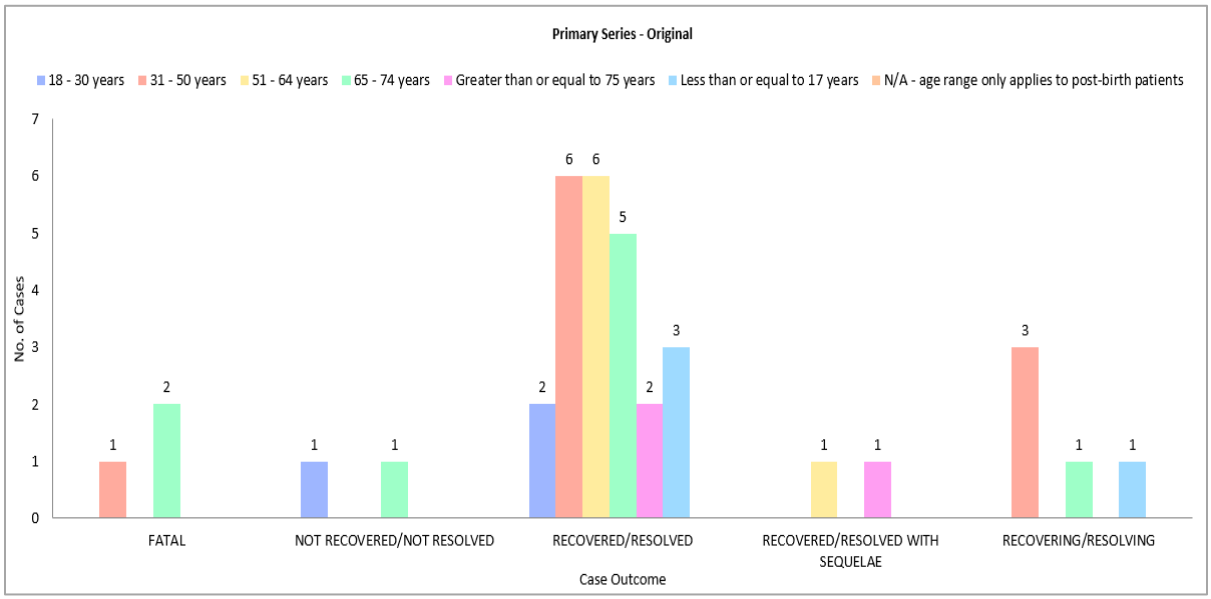
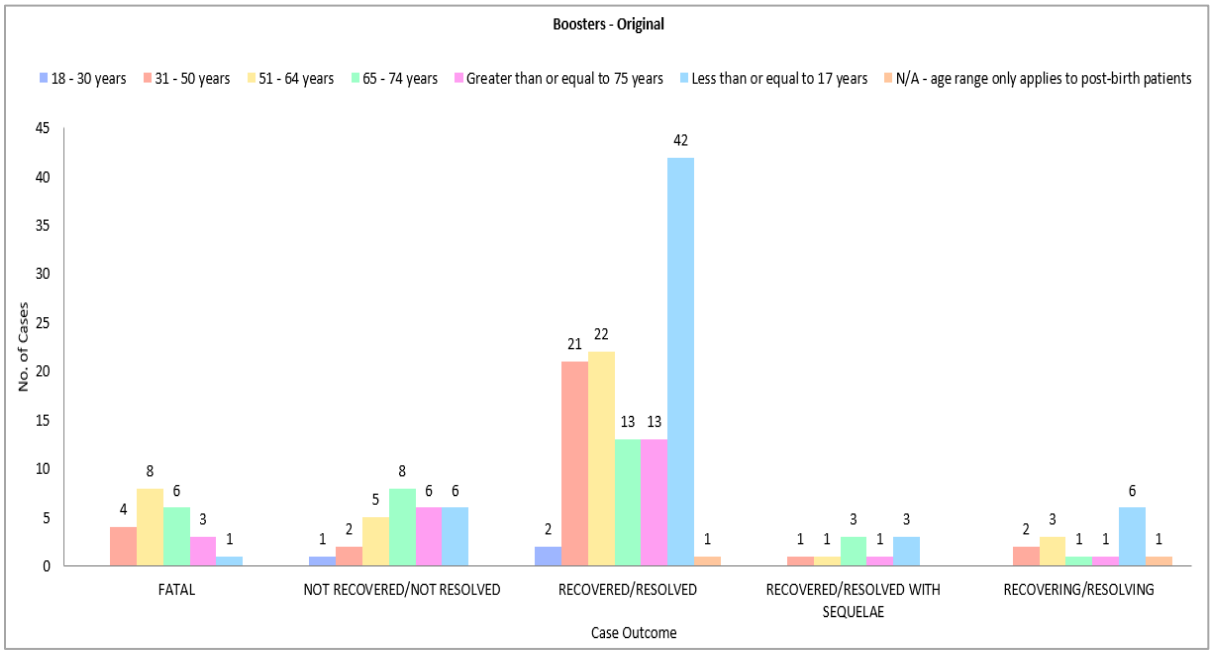


Figure 4. Clinical Trial Data: Overall Case Outcome by Age Group and Vaccine Type





The summary of medical history reported in the CT cases is provided in Table 22. All co-suspect medications were singularly reported during the reporting period.

Table 22. Clinical Trial Data: Medical History

Most frequently reported (≥2%) medical history (HLGT):

Medical History (HLGT)	Number of HLGT
Vascular hypertensive disorders	86
Lipid metabolism disorders	61
Allergic conditions	44
Glucose metabolism disorders (incl diabetes mellitus)	41 each
Bronchial disorders (excl neoplasms)	
Appetite and general nutritional disorders	37
Joint disorders	35
Gastrointestinal motility and defaecation conditions	33
Infections - pathogen unspecified	31 each
Depressed mood disorders and disturbances	
Lifestyle issues	27
Obstetric and gynaecological therapeutic procedures	23
Gastrointestinal therapeutic procedures	22
Coronary artery disorders	20 each
Prostatic disorders (excl infections and inflammations)	
Viral infectious disorders	19 each
Musculoskeletal and connective tissue disorders NEC	
Headaches	
Anxiety disorders and symptoms	
Thyroid gland disorders	18 each
Peripheral neuropathies	
Bone and joint therapeutic procedures	
Cardiac arrhythmias	17
Gallbladder disorders	16
Sleep disorders and disturbances	15 each
Epidermal and dermal conditions	
Hepatobiliary therapeutic procedures	
Therapeutic procedures and supportive care NEC	
Vascular therapeutic procedures	
Respiratory disorders NEC	14 each
Upper respiratory tract disorders (excl infections)	
Nervous system, skull and spine therapeutic procedures	
General system disorders NEC	12 each
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	
Age related factors	11 each
Head and neck therapeutic procedures	
Heart failures	10 each
Anterior eye structural change, deposit and degeneration	
Muscle disorders	
Seizures (incl subtypes)	9 each
Sexual function and fertility disorders	
Abdominal hernias and other abdominal wall conditions	8 each
Bacterial infectious disorders	
Bone and joint injuries	
Manic and bipolar mood disorders and disturbances	
Psychiatric disorders NEC	
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	

Table 22. Clinical Trial Data: Medical History

Medical History (HLGT)	Number of HLGT
Pregnancy, labour, delivery and postpartum conditions	7 each
Hearing disorders	
Injuries NEC	
Cardiac and vascular investigations (excl enzyme tests)	
Nephropathies	
Urinary tract signs and symptoms	
Uterine, pelvic and broad ligament disorders	
Renal and urinary tract therapeutic procedures	
Gastrointestinal signs and symptoms	6 each
Lipid analyses	
Purine and pyrimidine metabolism disorders	
Bone disorders (excl congenital and fractures)	
Neurological disorders NEC	
Cardiac therapeutic procedures	
Anaemias nonhaemolytic and marrow depression	5 each
Myocardial disorders	
Hepatic and hepatobiliary disorders	
Central nervous system vascular disorders	
Spinal cord and nerve root disorders	
Renal disorders (excl nephropathies)	
Eye therapeutic procedures	
Male genital tract therapeutic procedures	

Most frequently report (≥ 2%) medical history (PT):

Medical History (PT)	Number of PT
Hypertension	86
Type 2 diabetes mellitus	32
Obesity	31
Hyperlipidaemia	30 each
Seasonal allergy	
Depression	27
Asthma	25
Gastrooesophageal reflux disease	22 each
Hypercholesterolaemia	
Osteoarthritis	
Benign prostatic hyperplasia	18
Hypothyroidism	16
Back pain	15 each
Insomnia	
Cholecystectomy	14
Anxiety	13 each
Coronary artery disease	
Chronic obstructive pulmonary disease	11 each
Neuropathy peripheral	
Rhinitis allergic	
Atrial fibrillation	10 each
Cataract	
Cholelithiasis	
Dyslipidaemia	

Table 22. Clinical Trial Data: Medical History

Medical History (PT)	Number of PT
Hysterectomy	10 each
Postmenopause	
Caesarean section	9 each
Clinical trial participant	
Migraine	
Appendicitis	8 each
Cardiac failure congestive	
Drug hypersensitivity	
Food allergy	
Pregnancy	7 each
Non-tobacco user	
Appendicectomy	
Eczema	
Headache	
Knee arthroplasty	
Myocardial infarction	
Sleep apnoea syndrome	
Urinary tract infection	
Tobacco user	6 each
Arthralgia	
Blood cholesterol increased	
Constipation	
Coronary artery bypass	
Erectile dysfunction	
Gout	
Muscle spasms	
Tonsillectomy	
Bipolar disorder	5 each
Bronchiolitis	
Carpal tunnel syndrome	
Cataract operation	
Cholecystitis	
Diarrhoea	
Intervertebral disc degeneration	
Nephropathy	
Overweight	
Renal transplant	
Spinal osteoarthritis	

COVID-19 medical history (PT, n = 13):

COVID-19 Medical History (PT)	Number of PT
COVID-19	7
COVID-19 immunisation	6

Adverse Event Data

During the reporting period, a total of 309 cases originated from CTs containing 381 events were reported.

The MedDRA SOCs containing the greatest number of reported events[31] (≥3%) from clinical trial data in the reporting period were Infections and infestations (89), Injury, poisoning and procedural complications (39), Cardiac disorders (37), Neoplasms benign, malignant and unspecified (incl cysts and polyps), Nervous system disorders (30 each), General disorders and administration site conditions, Respiratory, thoracic and mediastinal disorders (25 each), Gastrointestinal disorders (16), Pregnancy, puerperium and perinatal conditions (13), Musculoskeletal and connective tissue disorders (12), Psychiatric disorders (10), and Hepatobiliary disorders (9).

In primary series, the most frequently (≥ 2%) reported PTs included Atrial fibrillation (4), Concussion, Condition aggravated, Diverticulitis, Myocardial infarction (3 each), Back pain, Cardiac failure congestive, Cholecystitis acute, Cholelithiasis, Death, Osteoarthritis, Pulmonary tuberculosis, and Respiratory syncytial virus bronchiolitis (2 each); while in boosters, the most frequently (≥ 2%) reported PTs included Pneumonia (8), Condition aggravated, Respiratory syncytial virus infection (7 each), Suicidal ideation, and Urinary tract infection (5 each).

A total of 381 SAEs were reported in 309 cases originated from 8 CTs, compared to 879 SAEs in 668 cases originated from 9 CTs retrieved in the PSUR #3.

The overall safety evaluation includes a review of the most frequently reported serious events by SOC and PT for events reported in ≥2% of all clinical trial cases during the reporting interval as compared to the cumulative period through 18 December 2022, as summarised in Table 23.

[31] Of note, multiple adverse events may be reported in a single case.

Table 23. Clinical Trial Data: Serious Events Reported in ≥2% Cases

	Reporting Period 19 Jun 2022 - 18 Dec 2022		Cumulatively through 18 Dec 2022	
MedDRA SOC MedDRA PT	**All Cases [a] (N=309) AEs (n=381)**	**BNT162b2/b2s01/BT Cases (N=304) AEs (n=376)**	**All Cases [c] (N=2724) AEs (n=3578)**	**BNT162b1/BNT162b2/BNT162b2s01/BNT162b3/BNT162c2/BT Cases (N=2576) AEs (n=3384)**
	n [b] (AERP, %)	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**
General disorders and administration site conditions				
Condition aggravated	10 (3.2%)	10 (3.3%)	90 (3.3%)	83 (3.2%)
Infections and infestations				
Pneumonia	9 (2.9%)	9 (3.0%)	65 (2.4%)	65 (2.5%)
Respiratory syncytial virus infection	7 (2.3%)	7 (2.3%)	9 (0.3%)	9 (0.3%)

a. Includes BNT162b2, BNT162b2s01, Blinded Therapy, and Placebo.
b. Reporting proportion calculated as n/N (% of cases) in the current reporting period or cumulatively.
c. Includes BNT162b1, BNT162b2, BNT162b2s01, BNT162b3, BNT162c2, Blinded Therapy, and Placebo. The variant vaccines b1 and c2 are study drugs in study BNT162-01, b2s01 in Study BNT162-14 and b3 in Study BNT162-04, respectively. Please refer to Section 7 for details on these studies.
AE = Adverse Event; AERP = Adverse Event Reporting Proportion; BT = Blinded Therapy; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of cases; n = Number of events; PT = Preferred Term; SOC = Summary Organ Class

During the reporting period, the most frequently reported SAEs in the clinical trials are unexpected[32] per the current IB (Version 9.0, dated 18 September 2022). Among these most frequently reported SAEs in all CT dataset, the reporting proportion of the PT Pneumonia (2.9%) and Respiratory syncytial virus infection (2.3%) during the reporting interval was higher compared to their proportions in the cumulative dataset (2.4% and 0.3%, respectively). Upon review, all frequently reported SAEs during the reporting interval are assessed as unrelated by the investigator and the Sponsor. Event outcomes were resolved/resolving (20), not resolved (5), and resolved with sequelae (1).

Conclusion

Based on the review of the CT cases, no new safety issues were identified.

[32] Section 7.8.1 Adverse reactions.

6.3.1.3. General Overview - Post-Authorisation Data

In the PRAC AR of the PSUR #3 (Procedure EMEA/H/C/PSUSA/00010898/202206), the following request was made: *In future PSURs, the MAH should only report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases decreases below 99% as presented in the current 3rd PSUR.*

Response

The number of cases downloaded from EudraVigilance is included in this Section. During the reporting period, 214,324 cases were downloaded from EudraVigilance and 213,812 cases (99.8% of the total downloaded cases) were included in the data tabulations presented in the PSUR. Please refer to Appendix 5.2 for more details.

A total of 282,992 case reports (including 213,812 downloaded from EudraVigilance) containing 838,865 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 507,683 case reports retrieved in the PSUR #3. Demographic information of all PM cases included in the safety database and received during the reporting interval are shown in Table 24.

Table 24. Demographic Information – All PM Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=282,992	BNT162b2 No. of Cases (%[a]) N=271,848	BNT162b2 + Omi BA.1 No. of Cases (%[a]) N=4861	BNT162b2 + Omi BA.4/BA.5 No. of Cases (%[a]) N=8802
MC	Yes	143,601 (50.7%)	138,757 (51.0%)	1182 (24.3%)	5541 (63.0%)
	No	139,391 (49.3%)	133,091 (49.0%)	3679 (75.9%)	3261 (37.0%)
Country/region of incidence (≥2% of all cases)	Austria	61,294 (21.7%)	61,122 (22.5%)	47 (1.0%)	131 (1.5%)
	Sweden	35,551 (12.6%)	35,400 (13.0%)	130 (2.7%)	38 (0.4%)
	Germany	27,212 (9.6%)	26,071 (9.6%)	284 (5.8%)	984 (11.2%)
	United States	22129 (7.8%)	18,715 (6.9%)	-	5230 (59.4%)
	France	18,821 (6.7%)	18,500 (6.8%)	96 (2.0%)	254 (2.9%)
	Japan	12,893 (4.6%)	11118 (4.1%)	952 (19.6%)	1014 (11.5%)
	Portugal	12,135 (4.3%)	12,020 (4.4%)	60 (1.2%)	60 (0.7%)
	Norway	11,845 (4.2%)	11,763 (4.3%)	42 (0.9%)	42 (0.5%)
	Denmark	11,346 (4.0%)	11,269 (4.1%)	50 (1.0%)	43 (0.5%)
	Poland	7349 (2.6%)	7324 (2.7%)	23 (0.5%)	3 (0.03%)
	Belgium	6762 (2.4%)	6319 (2.3%)	391 (8.0%)	63 (0.7%)
	Finland	5645 (2.0%)	5615 (2.1%)	14 (0.3%)	22 (0.2%)
	Other countries	50,010 (17.7%)	46,612 (17.1%)	2772 (57.0%)	918 (10.4%)
Gender	Female	172,540 (61.0%)	166,306 (61.2%)	3253 (66.9%)	3820 (43.4%)
	Male	82833 (29.3%)	79,971 (29.4%)	1218 (25.1%)	2229 (25.3%)
	Unknown/No Data	27,619 (9.8%)	25,571 (9.4%)	390 (8.0%)	2753 (31.3%)

Table 24. Demographic Information – All PM Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=282,992	BNT162b2 No. of Cases (%[a]) N=271,848	BNT162b2 + Omi BA.1 No. of Cases (%[a]) N=4861	BNT162b2 + Omi BA.4/BA.5 No. of Cases (%[a]) N=8802
Age (years)	N	249,814	242,262	3266	5548
	Min-Max	1 Day - 111 years	1 Day - 105 years	10 Days - 111 years	6 weeks - 101 years
	Mean	44.7	44.5	50.6	53.8
	Median	44	44	51	57
Age Range	≤ 17 years	12,838 (4.5%) [12,653][c]	12,453 (4.6%) [12,275]	96 (2.0%) [91]	517 (5.9%) [515]
	0 to 27 days	62 (0.02%) [6]	60 (0.02%) [6]	2 (0.04%) [-]	-
	28 days to 23 months	254 (0.09%) [146]	249 (0.09%) [145]	2 (0.04%) [-]	7 (0.08%) [5]
	2-11 years	5452 (1.9%) [5437]	5253 (1.9%) [5239]	14 (0.3%) [13]	314 (3.6%) [314]
	12-17 years	7070 (2.5%) [7064]	6891 (2.5%) [6885]	78 (1.6%) [78]	196 (2.2%) [196]
	18-30 years	45,152 (16.0%)	44,459 (16.4%)	416 (8.6%)	410 (4.7%)
	31-50 years	100,379 (35.5%)	98,199 (36.1%)	1122 (23.1%)	1287 (14.6%)
	51-64 years	56,892 (20.1%)	54,973 (20.2%)	839 (17.3%)	1337 (15.2%)
	65-74 years	24,284 (8.6%)	22,887 (8.4%)	597 (12.3%)	1054 (12.0%)
	≥ 75 years	12,786 (4.5%)	11,617 (4.3%)	353 (7.3%)	1010 (11.5%)
	Unknown	30,605 (10.8%)	27,208 (10.0%)	1435 (29.5%)	3186 (36.2%)
	N/A[b]	56 (0.02%)	52 (0.02%)	3 (0.1%)	1 (0.01%)
Case Seriousness	Serious	95,416 (33.7%)	92,970 (34.2%)	1133 (23.3%)	1828 (20.8%)
	Non-serious	187,576 (66.3%)	178,878 (65.8%)	3728 (76.7%)	6974 (79.2%)
Case Outcome	Fatal	1265 (0.4%)	1135 (0.4%)	40 (0.8%)	98 (1.1%)
	Not recovered	70,548 (24.9%)	67,443 (24.8%)	2008 (41.3%)	1275 (14.5%)
	Recovered/ Recovering	74,297 (26.3%)	70,894 (26.1%)	1657 (34.1%)	1943 (22.1%)
	Recovered with sequelae	4630 (1.6%)	4558 (1.7%)	45 (0.9%)	36 (0.4%)
	Unknown	132,252 (46.7%)	127,818 (47.0%)	1111 (22.9%)	5450 (61.9%)
Vaccine series	Primary	219,283 (77.5%)	218,916 (80.5%)	293 (6.0%)	804 (9.1%)
	Boosters[30]	63,709 (22.5%)	52,932 (19.5%)	4568 (94.0%)	7998 (90.9%)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Foetus cases-Age range only applies to post-birth subjects.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (foetus/neonates) exposed before or during the mother' pregnancy or babies exposed through breastfeeding. Number of cases reported in this table may not match with number of cases evaluated in individual Sections due to case-by-case review that is not possible to implement in the overall dataset.

During the reporting period, in the PM dataset the number of female subjects was 2.1 times higher than the number of male subjects (61.0% vs 29.3%); across the different age groups the ratio of female/male cases ranged between 1.1 in the less than or equal to 17 years to 2.6 in the 18-30 years group. In both primary series and boosters cases, the percentage of SAEs

reported in females was higher than in males through the majority of age groups. Percentage of SAEs by age group and vaccine type in primary series and boosters dataset is presented in Table 25.

Table 25. Post-Authorisation Data: Percentage of SAEs by Age Group and Vaccine Type in Primary Series and Boosters

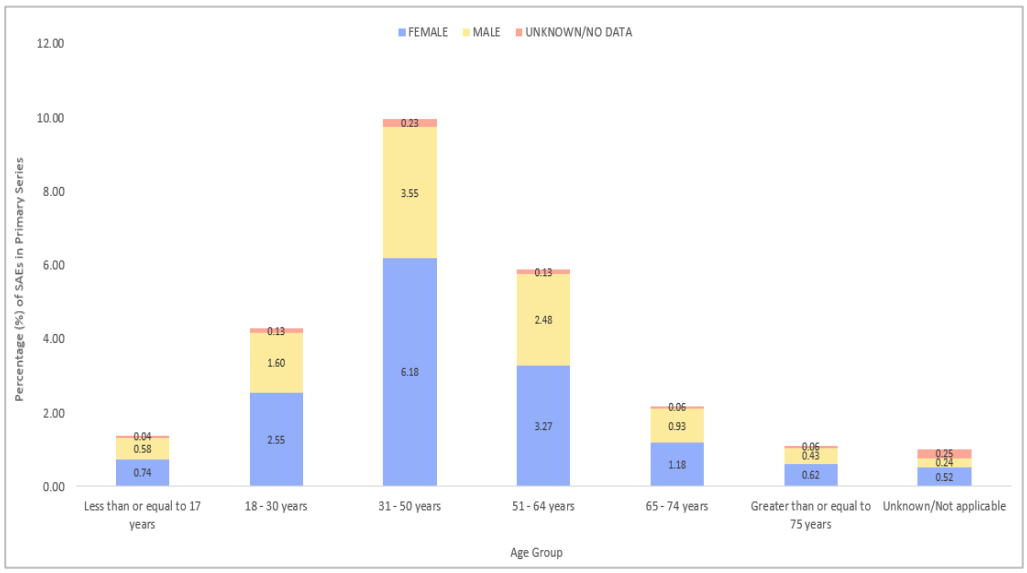
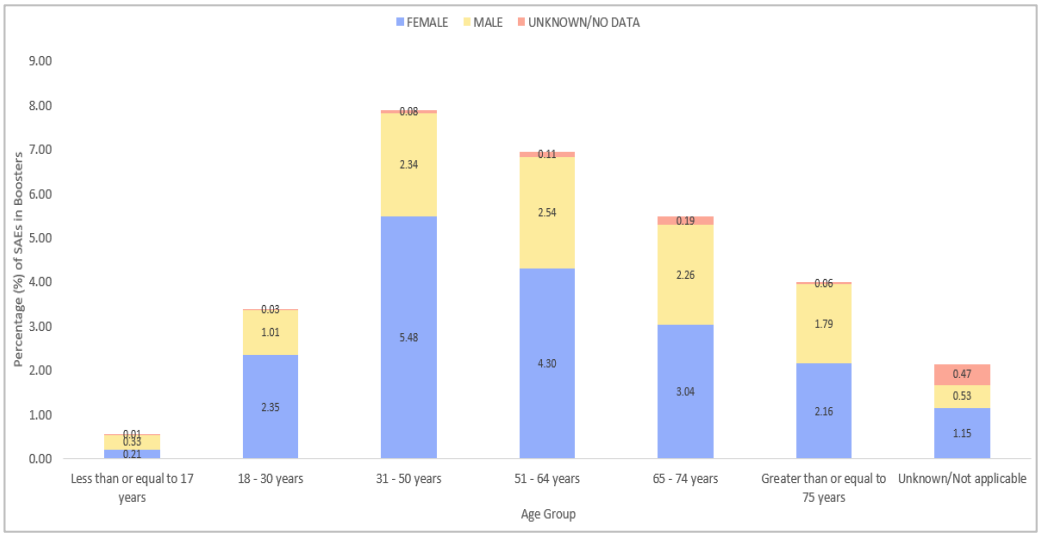
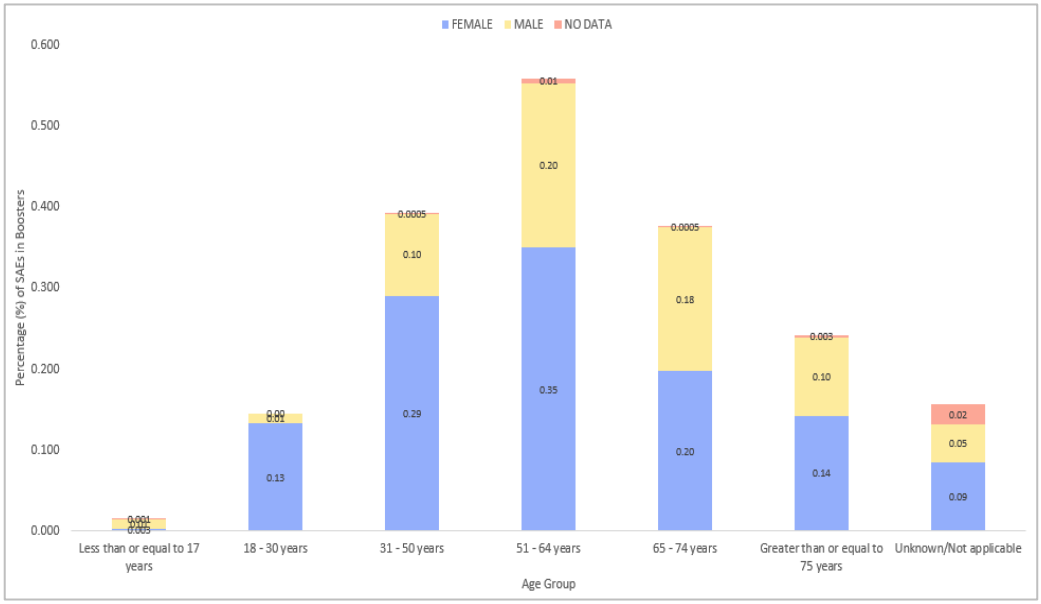
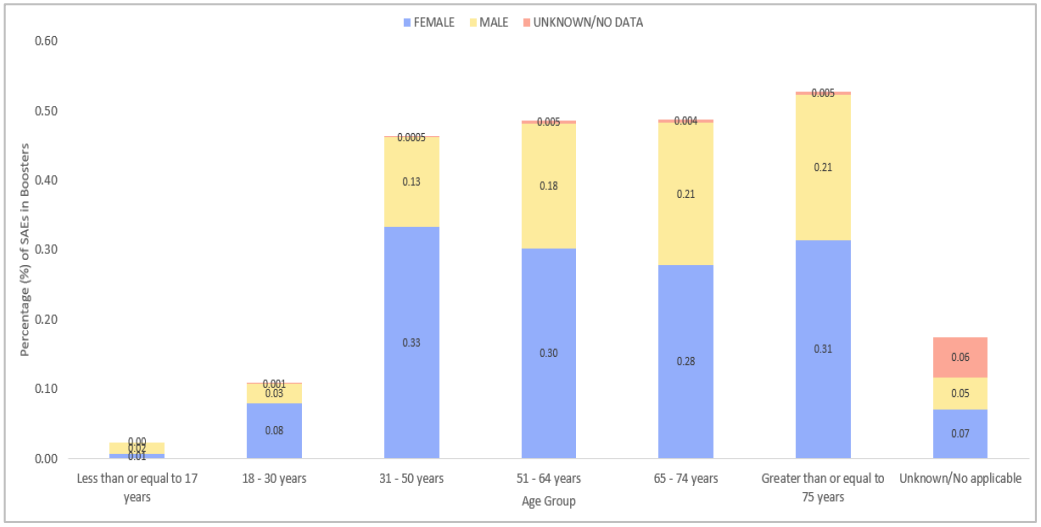
Primary series	
Original	
Boosters	
Original	

Table 25. Post-Authorisation Data: Percentage of SAEs by Age Group and Vaccine Type in Primary Series and Boosters

Bivalent BA.1	
Bivalent BA.4/ BA.5	

The summary of medical history and co-suspect medications reported in the PM cases is provided in Table 26 (all cases), in Table 27 (BNT162b2 Original cases), in Table 28 (Bivalent BNT162b2 + Omi BA.1), and in Table 29 (Bivalent BNT162b2 + Omi BA.4/BA.5).

Table 26. Post-Authorisation Data: Medical History and Co-Suspect Medications - All Cases

Most frequently reported (≥2%) medical history (HLGT):

Medical History (HLGT)	Number of HLGT
Allergic conditions	12,291
Viral infectious disorders	11,670
Vascular hypertensive disorders	9512
Bronchial disorders (excl neoplasms)	6537
Thyroid gland disorders	4534
Glucose metabolism disorders (incl diabetes mellitus)	4033
General system disorders NEC	3919
Epidermal and dermal conditions	3687
Joint disorders	3333
Obstetric and gynaecological therapeutic procedures	3288
Therapeutic procedures and supportive care NEC	2740
Lifestyle issues	2696
Headaches	2327
Infections - pathogen unspecified	2218
Depressed mood disorders and disturbances	2164
Gastrointestinal motility and defaecation conditions	2075
Appetite and general nutritional disorders	1887
Cardiac arrhythmias	1826
Anxiety disorders and symptoms	1778
Muscle disorders	1517
Menstrual cycle and uterine bleeding disorders	1489
Gastrointestinal inflammatory conditions	1412
Neurological disorders NEC	1346

Most frequently reported (≥2%) medical history (PT):

Medical History (PT)	Number of PT
Hypertension	9385
Asthma	5532
Drug hypersensitivity	3880
Seasonal allergy	3573
Hypersensitivity	2917
Hypothyroidism	2470
Pain	2039
Depression	2014
Diabetes mellitus	1801
Food allergy	1694
Migraine	1646
Type 2 diabetes mellitus	1471
Obesity	1397

COVID-19 medical history (PT):

COVID-19 Medical History (PT)	Number of PT
COVID-19	9568
Suspected COVID-19	548

Table 26. Post-Authorisation Data: Medical History and Co-Suspect Medications - All Cases

COVID-19 Medical History (PT)	Number of PT
Post-acute COVID-19 syndrome	225
Coronavirus infection	54
SARS-CoV-2 test positive	38
COVID-19 pneumonia	37
Exposure to SARS-CoV-2	27
Asymptomatic COVID-19	18
SARS-CoV-2 antibody test positive	8
Coronavirus test positive	2
COVID-19 treatment	1 each
Occupational exposure to SARS-CoV-2	

Most frequently reported (>100) co-suspect medications (other than COVID-19 vaccines):

Co-suspect Vaccines/Medications (Other Than COVID-19 Vaccines)	Number of Cases
Elasomeran	2774
Influenza vaccine	510
Adalimumab	305
Influenza vaccine inact SPLIT 4V	238
Influenza vaccine inact SAG 4V	225

Most frequently reported (>100) co-suspect COVID-19 vaccines:

Co-suspect COVID-19 Vaccines	Number of Cases
COVID-19 vaccine	3982
COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19)	1389
COVID-19 vaccine NRVV AD26 (JNJ 78436735)	210

Table 27. Post-Authorisation Data: Medical History and Co-Suspect Medications – BNT162b2 Cases

Most frequently reported (≥2%) medical history (HLGT):

Medical History (HLGT)	Number of HLGT
Allergic conditions	11,495
Viral infectious disorders	10,331
Vascular hypertensive disorders	8891
Bronchial disorders (excl neoplasms)	6189
Thyroid gland disorders	4317
General system disorders NEC	3804
Glucose metabolism disorders (incl diabetes mellitus)	3709
Epidermal and dermal conditions	3586
Obstetric and gynaecological therapeutic procedures	3263
Joint disorders	3153
Therapeutic procedures and supportive care NEC	2643
Lifestyle issues	2538
Headaches	2247
Infections - pathogen unspecified	2127
Depressed mood disorders and disturbances	2066
Gastrointestinal motility and defaecation conditions	1956
Lipid metabolism disorders	1909
Appetite and general nutritional disorders	1786
Cardiac arrhythmias	1707
Anxiety disorders and symptoms	1704
Menstrual cycle and uterine bleeding disorders	1479
Muscle disorders	1457
Gastrointestinal inflammatory conditions	1348
Neurological disorders NEC	1286

Most frequently reported (≥2%) medical history (PT):

Medical History (PT)	Number of PT
Hypertension	8775
Asthma	5269
Drug hypersensitivity	3558
Seasonal allergy	3407
Hypersensitivity	2796
Hypothyroidism	2344
Pain	1997
Depression	1920
Diabetes mellitus	1638
Food allergy	1549
Type 2 diabetes mellitus	1359
Obesity	1323

COVID-19 medical history (PT):

COVID-19 Medical History (PT)	Number of PT
COVID-19	8343
Suspected COVID-19	499

Table 27. Post-Authorisation Data: Medical History and Co-Suspect Medications – BNT162b2 Cases

COVID-19 Medical History (PT)	Number of PT
Post-acute COVID-19 syndrome	205
Coronavirus infection	49
SARS-CoV-2 test positive	36
COVID-19 pneumonia	34
Exposure to SARS-CoV-2	25
Asymptomatic COVID-19	18
SARS-CoV-2 antibody test positive	8
Coronavirus test positive	2
COVID-19 treatment	1

Most frequently reported (>100) co-suspect medications (other than COVID-19 vaccines):

Co-suspect Vaccines/Medications (Other Than COVID-19 Vaccines)	Number of Cases
Elasomeran	2692
Adalimumab	301
Influenza vaccine	243

Most frequently reported (>100) co-suspect COVID-19 vaccines:

Co-suspect COVID-19 Vaccines	Number of Cases
COVID-19 vaccine	3563
COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19)	1380
COVID-19 vaccine NRVV AD26 (JNJ 78436735)	205

Table 28. Post-Authorisation Data: Medical History and Co-Suspect Medications – Bivalent BNT162b2 + Omi BA.1 Cases

Most frequently reported (≥2%) medical history (HLGT):

Medical History (HLGT)	Number of HLGT
Viral infectious disorders	1074
Allergic conditions	330
Vascular hypertensive disorders	198
Bronchial disorders (excl neoplasms)	133
Glucose metabolism disorders (incl diabetes mellitus)	118
Joint disorders	76
Thyroid gland disorders	72
General system disorders NEC	56
Epidermal and dermal conditions	51
Lipid metabolism disorders	46
Depressed mood disorders and disturbances	42
Therapeutic procedures and supportive care NEC	40

Table 28. Post-Authorisation Data: Medical History and Co-Suspect Medications – Bivalent BNT162b2 + Omi BA.1 Cases

Most frequently reported (≥2%) medical history (PT):

Medical History (PT)	Number of PT
Hypertension	196
Drug hypersensitivity	109
Asthma	106
Seasonal allergy	79
Food allergy	67
Diabetes mellitus	62
Hypersensitivity	49
Type 2 diabetes mellitus	45
Depression	42 each
Hypothyroidism	

COVID-19 medical history (PT):

COVID-19 Medical History (PT)	Number of PT
COVID-19	993
Suspected COVID-19	53
Post-acute COVID-19 syndrome	13
Coronavirus infection	1 each
COVID-19 pneumonia	
Exposure to SARS-CoV-2	

Most frequently reported (>10) co-suspect medications (other than COVID-19 vaccines):

Co-suspect Vaccines/Medications (Other Than COVID-19 Vaccines)	Number of Cases
Influenza vaccine	62
Elasomeran	35
Influenza vaccine inact SPLIT 4V	28
influenza vaccine inact SAG 4V	19

Most frequently reported (>10) co-suspect COVID-19 vaccines:

Co-suspect COVID-19 Vaccines	Number of Cases
COVID-19 vaccine	48
COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19)	17

Table 29. Post-Authorisation Data: Medical History and Co-Suspect Medications – Bivalent BNT162b2 + Omi BA.4/BA.5 Cases

Most frequently reported (≥2%) medical history (HLGT):

Medical History (HLGT)	Number of HLGT
Allergic conditions	587
Vascular hypertensive disorders	522
Viral infectious disorders	315
Bronchial disorders (excl neoplasms)	279
Glucose metabolism disorders (incl diabetes mellitus)	245
Thyroid gland disorders	187
Joint disorders	127
Gastrointestinal motility and defaecation conditions	110
Lipid analyses	106
Appetite and general nutritional disorders	95
Coronary artery disorders	79 each
Depressed mood disorders and disturbances	
General system disorders NEC	78
Anxiety disorders and symptoms	76
Central nervous system vascular disorders	71
Infections - pathogen unspecified	69
Epidermal and dermal conditions	61
Cardiac and vascular investigations (excl enzyme tests)	57 each
Headaches	
Bone disorders (excl congenital and fractures)	48 each
Mental impairment disorders	
Respiratory disorders NEC	
Heart failures	46

Most frequently reported (≥2%) medical history (PT):

Medical History (PT)	Number of PT
Hypertension	512
Drug hypersensitivity	267
Asthma	209
Diabetes mellitus	123
Hypothyroidism	111
Seasonal allergy	101
Food allergy	100
Hypersensitivity	96
Type 2 diabetes mellitus	79
Gastrooesophageal reflux disease	75
Depression	73
Obesity	72
Anxiety	62 each
Blood cholesterol increased	
Chronic obstructive pulmonary disease	58
Hyperlipidaemia	52
Atrial fibrillation	51
Hypercholesterolaemia	48

Table 29. Post-Authorisation Data: Medical History and Co-Suspect Medications – Bivalent BNT162b2 + Omi BA.4/BA.5 Cases

COVID-19 medical history (PT):

COVID-19 Medical History (PT)	Number of PT
COVID-19	271
Post-acute COVID-19 syndrome	7
Coronavirus infection	4
COVID-19 pneumonia	2 each
SARS-CoV-2 test positive	
Suspected COVID-19	
Exposure to SARS-CoV-2	1 each
Occupational exposure to SARS-CoV-2	

Most frequently reported (>100) co-suspect medications (other than COVID-19 vaccines):

Co-suspect Vaccines/Medications (Other Than COVID-19 Vaccines)	Number of Cases
Influenza vaccine	243
Influenza vaccine inact SPLIT 4V	143
influenza vaccine inact SAG 4V	134
Elasomeran	104

Most frequently reported (>100) co-suspect COVID-19 vaccines:

Co-suspect COVID-19 Vaccines	Number of Cases
COVID-19 vaccine	401

Adverse Event Data

A total of 838,865 AEs (of which 232,740 were serious and 606,521 non-serious[33]) were reported in 282,992 PM cases, compared to 1,596,793 AEs (of which 439,443 were serious and 1,158,240 non-serious) reported in 507,683 PM cases, retrieved in the PSUR #3.

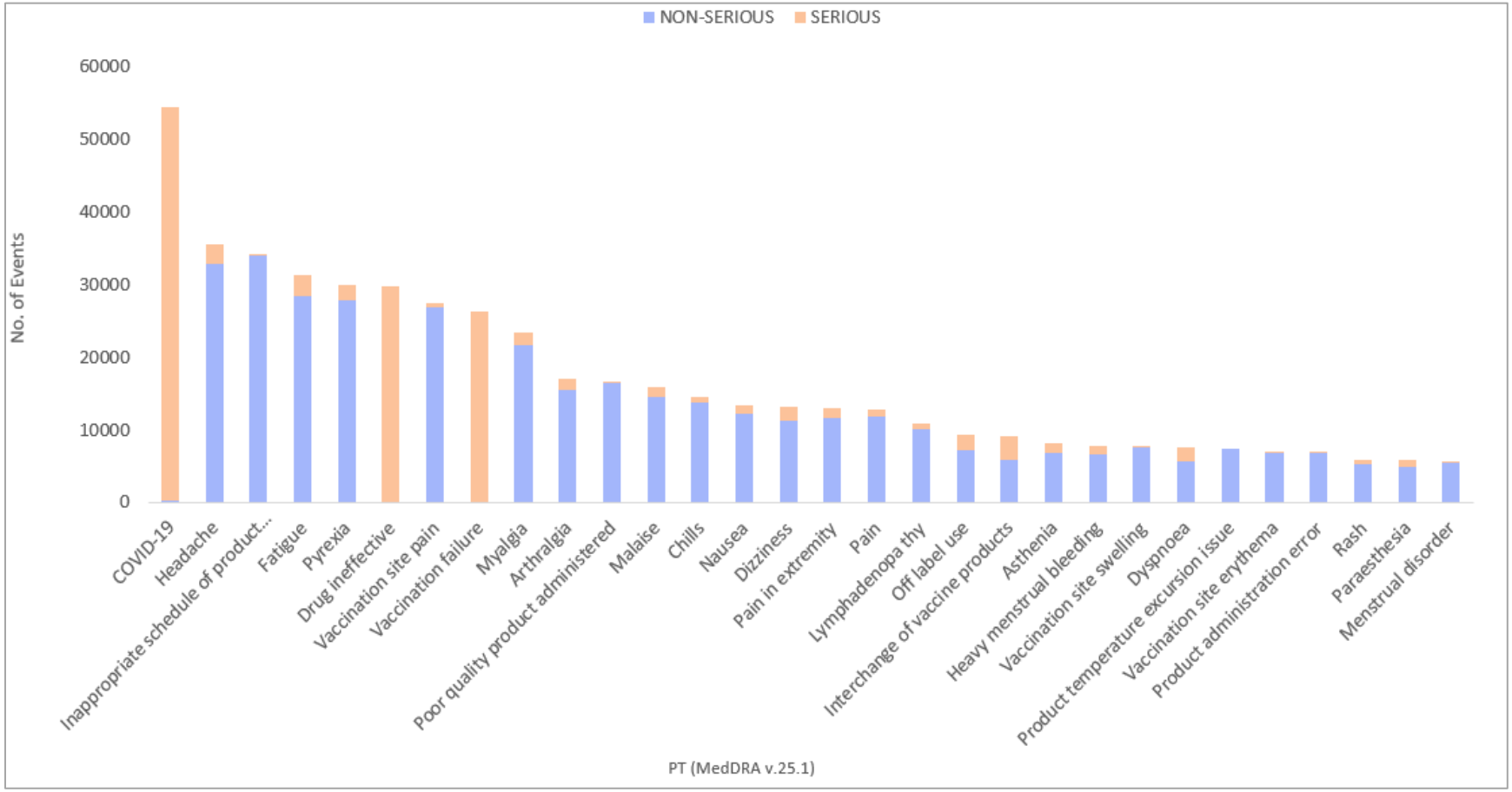
The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (261,953), Nervous system disorders (94,886), Injury, poisoning and procedural complications (84,718), Musculoskeletal and connective tissue disorders (77,153), Infections and infestations (67,444), Reproductive system and breast disorders (44,523), Gastrointestinal disorders (37,273), Skin and subcutaneous tissue disorders (29,520), Respiratory, thoracic and mediastinal disorders (23,915), Cardiac

[33] Multiple episodes of the same event were reported with different seriousness in some cases hence the sum of the event seriousness exceed the total number of events.

disorders (18,025), Blood and lymphatic system disorders (15,626), Surgical and medical procedures (13,457), Investigations (12,956), Psychiatric disorders (11,642), Vascular disorders (8252), Eye disorders (8118), Product issues (7824), and Ear and labyrinth disorders (6121).

Out of the 838,865 AEs in the PM dataset, 72.3% of them were non-serious. Figure 5 shows the seriousness of the most frequently reported PTs (≥ 2% of the cases) where most of the occurrences were non-serious with the exception of COVID-19, Drug ineffective, and Vaccination failure.

Figure 5. Post-Authorisation Data: Event Seriousness of the PTs ≥2% of Cases



Out of the 838,865 AEs in the PM dataset, 27.7% of them were serious. A review of the most frequently reported (≥ 2%) SAEs by SOC and by PT during the interval period as compared to the cumulative period through 18 December 2022 is provided in Table 30.

Table 30. Post-Authorisation Data: Serious Events Reported in ≥2% Cases

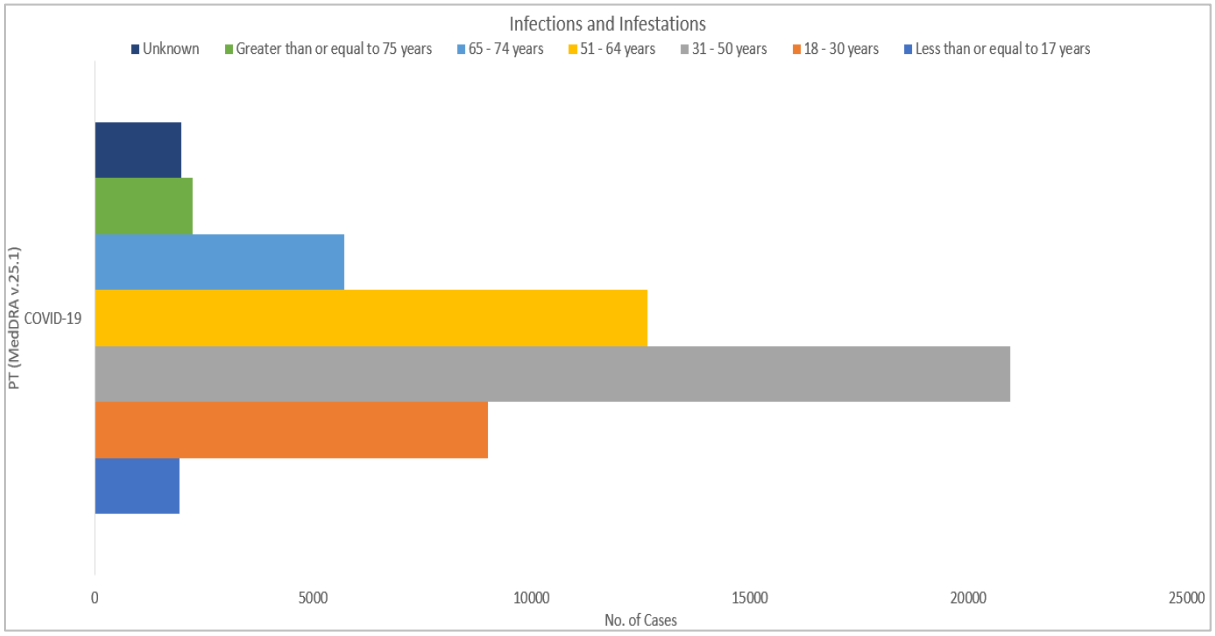
	Reporting Period 19 Jun 2022 - 18 Dec 2022				**Cumulatively through 18 Dec 2022**			
MedDRA SOC MedDRA PT	**All Cases (N=282,992) AEs (n=838,865)**	**BNT162b2 (N=271,848) AEs (n=800,366)**	**BNT162b2 + BA.1 (N=4861) AEs (n=19,777)**	**BNT162b2 + BA.4/BA.5 (N=8802) AEs (n=23,397)**	**All Cases (N=1,766,357) AEs (n=5,821,996)**	**BNT162b2 (N=1,755,205) AEs (n=5,783,481)**	**BNT162b2 + BA.1 (N=4862) AEs (n=19,779)**	**BNT162b2 + BA.4/BA.5 (N=8802) AEs (n=23,397)**
	n[a] (AERP, %[b])	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**	**n (AERP, %)**
Infections and infestations								
COVID-19[c]	54,254 (19.2%)	53,835 (19.8%)	93 (1.9%)	672 (7.6%)	127,053 (7.2%)	126,635 (7.2%)	94 (1.9%)	672 (7.6%)
General disorders and administration site conditions								
Drug ineffective[d]	29,812 (10.5%)	29,355 (10.8%)	109 (2.2%)	592 (6.7%)	71,005 (4.0%)	70,548 (4.0%)	109 (2.2%)	592 (6.7%)
Vaccination failure[e]	26,299 (9.3%)	26,295 (9.7%)	10 (0.2%)	148 (1.7%)	64,503 (3.7%)	64,499 (3.7%)	11 (0.2%)	148 (1.7%)

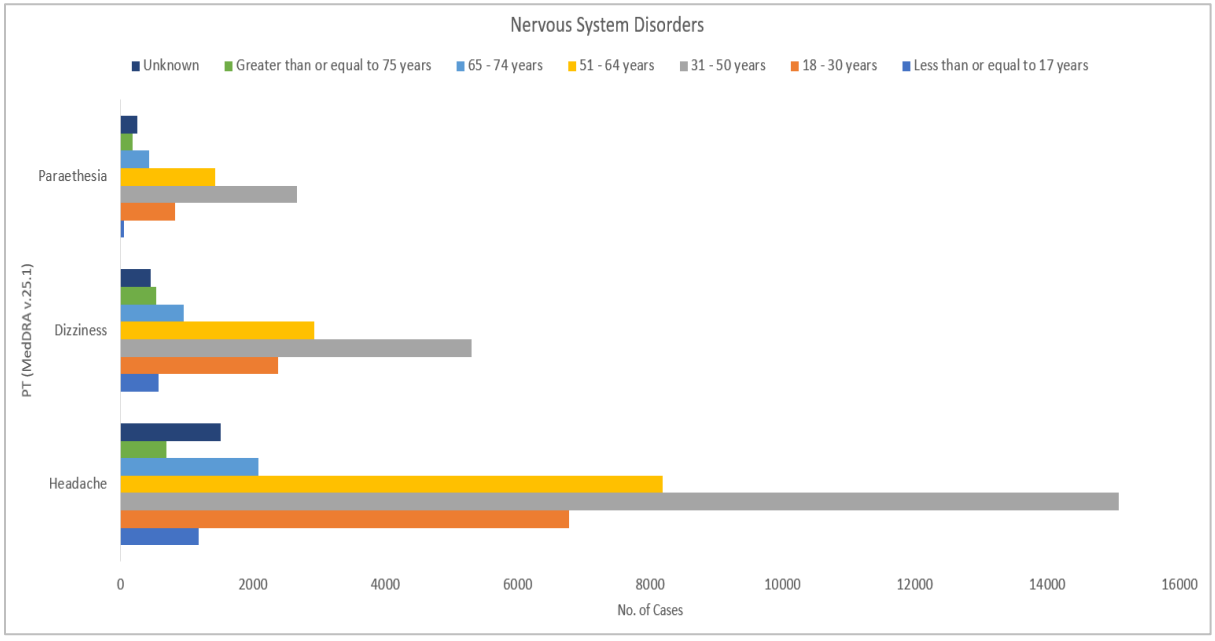
a. Reporting proportion calculated as n/N (% of all incremental cases, incremental serious cases and all cumulative cases).
b. The sum of percentages may not exactly match 100% due to rounding in calculations.
c. Listed per case processing conventions, except for fatal cases.
d. Drug ineffective represents efficacy-related conditions.
e. Listed per case processing conventions.

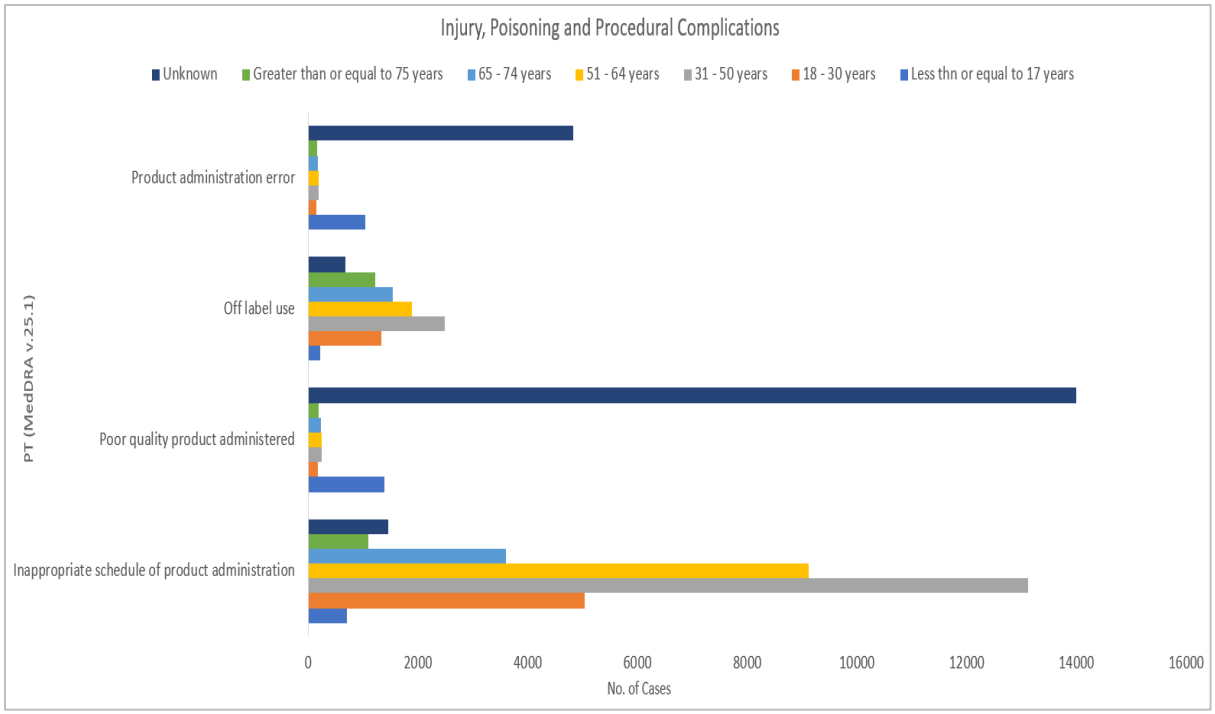
N = Number of cases; n = Number of events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; PT = Preferred Term; AE = Adverse Event; AERP = Adverse Event Reporting Proportion

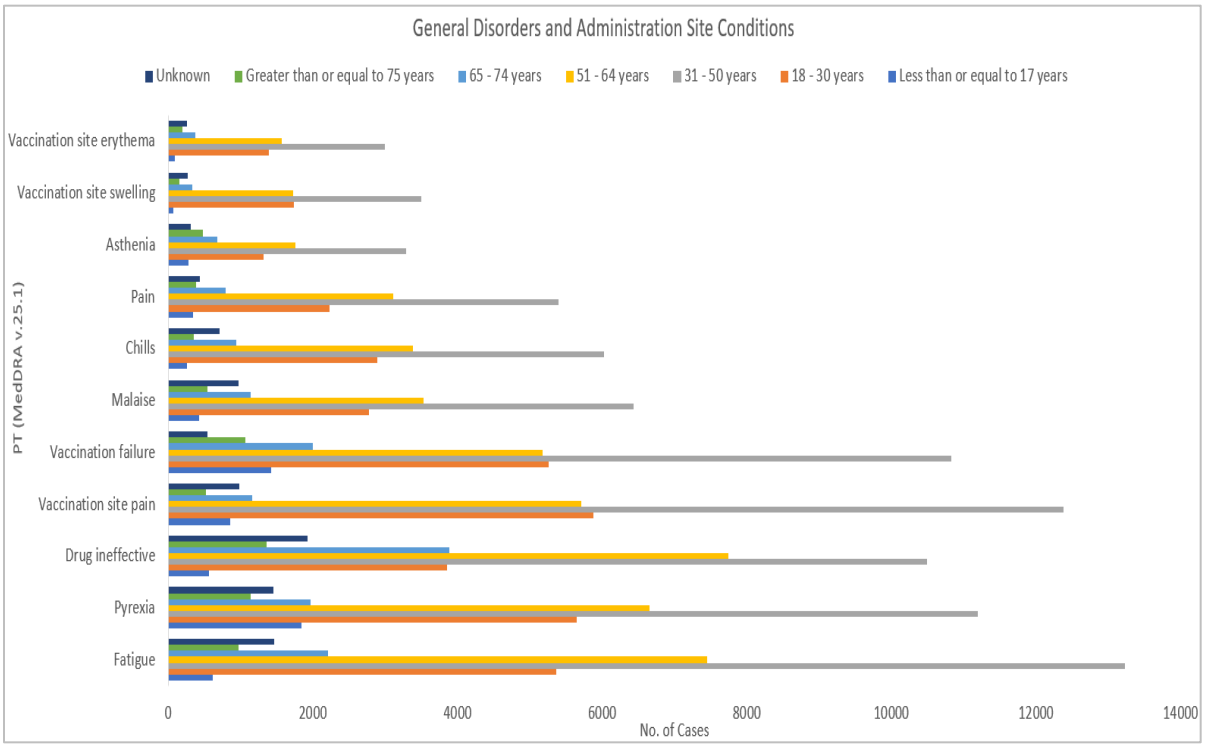
Figure 6 provides information about the age breakdown in the clinical AEs reported in more than 2% of the cases by SOC in the overall PM dataset; the age group 31-50 years is the one reporting higher proportion of events than other age groups except for PTs Product administration error, Poor quality product administered, and Product temperature excursion issue, with which subject' ages are mostly unknown. This is consistent being the largest group in terms of number of cases.

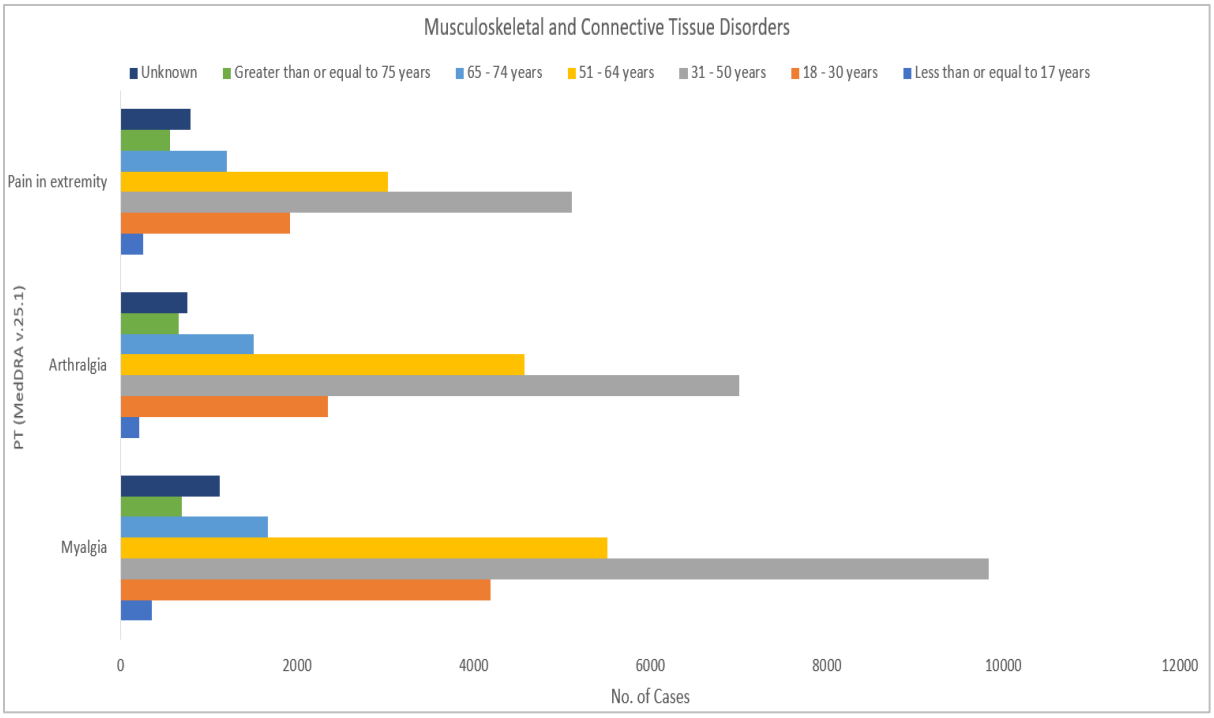
Figure 6. Clinical AEs Reported in More Than 2% of the Cases by SOC and Age Group

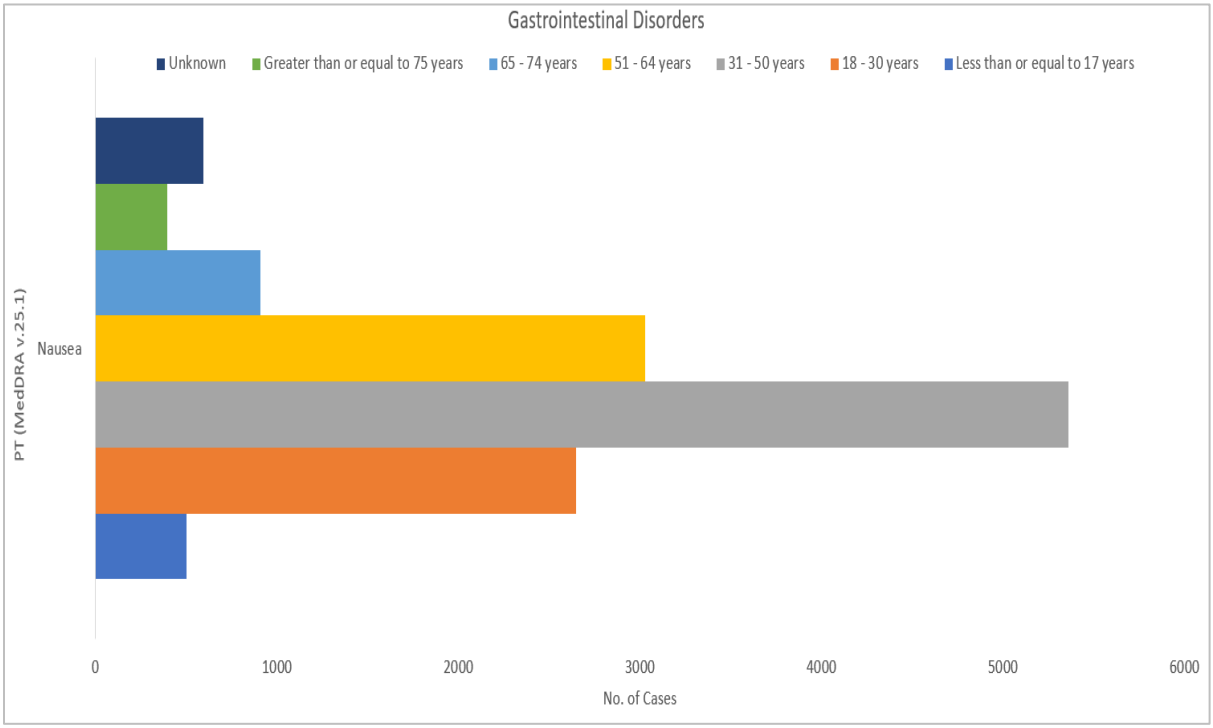


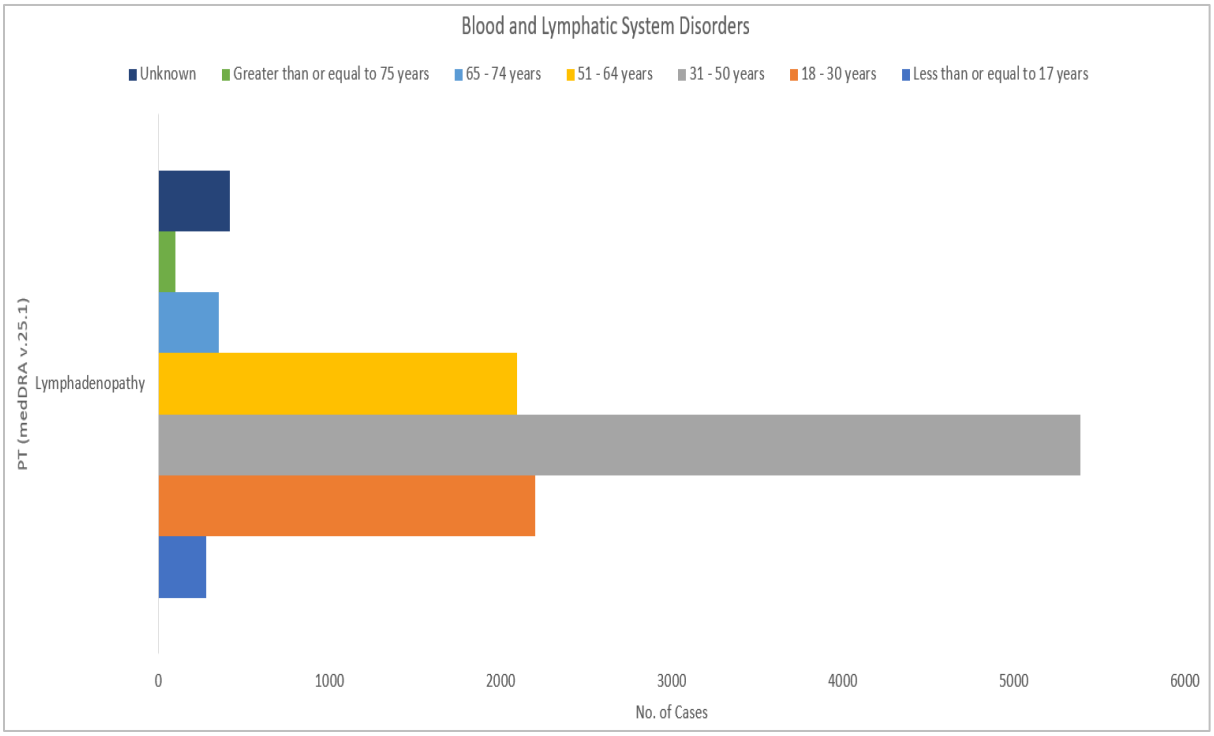


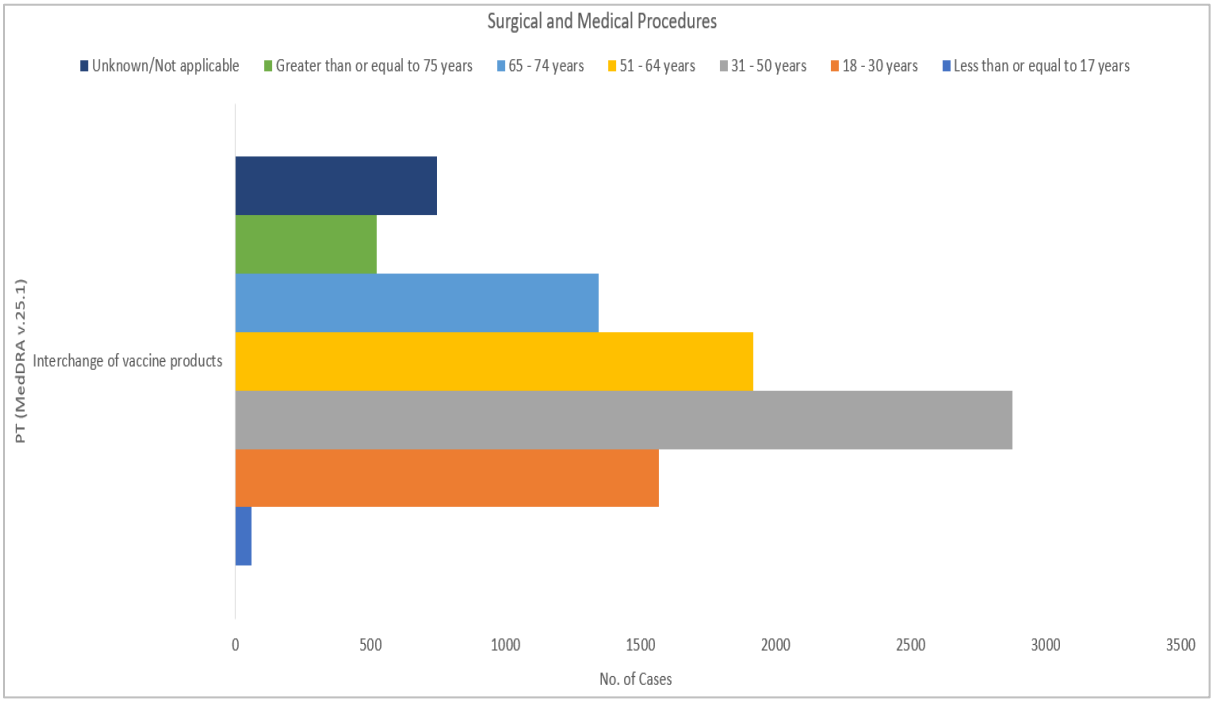

Injury, Poisoning and Procedural Complications
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less thn or equal to 17 years
Product administration error
Off label use
Poor quality product administered
Inappropriate schedule of product administration
PT (MedDRA v.25.1)
0
2000
4000
6000
8000
10000
12000
14000
16000
No. of Cases

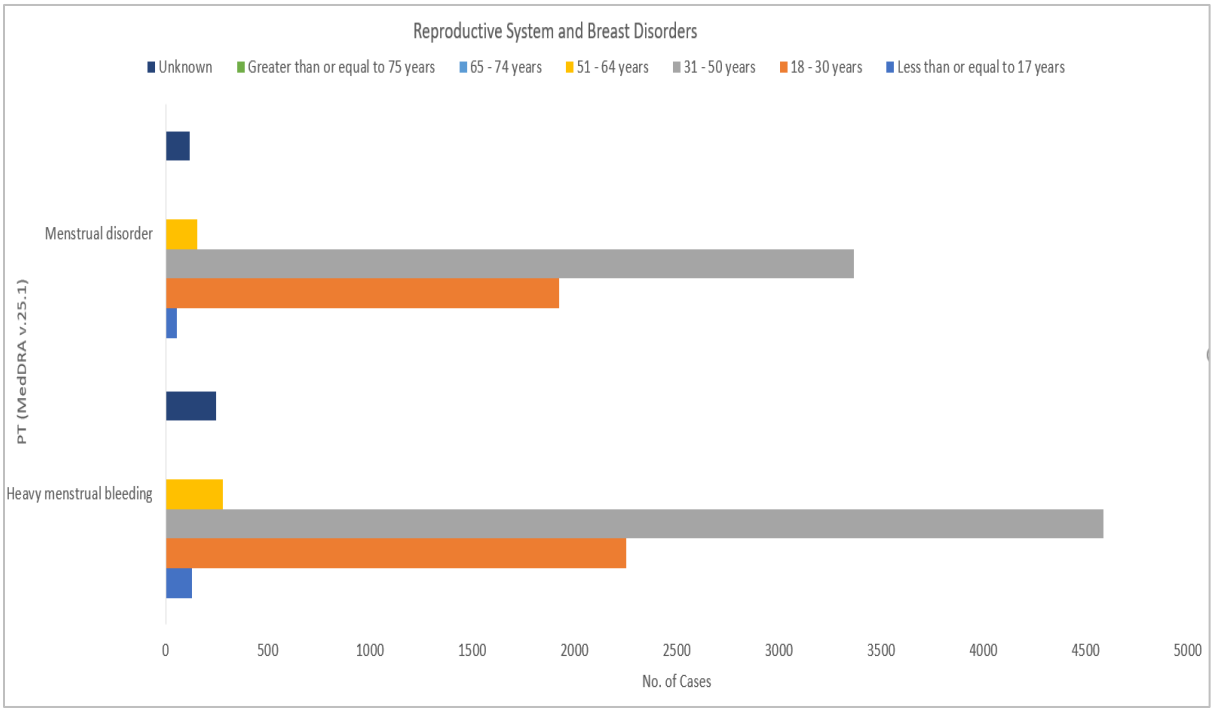

General Disorders and Administration Site Conditions
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
Vaccination site erythema
Vaccination site swelling
Asthenia
Pain
Chills
Malaise
Vaccination failure
Vaccination site pain
Drug ineffective
Pyrexia
Fatigue
PT (MedDRA v.25.1)
0
2000
4000
6000
8000
10000
12000
14000
No. of Cases

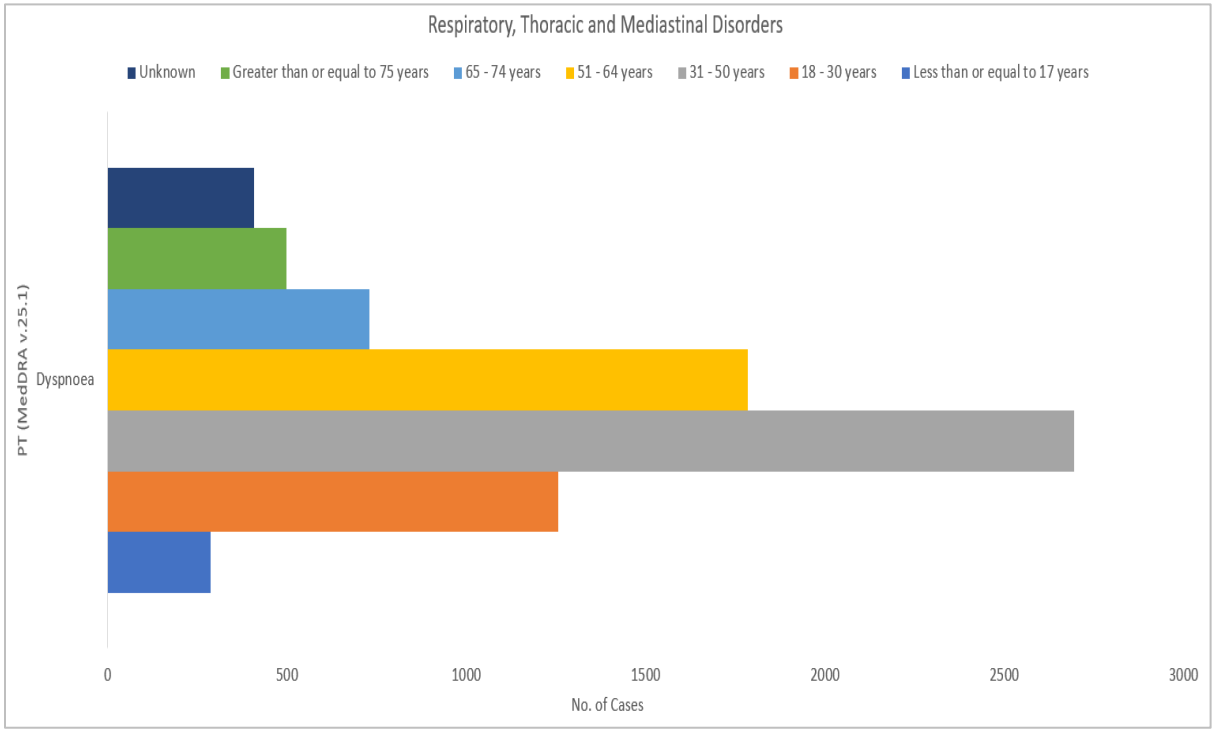

Musculoskeletal and Connective Tissue Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
Pain in extremity
Arthralgia
Myalgia
PT (MedDRA v.25.1)
0
2000
4000
6000
8000
10000
12000
No. of Cases

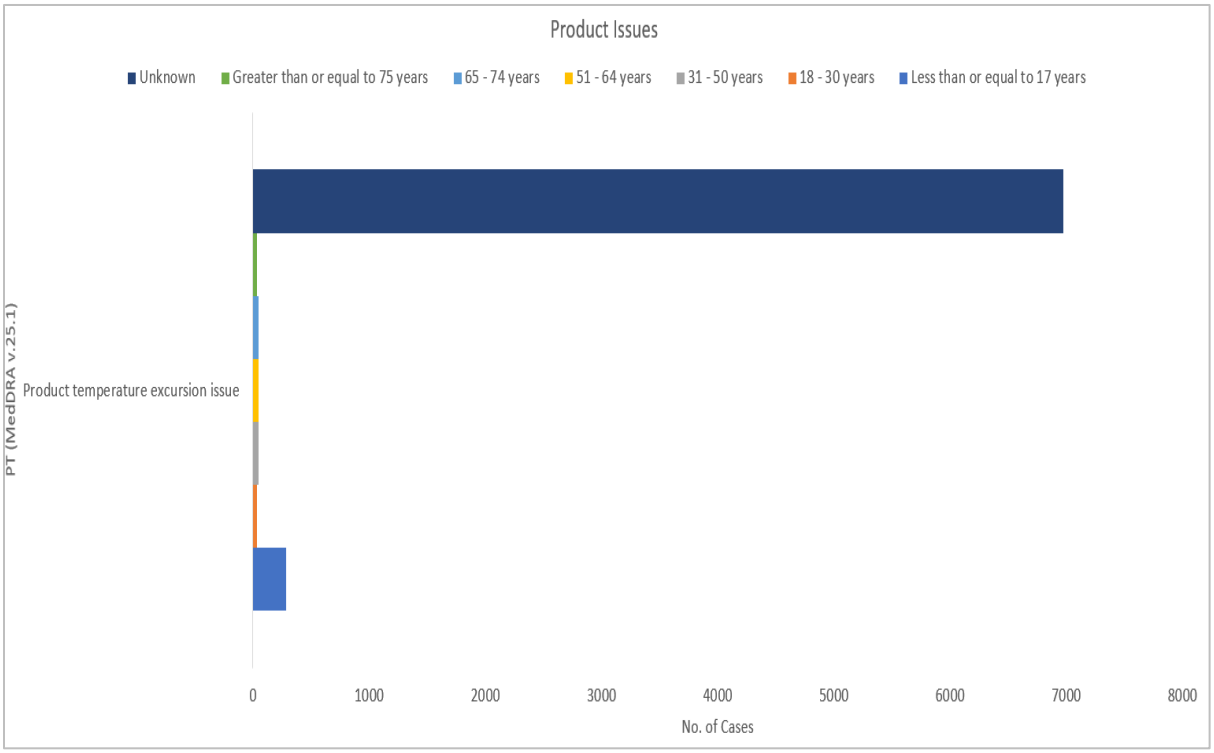

Gastrointestinal Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
Nausea
PT (MedDRA v.25.1)
0
1000
2000
3000
4000
5000
6000
No. of Cases

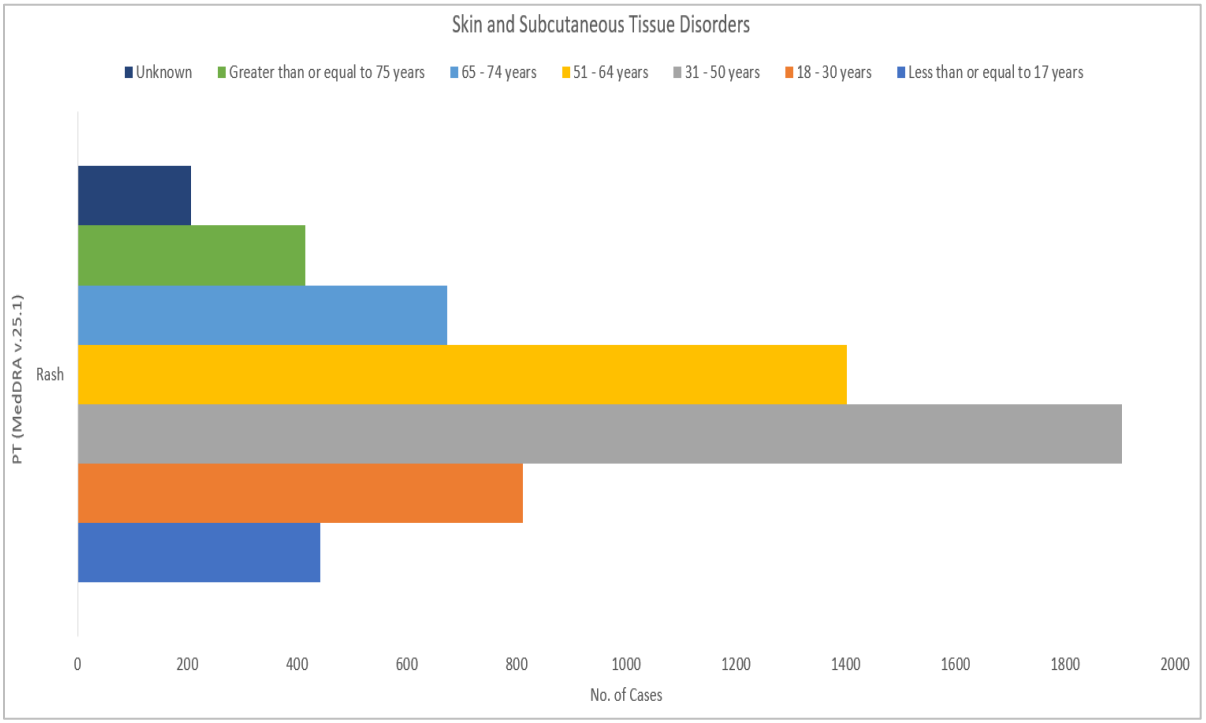

Blood and Lymphatic System Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (medDRA v.25.1)
Lymphadenopathy
0
1000
2000
3000
4000
5000
6000
No. of Cases


Surgical and Medical Procedures
Unknown/Not applicable
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (MedDRA v.25.1)
Interchange of vaccine products
0
500
1000
1500
2000
2500
3000
3500
No. of Cases


Reproductive System and Breast Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (MedDRA v.25.1)
Menstrual disorder
Heavy menstrual bleeding
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
No. of Cases


Respiratory, Thoracic and Mediastinal Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (MedDRA v.25.1)
Dyspnoea
0
500
1000
1500
2000
2500
3000
No. of Cases


Product Issues
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (MedDRA v.25.1)
Product temperature excursion issue
0
1000
2000
3000
4000
5000
6000
7000
8000
No. of Cases


Skin and Subcutaneous Tissue Disorders
Unknown
Greater than or equal to 75 years
65 - 74 years
51 - 64 years
31 - 50 years
18 - 30 years
Less than or equal to 17 years
PT (MedDRA v.25.1)
Rash
0
200
400
600
800
1000
1200
1400
1600
1800
2000
No. of Cases

Conclusion

Overall, during the reporting period, the serious cases represented 33.7% of the total PM; fatal outcomes occurred in less than 0.5% of the cases. About two-thirds of the cases occurred in female subjects. In both primary series and boosters dataset, the percentage of SAEs reported in females was higher than in males through the majority of age groups. The most frequently SAEs reporting age groups were 31-50 years in primary series (original) and boosters (original), 51-64 years in boosters (bivalent BA.1), and ≥ 75 years in boosters (bivalent BA.4/BA.5). The majority of the most frequently (≥ 2%) reported AEs (listed in the current RSI) are non-serious.

Based on the review of the PM cases, no new safety issues were identified.

6.3.1.3.1. Primary Series BNT162b2 Original

Demographic information of all original BNT162b2 primary series cases[34] received during the reporting interval is shown in Table 31.

Table 31. Demographic Information – BNT162b2 Original Primary Series Cases Received during the Reporting Interval

Characteristics		PM No. of Cases (%[a]) N=219283
MC	Yes	119918 (54.7%)
	No	99365 (45.3%)
Country/region of incidence (≥2% of all cases)	Austria	57691 (26.3%)
	Sweden	31416 (14.3%)
	Germany	16939 (7.7%)
	France	12405 (5.7%)
	Portugal	11837 (5.4%)
	US	11304 (5.2%)
	Norway	9367 (4.3%)
	Denmark	9032 (4.1%)
	Japan	8397 (3.8%)
	Poland	6562 (3.0%)
	Belgium	5775 (2.6%)
	Finland	5303 (2.4%)
	Other countries	33255 (15.2%)
Gender	Female	133484 (60.9%)
	Male	64550 (29.4%)
	Unknown/No Data	21249 (9.7%)
Age (years)	N	196280
	Min-Max	0-105
	Mean	43.3
	Median	43.0
Age Range	≤ 17 years	11156 (5.1%) [11022][c]

[34] Including cases where the events occurred after dose 1 or dose 2 or dose Unknown if the Age in Years>4 and after dose 3 in the 6 months through less than 5 years of age group.

Table 31. Demographic Information – BNT162b2 Original Primary Series Cases Received during the Reporting Interval

Characteristics		PM No. of Cases (%[a]) N=219283
	0 to 27 days	41 (0.0%) [6][c]
	28 days to 23 months	222 (0.1%) [134][c]
	2-11 years	4763 (2.2%) [4752][c]
	12-17 years	6130 (2.8%)
	18-30 years	36924 (16.8%)
	31-50 years	83174 (37.9%)
	51-64 years	44178 (20.1%)
	65-74 years	15530 (7.1%)
	≥ 75 years	6942 (3.2%)
	Unknown	21349 (9.7%)
	N/A[b]	30 (0.0%)
Case Seriousness	Serious	69156 (31.5%)
	Non-serious	150127 (68.5%)
Case Outcome	Fatal	705 (0.3%)
	Not recovered	49089 (22.4%)
	Recovered/Recovering	56487 (25.7%)
	Recovered with sequelae	3175 (1.4%)
	Unknown	109827 (50.1%)
Presence of comorbidities[d]	Yes	14800 (6.7%)
	No	204483 (93.3%)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Foetus cases-Age range only applies to post-birth subjects.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (foetus/neonates) exposed before or during the mother' pregnancy or babies exposed through breastfeeding. Number of cases reported in this table may not match with number of cases evaluated in individual sections due to case by case review that is not possible to implement in the overall dataset.
d. Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, described as special populations in Section 16.3.5.4 and Section 16.3.5.5, respectively, and the Frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis), described as missing information in Section 16.4.2.

6.3.1.3.2. Booster Doses

Reference is made to the response to the Canadian Clinical Clarification Request dated 12 September 2022, where the following request for the pharmacovigilance activities was made:

The sponsor is requested to confirm that the information in these reports (Safety Summary Reports and PSUR) will be stratified by vaccine.

Response

Demographic information and summary of the most commonly reported PTs in bivalent vaccines cases is provided in Section 6.3.1.3.2.2. *Bivalent BNT162b2 Booster Doses*. Appendix 2.2.1. through Appendix 2.2.4. are summary tabulations providing the cumulative

and incremental number of PTs reported for each bivalent vaccine type. In each safety section the number of cases occurred with bivalent vaccines is noted.

A summary of the approvals of booster doses for the different age groups and associated regulatory procedures is provided in Table 32 for the reporting period.

First booster is indeed the third dose after completing a 2-dose primary series of BNT162b2 (as a homologous booster dose), or the first booster following completion of primary vaccination with another authorised COVID-19 vaccine (as a heterologous booster dose).

Second booster is indeed the fourth dose after completing a 2-dose primary series and the first booster dose with BNT162b2 (as a homologous booster dose) or the second booster dose following completion of primary vaccination and a first booster dose with any authorised COVID-19 vaccine (as a heterologous booster dose).

Table 32. Summary of Approval of Booster Doses in the Reporting Period

	Age Group	Procedure and Description	Approval Date
EU			
First booster	**16+ years**	**EMEA/H/C/005735/II/0139** PI update regarding individuals 16+ years based on six-month post (booster) dose 3 data from clinical studies C4591001 and C4591031 data.	Procedure ongoing pending approval.
	5 to < 12 years	**EMEA/H/C/005735/II/0129** PI update- one month post dose (booster) dose 3 (1MPD3) based on clinical study C4591007 data.	CHMP opinion: 15 September 2022 EC decision: 16 September 2022
		EMEA/H/C/005735/II/0160 PI update- six month post dose (booster) dose 2 (6MPD2) based on clinical study C4591007 data.	Procedure ongoing pending approval.
Second booster	**12+ years**	**EMEA/H/C/005735/II/0140** Bivalent Original/Omicron BA.1* as from 12+ years - Rolling submission.	CHMP Opinion: 01 September 2022 EC decision: 01 September 2022.
		EMEA/H/C/005735/II/0143 Bivalent Original/Omicron BA.4-5* as from 12+ years - Rolling submission.	CHMP Opinion: 12 September 2022 EC decision: 12 September 2022.
		EMEA/H/C/005735/II/0145 • C4591031 substudy D, 640 subjects aged 18-55 years. • C4591031 substudy E, 1841 subjects aged 55 years of age or older. However, PI was extrapolated to include 12+ years.	CHMP Opinion: 27 October 2022 EC decision: 28 October 2022.
	5 to < 12 years	**EMEA/H/C/005735/X/0147**	CHMP Opinion: 10 November 2022

Table 32. Summary of Approval of Booster Doses in the Reporting Period

	Age Group	Procedure and Description	Approval Date
		Bivalent Original/Omicron BA.4-5* as from 5 to < 12 years.	EC decision: 10 November 2022.
US			
First booster	**6 months to 4 years**	The US FDA authorised the Pfizer-BioNTech COVID-19 bivalent vaccine (Original and Omicron BA.4/BA.5) as a third primary series dose administered at least 8 weeks after a second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine as part of the 3-dose primary series for this age group.	08 December 2022
Second booster	**12+ years**	The US FDA issued an EUA to approve the use of a booster dose of the Pfizer-BioNTech COVID-19 bivalent vaccine, (Original and Omicron BA.4/BA.5) in individuals 12 years and older after either completion of primary vaccination with any FDA approved or authorised monovalent COVID-19 vaccine or receipt of the most recent booster dose with any FDA authorised or approved monovalent COVID-19 vaccine.**	31 August 2022
	5 to < 12 years	The US FDA authorised the Pfizer-BioNTech COVID-19 bivalent vaccine (Original and Omicron BA.4/BA.5) in individuals 5 through 11 years of age as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorised or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorised or approved monovalent COVID-19 vaccine.**	12 October 2022

*: The Bivalent vaccines (Original/Omicron BA.1 and Original/Omicron BA.4-5) are for use in individuals, who have previously received at least a primary vaccination course against COVID-19.
**: On 08 December 2022, because the authorised primary series for individuals 6 months through 4 years of age no longer consisted of only monovalent Pfizer-BioNTech COVID-19 Vaccine doses, FDA revised the scope of authorisation for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use in individuals 5 through 11 years of age and individuals 12 years of age and older so that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent can be administered as a booster dose regardless of whether primary vaccination was completed with a monovalent COVID-19 vaccine.

Search criteria: Dose number equal or greater than 3 or Dose Description containing the term "BOOSTER" or LLT equal to BOOSTER, unless the subject age is between 6 months and 4 years of age.

The search yielded 63,933 cases (224 CT cases and 63,709 PM cases). The details for CT cases are tabulated in Table 21.

Upon review of 63,709 PM cases,

- 90 cases involving foetus/babies were excluded due to indirect exposure (transplacental/ transmammary) to BNT162b2 original or bivalent booster.

– 1317 cases were determined to be non-contributory and were not included in the discussion since in these cases the booster dose administered was not BNT162b2 (1224 cases) or the case did not contain any information that the individual received a booster dose (93 cases).

Among the relevant 62,302 PM cases, 51,109 cases involved original BNT162b2 booster doses and 11,193 cases involved bivalent BNT162b2 booster doses (Omi bivalent BA.1 [4363 cases] and Omi bivalent BA.4/BA.5 [6830 cases]).

Majority of the frequently (≥2%) reported events in the BNT162b2 (original) booster/ Bivalent BNT162b2 + Omi bivalent BA.1 booster/ Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 dataset are largely reflective of reactogenicity and events associated with the immunisation process. Among the frequently (≥2%) reported events, the following clinical AEs were commonly seen in all 3 types of booster [BNT162b2 (original) booster/ Bivalent BNT162b2 + Omi bivalent BA.1 booster/ Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5]: PTs Arthralgia, Chills, COVID-19, Dizziness, Drug ineffective, Dyspnoea, Headache, Fatigue, Pyrexia, Malaise, Myalgia, Nausea, Lymphadenopathy, Pain, Pain in extremity, Vaccination site pain (except COVID-19 and Drug ineffective, all other events are listed or consistent with the listed events as per the RSI; COVID-19 and Drug ineffective are listed events as per case processing conventions, except fatal cases).

It was noted that a large proportion of the cases (1943 of 4363 cases [44.5% of the dataset]) reporting the administration of the bivalent BNT162b2 + Omi bivalent BA.1 booster vaccine originated from the Netherlands. The reason of this increase appears to be due to a large vaccination campaign carried out in the Netherlands administering bivalent BNT162b2 + Omi bivalent BA.1 booster vaccine that was still in place as of 15 December 2022. This has resulted in an increase of AE reports over a short time period, impacting the proportion of overall reported events following the administration of the BNT162b2 bivalent + Omi bivalent BA.1 booster vaccine.

Upon review the most reported AEs are indicative of reactogenicity events (e.g., PTs Vaccination site lymphadenopathy, Vaccination site inflammation, Vaccination site swelling, Vaccination site warmth, Vaccination site erythema, and Vaccination site reaction) and most of the events were non-serious.

No significant difference was observed in the safety profile of original vs bivalent vaccines.

6.3.1.3.2.1. Original BNT162b2 Booster Doses

Demographic information of all original BNT162b2 booster cases[30] received during the reporting interval are shown in Table 33.

Table 33. Demographic Information – BNT162b2 (All Original) Booster Cases

Characteristics		PM No. of Cases (%[a]) N=51,109
MC	Yes	18,615 (36.4)
	No	32,494 (63.6)

Table 33. Demographic Information – BNT162b2 (All Original) Booster Cases

Characteristics		PM No. of Cases (%[a]) N=51,109
Country/region of incidence (≥2% of all cases)	Germany	8628 (16.9)
	US	6882 (13.5)
	France	6002 (11.7)
	Sweden	3966 (7.8)
	Austria	3426 (6.7)
	Japan	2788 (5.5)
	Norway	2292 (4.5)
	Denmark	2238 (4.4)
	UK	2205 (4.3)
	Netherlands	1534 (3.0)
	Philippines	1485 (2.9)
	New Zealand	1381 (2.7)
	Spain	1015 (2.0)
	Other countries	7267 (14.2)
Gender	Female	31,818 (62.3)
	Male	14,926 (29.2)
	Unknown/No Data	4365 (8.5)
Age (Years)	N	44,645
	Min-Max	0.8-103
	Mean	49.8
	Median	50.0
Age Range	≤17 years	1214 (2.4)
	18-30 years	7447 (14.6)
	31-50 years	14,471 (28.3)
	51-64 years	10,444 (20.4)
	65-74 years	7147 (14.0)
	≥75 years	4587 (9.0)
	Unknown	5799 (11.3)
Case Seriousness	Serious	22,594 (44.2)
	Non-serious	28,515 (55.8)
Case Outcome	Fatal	413 (0.8)
	Not recovered	17,805 (34.8)
	Recovered/Recovering	14,081 (27.6)
	Recovered with sequelae	1318 (2.6)
	Unknown	17,492 (34.2)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.

Demographic information of all original BNT162b2 booster cases by age group received during the reporting interval is shown in Table 34.

Table 34. Demographic Information – All Original BNT162b2 Booster Cases by Age Group

Age group		6 months -4 years No. of Cases (%[a]) N=20	5-11 years No. of Cases (%[a]) N=440	12 years and older No. of Cases (%[a]) N=46,032	Unknown No. of Cases (%[a]) N=4617
Characteristics					
MC	Yes	16 (80.0)	351 (79.8)	15,347 (33.3)	2901 (62.8)
	No	4 (20.0)	89 (20.2)	30,685 (66.7)	1716 (37.2)
Country/region of incidence (≥2% in at least 1 of the age groups)	Germany	2 (10.0)	6 (1.4)	8230 (17.9)	390 (8.4)
	France	0 (0)	0 (0)	5963 (13.0)	39 (0.8)
	US	17 (85.0)	310 (70.5)	5272 (11.5)	1283 (27.8)
	Sweden	0 (0)	0 (0)	3953 (8.6)	13 (0.3)
	Austria	1 (5.0)	4 (0.9)	3406 (7.4)	15 (0.3)
	Norway	0 (0)	0 (0)	2282 (5.0)	10 (0.2)
	Denmark	0 (0)	0 (0)	2224 (4.8)	14 (0.3)
	Japan	0 (0)	55 (12.5)	2070 (4.5)	663 (14.4)
	UK	0 (0)	2 (0.5)	2019 (4.4)	184 (4.0)
	Netherlands	0 (0)	1 (0.2)	1523 (3.3)	10 (0.2)
	Philippines	0 (0)	5 (1.1)	1466 (3.2)	14 (0.3)
	Spain	0 (0)	0 (0)	1004 (2.2)	11 (0.2)
	Canada	0 (0)	27 (6.1)	443 (1.0)	94 (2.0)
	Brazil	0 (0)	0 (0)	129 (0.3)	96 (2.1)
	New Zealand	0 (0)	0 (0)	110 (0.2)	1271 (27.5)
	Puerto Rico	0 (0)	21 (4.8)	24 (0.1)	23 (0.5)
	Other countries	0 (0)	9 (2.0)	5914 (12.8)	487 (10.5)
Gender	Female	10 (50.0)	161 (36.6)	30,599 (66.5)	1048 (22.7)
	Male	7 (35.0)	165 (37.5)	14,161 (30.8)	593 (12.8)
	Unknown/No Data	3 (15.0)	114 (25.9)	1272 (2.8)	2976 (64.4)
Age (years)	N	20	366	44,259	N/A
	Min-Max	0.8-4	5-11	12-103	N/A
	Mean	2.9	8.3	50.1	N/A
	Median	3.0	8.0	50.0	N/A
Case Seriousness	Serious	0 (0)	29 (6.6)	21,374 (46.4)	1191 (25.8)
	Non-serious	20 (100.0)	411 (93.4)	24,658 (53.6)	3426 (74.2)
Case Outcome	Fatal	0 (0)	2 (0.5)	397 (0.9)	14 (0.3)
	Not recovered	0 (0)	13 (3.0)	17,419 (37.8)	373 (8.1)
	Recovered/Recovering	1 (5.0)	41 (9.3)	13,684 (29.7)	355 (7.7)
	Recovered with sequelae	0 (0)	0 (0)	1307 (2.8)	11 (0.2)
	Unknown	19 (95.0)	384 (87.3)	13,225 (28.7)	3864 (83.7)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.

The most frequently (≥2%) reported events in this subset of individuals is detailed in Table 35.

Table 35. BNT162b2 (All Original) Booster Cases – Most frequently (≥2%) reported PTs

PTs	Total Number of Events (AERP%)
COVID-19[a]	10,577 (20.7)
Drug ineffective[a]	6735 (13.2)
Headache[b]	5434 (10.6)
Off label use[c]	5289 (10.3)
Fatigue[b]	5120 (10.0)
Pyrexia[b]	5072 (9.9)
Vaccination failure[a]	4612 (9.0)
Interchange of vaccine products[d]	4302 (8.4)
Myalgia[b]	3755 (7.3)
Lymphadenopathy[b]	3616 (7.1)
Immunisation[e]	3579 (7.0)
Vaccination site pain[b]	3233 (6.3)
Arthralgia[b]	2872 (5.6)
Malaise[b]	2816 (5.5)
Dizziness[b]	2517 (4.9)
Pain in extremity[b]	2357 (4.6)
Chills[b]	2341 (4.6)
Poor quality product administered[c]	2243 (4.4)
Nausea[b]	2027 (4.0)
Pain[b]	1816 (3.6)
Dyspnoea[b]	1736 (3.4)
Asthenia[b]	1548 (3.0)
Product temperature excursion issue[c]	1414 (2.8)
Rash[b]	1359 (2.7)
Wrong product administered[c]	1310 (2.6)
Paraesthesia[f]	1213 (2.4)
Heavy menstrual bleeding[g]	1209 (2.4)

a. Listed as per case processing conventions, except for fatal cases.
b. Listed or consistent with listed AEs in the current RSI.
c. Listed per case processing conventions, except when associated with unlisted AEs.
d. PT coded per case processing conventions to identify cases reporting use of vaccines from different MAHs.
e. PT coded per case processing conventions to identify cases reporting a booster dose when administered off-label as per the local label.
f. Paraesthesia / Hypoesthesia were included as ADRs in the EU-SmPC Section 4.8 as per PRAC recommendation (Procedure number EMEA/H/C/005735/II/0080).
g. Unlisted in the current RSI

6.3.1.3.2.2. Bivalent BNT162b2 Booster Doses

Demographic information of all BNT162b2 bivalent booster cases[30] received during the reporting interval is shown in Table 36.

Table 36. Demographic Information – BNT162b2 (All Bivalent Vaccines) All Booster Cases

Characteristics		PM No. of Cases (%[a]) N=11,193
MC	Yes	4789 (42.8)
	No	6404 (57.2)
Country/region of incidence (≥2% of all cases)	US	3651 (32.6)
	Netherlands	1952 (17.4)
	Japan	1657 (14.8)
	Germany	1126 (10.1)
	UK	486 (4.3)
	Belgium	435 (3.9)
	Spain	420 (3.8)
	France	311 (2.8)
	Other countries	1155 (10.3)
Gender	Female	6366 (56.9)
	Male	2926 (26.1)
	Unknown/No Data	1901 (17.0)
Age (Years)	N	7698
	Min-Max	1.2-111
	Mean	53.7
	Median	55.0
Age Range	≤ 17 years	353 (3.2)
	18-30 years	697 (6.2)
	31-50 years	2183 (19.5)
	51-64 years	1971 (17.6)
	65-74 years	1480 (13.2)
	≥ 75 years	1203 (10.7)
	Unknown	3306 (29.5)
Case Seriousness	Serious	2803 (25.0)
	Non-serious	8390 (75.0)
Case Outcome	Fatal	128 (1.1)
	Not recovered	3148 (28.1)
	Recovered/Recovering	3426 (30.6)
	Recovered with sequelae	73 (0.7)
	Unknown	4418 (39.5)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.

Demographic information of all Bivalent BNT162b2 + Omi Bivalent BA.1 booster cases received by age group during the reporting interval is shown in Table 37.

Table 37. Demographic Information – Bivalent BNT162b2 + Omi Bivalent BA.1 Cases by Age Group

Characteristics		Age Groups			
		6 months -4 years No. of Cases (%[a]) N=1	5-11 years No. of Cases (%[a]) N=4	12 years and older No. of Cases (%[a]) N=3946	Unknown No. of Cases (%[a]) N=412
MC	Yes	0 (0)	3 (75.0)	825 (20.9)	180 (43.7)
	No	1 (100.0)	1 (25.0)	3121 (79.1)	232 (56.3)
Country/region of incidence (≥2% in at least 1 of the age groups)	Netherlands	0 (0)	0 (0)	1940 (49.2)	3 (0.7)
	Japan	0 (0)	3 (75.0)	501 (12.7)	185 (44.9)
	UK	0 (0)	0 (0)	369 (9.4)	115 (27.9)
	Belgium	0 (0)	0 (0)	350 (8.9)	23 (5.6)
	Germany	0 (0)	0 (0)	218 (5.5)	42 (10.2)
	Sweden	0 (0)	0 (0)	118 (3.0)	2 (0.5)
	France	0 (0)	0 (0)	78 (2.0)	3 (0.7)
	Switzerland	1 (100.0)	0 (0)	27 (0.7)	0 (0)
	Ireland	0 (0)	1 (25.0)	30 (0.8)	3 (0.7)
	Other countries	0 (0)	0 (0)	315 (8.0)	36 (8.7)
Gender	Female	1 (100.0)	3 (75.0)	2903 (73.6)	154 (37.4)
	Male	0 (0)	0 (0)	994 (25.2)	90 (21.8)
	Unknown/No Data	0 (0)	1 (25.0)	49 (1.2)	168 (40.8)
Age (years)	N	1	3	2976	N/A
	Min-Max	N/A	9-11	12-111	N/A
	Mean	2.0	9.7	50.3	N/A
	Median	2.0	9.0	50.0	N/A
Case Seriousness	Serious	0 (0)	0 (0)	939 (23.8)	89 (21.6)
	Non-serious	1 (100.0)	4 (100)	3007 (76.2)	323 (78.4)
Case Outcome	Fatal	0 (0)	0 (0)	33 (0.8)	1 (0.2)
	Not recovered	0 (0)	0 (0)	1877 (47.6)	46 (11.2)
	Recovered/Recovering	1 (100.0)	0 (0)	1470 (37.3)	85 (20.6)
	Recovered with sequelae	0 (0)	0 (0)	36 (0.9)	2 (0.5)
	Unknown	0 (0)	4 (100.0)	530 (13.4)	278 (67.5)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.

The most frequently (≥2%) reported events in this subset of individuals is detailed in Table 38.

Table 38. Bivalent BNT162b2 + Omi Bivalent BA.1 Booster Cases – Most frequently (≥2%) reported PTs

PTs	Total Number of Events (AERP%)
Headache[a]	1288 (29.5)
Malaise[a]	1176 (27.0)
Fatigue[a]	1101 (25.2)
Myalgia[a]	1078 (24.7)
Pyrexia[a]	962 (22.0)
Chills[a]	835 (19.1)
Vaccination site pain[a]	800 (18.3)

Table 38. Bivalent BNT162b2 + Omi Bivalent BA.1 Booster Cases – Most frequently (≥2%) reported PTs

PTs	Total Number of Events (AERP%)
Arthralgia[a]	670 (15.4)
Nausea[a]	649 (14.9)
Interchange of vaccine products[b]	631 (14.5)
Vaccination site lymphadenopathy[a]	418 (9.6)
Vaccination site inflammation[a]	270 (6.2)
Vaccination site swelling[a]	269 (6.2)
Lymphadenopathy[a]	248 (5.7)
Vaccination site warmth[a]	238 (5.5)
Off label use[c]	217 (5.0)
Pain in extremity[a]	210 (4.8)
Vaccination site erythema[a]	199 (4.6)
Dizziness[a]	172 (3.9)
Heavy menstrual bleeding[d]	163 (3.7)
Dyspnoea[a]	147 (3.4)
Immunisation[f]	127 (2.9)
Diarrhoea[a]	120 (2.8)
Body temperature increased[a]	119 (2.7)
Pain[a]	118 (2.7)
Vomiting[a]	112 (2.6)
COVID-19[e]	106 (2.4)
Drug ineffective[e]	106 (2.4)
Vaccination site reaction[a]	105 (2.4)
Intermenstrual bleeding[d]	93 (2.1)

a. Listed or consistent with the listed AEs in the current RSI.
b. PT coded per case processing conventions to identify cases reporting use of vaccines from different MAHs.
c. Listed per case processing conventions, except when associated with unlisted AEs.
d. Unlisted in the current RSI.
e. Listed per case processing conventions, except for fatal cases.
f. PT coded per case processing conventions to identify cases reporting a booster dose when administered off-label as per the local label.

Demographic information of all Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 booster cases received during the reporting interval are shown in the Table below.

Table 39. Demographic Information – Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 Cases by Age Group

Characteristics		Age Groups			
		6 months -4 years No. of Cases (%[a]) N=4	5-11 years No. of Cases (%[a]) N=165	12 years and older No. of Cases (%[a]) N=4687	Unknown No. of Cases (%[a]) N=1974
MC	Yes	4 (100.0)	129 (78.2)	2194 (46.8)	1454 (73.7)
	No	0 (0)	36 (21.8)	2493 (53.2)	520 (26.3)
Country/region of incidence	US	3 (75.0)	157 (95.2)	1834 (39.1)	1657 (83.9)
	Germany	0 (0)	1 (0.6)	781 (16.7)	84 (4.3)
	Japan	1 (25.0)	5 (3.0)	779 (16.6)	183 (9.3)

Table 39. Demographic Information – Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 Cases by Age Group

Characteristics		Age Groups			
		6 months -4 years No. of Cases (%[a]) N=4	5-11 years No. of Cases (%[a]) N=165	12 years and older No. of Cases (%[a]) N=4687	Unknown No. of Cases (%[a]) N=1974
(≥2% in at least 1 of the age groups)	Spain	0 (0)	0 (0)	404 (8.6)	0 (0)
	France	0 (0)	0 (0)	226 (4.8)	4 (0.2)
	Austria	0 (0)	0 (0)	126 (2.7)	2 (0.1)
	Italy	0 (0)	0 (0)	123 (2.6)	7 (0.4)
	Other countries	0 (0)	2 (1.2)	414 (8.8)	37 (1.9)
Gender	Female	0 (0)	74 (44.8)	2964 (63.2)	267 (13.5)
	Male	2 (50.0)	58 (35.2)	1598 (34.1)	184 (9.3)
	Unknown/No Data	2 (50.0)	33 (20.0)	125 (2.7)	1523 (77.2)
Age (years)	N	4	156	4558	N/A
	Min-Max	1.2-4	5-11	12-101	N/A
	Mean	3.3	8.3	57.6	N/A
	Median	4.0	8.0	59.5	N/A
Case Seriousness	Serious	0 (0)	2 (1.2)	1593 (34.0)	180 (9.1)
	Non-serious	4 (100.0)	163 (98.8)	3094 (66.0)	1794 (90.9)
Case Outcome	Fatal	0 (0)	0 (0)	92 (2.0)	2 (0.1)
	Not recovered	0 (0)	10 (6.1)	1161 (24.8)	54 (2.7)
	Recovered/ Recovering	0 (0)	8 (4.8)	1790 (38.2)	72 (3.6)
	Recovered with sequelae	0 (0)	0 (0)	35 (0.7)	0 (0)
	Unknown	4 (100.0)	147 (89.1)	1609 (34.3)	1846 (93.5)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.

The most frequently (≥2%) reported events in this subset of individuals is detailed in Table 40.

Table 40. Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 – Most frequently (≥2%) reported PTs

PTs	Total Number of Events (AERP%)
Poor quality product administered[a]	1564 (22.9)
Product temperature excursion issue[a]	965 (14.1)
Pyrexia[b]	828 (12.1)
COVID-19[c]	689 (10.1)
Headache[b]	660 (9.7)
Drug ineffective[c]	591 (8.7)
Product administration error[a]	579 (8.5)
Off label use[a]	547 (8.0)
Fatigue[b]	486 (7.1)
Vaccination site pain[b]	464 (6.8)
Interchange of vaccine products[d]	446 (6.5)

Table 40. Bivalent BNT162b2 + Omi Bivalent BA.4/BA.5 – Most frequently (≥2%) reported PTs

PTs	Total Number of Events (AERP%)
Product use issue[a]	442 (6.5)
Malaise[b]	403 (5.9)
Chills[b]	336 (4.9)
Pain in extremity[b]	314 (4.6)
Myalgia[b]	312 (4.6)
Pain[b]	275 (4.0)
Arthralgia[b]	262 (3.8)
Dizziness[b]	256 (3.7)
Nausea[b]	254 (3.7)
Overdose[a]	209 (3.1)
Lymphadenopathy[b]	197 (2.9)
Asthenia[b]	163 (2.4)
Dyspnoea[b]	160 (2.3)
Pruritus[b]	154 (2.3)
Product preparation error[a]	151 (2.2)
Diarrhoea[b]	149 (2.2)
Vaccination failure[c]	148 (2.2)
Vomiting[b]	138 (2.0)

a. Listed per case processing conventions, except when associated with unlisted AEs.
b. Listed or consistent with the listed AEs in the current RSI.
c. Listed per case processing conventions, except for fatal cases.
d. PT coded per case processing conventions to identify cases reporting use of vaccines from different MAHs.

6.3.1.3.3. Batch-Related issues

The most frequently reported lot numbers in PM case reports (≥3000 cases) are listed in Table 41 below.

Table 41. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases
FD6840	14556
FE6208	13982
FD4555	11490
FD1921	9556
FD0168	9195
FF0680	6982
FC0681	5671
FF3318	5621
FC2473	5384
EJ6797	4377
EY7015	4272
FA4598	4199
EY3014	3806
FE8244	3165

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium).

The AEs most frequently reported (≥ 4%) with these lot numbers included COVID-19 (38,033), Inappropriate schedule of product administration (19,898), Vaccination failure (19,651), Drug ineffective (18,420), Vaccination site pain (5534), Headache (3730), and Fatigue (3356). These AEs do not differ from those reported in the overall incremental dataset.

There were no safety issues related to quality identified during product complaint investigations.

Overall, the most frequently (> 40 occurrences) reported product issues regardless of lot number included the following PTs: Product temperature excursion issue (7464), Product label issue (115), Product expiration date issue (58), Product distribution issue (51), and Liquid product physical issue (42).

- Cases reporting the PT Product temperature excursion issue described product storage deviations.

- Cases reporting the PT Product label issue described vaccine administration after the beyond-use date and the monovalent and bivalent boxes looking similar.

- Cases reporting PT Product expiration date issue described vaccine administration after the beyond-use date.

- Cases reporting PT Product distribution issue described subjects receiving monovalent instead of bivalent vaccine.

- Cases reporting PT Liquid product physical issue described quality issues such as cloudy vial, particles present, or increased viscosity. Of the 42 cases reporting a quality issue, a product quality investigation was performed in 17 cases. In the 17 cases reporting a product quality investigation, no related quality issues were identified.

- The number of product issues did not show a trend that would require a change to the RSI. Vaccine administration and details on product storage are adequately described in the RSI. The expiry date is printed on every package. The monovalent and bivalent primary series/booster doses are adequately described on the product packaging/labelling. No quality issues were identified from the product quality investigations performed for the cases that reported PT Liquid product physical issue.

Surveillance for any potential product quality issues includes review of quarterly AE/PC reports and monthly SAE/PC reports, and review of weekly AE-batch/lot trending reports. In support to this process as needed, a review of AE data related to respective PCs may be requested to support trend analysis and notifications.

Alerts in the AE/PC reports are reviewed and closed or escalated based on clinical judgement and product knowledge. Any potential signals indicating a potential relationship between a

safety issue and a particular batch lot, and that was not already evaluated as part of other signal activities, would undergo evaluation and escalation as per standard procedures.

Conclusion

Based on the review of the cases with the most frequently reported lot numbers, no new safety issues were identified.

6.3.1.3.4. Analysis by Dose

Potential for systemic adverse reactions is analysed by dose of the vaccine in Section 16.3.3.3 *Systemic Adverse Reactions.*

6.3.1.3.5. Product Quality Analysis

The following request was made from Canada MHPD on 20 September 2022, following their review of the abbreviated SMSR #6: *Poor quality product administered was amongst the most frequently reported Preferred Terms in those who received a booster dose, and in those 5 to 11 years of age. Please provide an analysis of potential quality issues in the next PSUR, and discuss if additional risk minimization measures should be put into place.*

Response

Please refer to the content of this Section.

Search criteria – PT: Poor quality product administered.

Clinical Trial Data

- During the current reporting period and previous PSUR #3 reporting period, there were no serious cases in the CT dataset.

Post-Authorisation Data

- Number of relevant cases: 16,480 (5.8% of 282,992) cases, the total PM dataset, compared to 17,859 cases (3.5%) retrieved in the PSUR #3.
- MC cases (10,765); NMC cases (5715).
- Country/region of incidence (≥ 2%): US (7098), Japan (6205), New Zealand (1570), Canada (535), Australia (385).
- Subjects' gender: female (1040), male (815) and unknown (14,625).
- Subjects' age in years: n = 2128, range: 2 months – 102 years, mean: 32.3, median: 18.5.
- Age groups: 2m (1), 6m-4yo (109), 5yo-11yo (700), 12+ yo (1318), Unknown (14,352).
- Dose: Primary series (14,718), Booster (1822).

- Co-suspect medications (n = 63 cases): the most frequently (≥4) reported relevant co-suspect medications included influenza vaccine (37), DPT and meningococcal vaccine (8 each), HPV vaccine (6), hepatitis B vaccine, pneumococcal vaccine and varicella vaccine (4 each).

- Number of Poor quality product administered events: 16,480.

- Poor quality product administered seriousness: serious (12), non-serious (16,468).

- Poor quality product administered outcome: resolved/resolving (9), not resolved (1), unknown (16,470). There were no fatal events.

- Most frequently co-reported relevant PTs (≥2%): Product temperature excursion issue (7460) Product administration error (6699), and Product storage error (2184).

- The verbatim reported events described scenarios such as Pfizer COVID-19 Vaccine administered after the beyond-use date, Expired diluent and/ or Product storage deviation.

- Number of cases co-reporting a clinical event: 30

- Most frequent clinical co-reported events (≥ 6): Fatigue (10), Myalgia, Pain in extremity and Pyrexia (6 each)

- Number of Product quality complaints: 183.[35] Of these 183 cases, only three cases co-reported medical adverse events:

  – The first case described a [redacted] subject who received BNT162b2 on [redacted] (expiration date: 30 November 2021). The subject's relevant medical history included: Dust allergy and Hay fever. The subject's concomitant medications were not reported. More than two months after receiving the second dose, the subject experienced one-sided pelvic and back pain 1-2 times a month, which felt like pinched nerves, sore muscles or period pains. The pain became most intense at the end of March/beginning of [redacted] and continued until [redacted] The pain was treated with painkillers and yoga. On [redacted], the subject experienced COVID-19. On [redacted], after a walk, the subject had a circulatory collapse, peripheral pulmonary embolism, multiple coagulation disorders “my left leg turned blue and was in severe pain”. [redacted] underwent surgery for a thrombectomy of left common iliac vein, external iliac vein and left femoral vein with stenting of left iliac veins. During the thrombectomy, the surgeon discovered several other thromboses that were 3-4 months old and also removed them. Treatment with enoxaparin, rivaroxaban and long-term apixaban for blood clotting. Formo Aristo and tiotropium bromide for restricted lung functioning (diagnosed with chronic obstructive

[35] These cases described scenarios such as cloudiness of vaccine, crack/stain of vial, crystallization of product, viscosity of product.

pulmonary disease). The events of myalgia, thrombosis, pelvic pain, pain in extremity, were considered resolved. The events of respiratory distress, dyspnoea, back pain, pneumonitis, pulmonary embolism had not resolved at the time of this report. The outcome for the remaining events was unknown.

- The second case described an [redacted] subject who received BNT162b2 on [redacted]. The subject's relevant medical history included: hyperlipidaemia, prediabetes, obesity, non-smoker, polymyalgia rheumatica, hypertension, thrombocytopenia. Concomitant medications included: tramadol; prednisone, amour thyroid. The subject felt the vaccine had not been properly tested and that they had been injected with poison. After the first dose of BNT162b2, the subject experienced on an unknown date Peripheral swelling, Muscle rupture, Haemorrhage, Atrial fibrillation, Tachycardia, Chest pain, Cellulitis, Cardiac disorder, Pulmonary thrombosis, Cardiomyopathy, Mobility decreased, Dizziness, Impaired driving ability, Impaired quality of life, Vertigo, Pain, Fear of death, Arthropod bite, Arthralgia, Pain in extremity, Rash, Wound secretion, Skin lesion, Erythema, Fatigue, Dysstasia, Thrombosis and Orthostatic hypotension. Arterial tortuosity syndrome, Cerebrovascular accident, Gait disturbance, Hypertension and Myocardial infarction occurred 179 days after dose 2; Renal ischaemia occurred 182 days after dose 2 and Carotid arteriosclerosis after 294 days. Since [redacted] has had vaccines, [redacted] has had atrial fibrillation 6 times. The subject experienced tachycardia and chest pain almost daily. At the time of the report, the events of Pain, Hypertension, Cerebrovascular accident and Myocardial infarction were resolving or resolved. The events of Peripheral swelling, Muscle rupture, Haemorrhage, Atrial fibrillation, Tachycardia, Chest pain, Dizziness, Skin lesion, Erythema and Fatigue had not resolved. The outcome of the remaining events was unknown. No other pertinent information was provided.

- In the third case, a [redacted] subject received BNT162b2 on [redacted]. The subject's experienced COVID-19 9 days after receiving the first vaccine. Concomitant medication included: desorelle zilnic. Four days after receiving the second vaccine, the subject developed Nausea, Intermenstrual bleeding, Headache, Hormone level abnormal, Fatigue, Pyrexia. All events were considered nonserious and at the time of the report had not resolved. No other pertinent information was provided.

Conclusion

The number of product quality events did not show a trend that would require a change to the RSI. The most commonly scenarios in which the PT Poor quality product administered was coded, referred to administration of BNT162b2 after the beyond-use date, expired diluent and/or product storage deviation. Vaccine administration and details on product storage are adequately described in the RSI. The expiry date is printed on every package. Thus, the MAH considers the current risk minimisation measures sufficient.

7. SUMMARIES OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

Table 42 below summarizes the study treatments in the clinical studies by original vaccine or the Omicron-modified vaccine.

Table 42. Clinical Trials: Study Treatments – Original and Bivalent Vaccines

Original	BNT162b2	C4591001, C4591005, C4591007, C4591015, C4591020, C4591024, C4591030, C4591031, BNT162-01,[a] BNT162-06, BNT162-14, BNT162-17
Other constructs	BNT162b1	BNT162-01, BNT162-03
	BNT162b3	BNT162-04
Variant and variant-adapted vaccines	BNT162b2 (B.1.351)	BNT162-14[b]
	BNT162b2 (B.1.1.7) BNT162b2 (B.1.1.7 + B.1.617.2) BNT162b2 (B.1.617.2) BNT162b2 (B.1.1.529)	BNT162-17
	Original + Omi BA.1	C4591031 Substudy E, C4591044
	Original + Omi BA.2[c]	C4591044
	Original + Omi BA.4/BA.5	C4591044, C4591048, BNT162-21[d]
	Original + Omi	C4591036[e]

a. BNT162 a1, BNT162b1 and BNT162c2 were also study vaccine in this trial.
b. BNT162b2 (B.1.351), which is also referred as BNT162b2s01 and BNT162b2SA.
c. BNT162b5.
d. BNT162b4 is also study treatment in this study.
e. Low-Interventional.

Appendix 4.2 provides a list of interventional targeted safety studies. No targeted safety studies were completed or ongoing during the reporting interval.

7.1. Completed Clinical Trials

Safety Trials

During the reporting period, no interventional safety studies were completed with a final CSR.

Other Trials that reported new significant efficacy information

During the reporting period, no trials that reported new significant efficacy information were completed with a final CSR.

Remaining Trials

During the reporting interval, there were 5 completed clinical trials (C4591005, C4591020, BNT162-03, BNT162-04, BNT162-06) with a final CSR (available upon request). No clinically important new information has emerged from these clinical trials; overall conclusions for the study are provided below.

Table 43. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
C4591005	A phase 1/2, 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.	Two doses of 30 µg BNT162b2 administered at least 21 days apart had an acceptable safety profile and produced a robust immune response, regardless of age, in Japanese adults 20 to 85 years of age.
C4591020	A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT162b2 against COVID-19 in healthy adults 18 through 55 years of age.	Immune responses were observed after administration of 2 doses of the lyophilized SDV, frozen-liquid MDV, or RTU formulations of BNT162b2 30 µg, although the lyophilized formulation did not meet noninferiority criterion compared with the frozen-liquid MDV formulation. BNT162b2 drug product with a larger LNP size showed similar SARS-CoV-2 spike-binding IgG responses as the RTU BNT162b2, which supports the current acceptance criterion for drug product particle size. Participants who received 2 doses of the lyophilized formulation and received dose 3 of the frozen-liquid MDV had a boosted response based on GMCs and GMFRs. Local reactions and systemic events commonly observed in all 3 formulations were short-lived, and the safety profile was tolerable.
BNT162-03[36]	Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A phase I, randomized, placebo-controlled, observer-blinded study.	BNT162b1 at 10 µg and 30 µg dose level induced a robust SARS-CoV-2 neutralizing antibody response, S1-binding IgG antibody responses and cellular immune response after a 2-dose regimen with a 21-day interval in both adult and elderly subjects, and the safety and tolerability profiles were also satisfactory in both age groups, which indicate favorable risk/benefit ratio of the 2 doses of BNT162b1.
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.	BNT162b3 had an acceptable safety profile at the 3 µg and 10 µg doses in younger participants aged 18 to 55 years but the reactogenicity of the 20 µg dose 2 in younger participants was less favorable than the lower doses, resulting in the SRC recommending that dose 2 at 30 µg not be administered. In older participants aged 56 to 85 years, BNT162b3 had an acceptable safety profile at the 3 µg, 10 µg, 20 µg, and 30 µg doses. Both younger and older participants dosed with BNT162b3 showed strong IMP-induced antibody responses. Virus-neutralizing GMTs were detected after dose 1 and showed a substantial, second-dose

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

Table 43. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
		response by 7 d after dose 2. Due to changes in the overall clinical development plan, the decision was made not to conduct Part B of this study.
BNT162-06[36]	Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population: A phase II, randomized, placebo-controlled, observer-blind study.	BNT162b2 at 30 µg dose level induced a robust SARS-CoV-2 neutralizing antibody response, S1-binding IgG antibody responses and cellular immune response after a 2-dose regimen with a 21-day interval in both adult and elderly subjects, and the safety and tolerability profiles were also satisfactory in both age groups, which indicate favorable risk/benefit ratio of the 2 doses of BNT162b2.

7.2. Ongoing Clinical Trials

During the reporting period, there were 13 ongoing[37] sponsor-initiated clinical trials.

Safety Trials (see Appendix 4.2 for a list of ongoing interventional safety studies)

There were 2 ongoing clinical trials.

Original Vaccine

- PASS:
  - C4591015: [*A phase 2/3, placebo-controlled, randomized, observer-blind 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*] is an ongoing PASS. No clinically important new information has emerged from this ongoing PASS.
  - C4591024[38]: [*A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants*

[37] Includes ongoing studies as well as studies in which participant enrollment and follow-up have been completed, but the analysis and CSR are in-progress.

[38] On 10 November 2022 in the final Assessment report for PAM-MEA-016.4, the CHMP granted permission to cease enrollment in Study C4591024 due to the futility reasons. The study started to recruit participants in October 2021, when all countries provided vaccine against COVID-19 after the authorization at first to the most vulnerable population, which includes the immunocompromised individuals, making difficult the enrollment of vaccine naïve immunocompromised participants without a prior history of COVID-19

≥*2 years of age*] is an ongoing PASS. No clinically important new information has emerged from this ongoing PASS.

- Other trials where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product:

  – None.

Other Trials that reported new significant efficacy information

There were 8 ongoing clinical trials, of which 4 are with the BNT162b2 original vaccine, 3 are with the bivalent vaccine; in the 8th clinical trial (C4591031) both original and bivalent vaccine were administered:

Original vaccine

– C4591001: *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.*

– C4591007[39]: *A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults.*

– C4591031[40]: *A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.*

– BNT162-01[41]: *A multi-site, phase I/II, 2-Part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults.*

– BNT162-14: *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.*

infection. Currently, enrolled participants should continue in the study and the results of the planned analyses such as safety and immunogenicity evaluations should be completed.

[39] One interim CSR was issued for Study C4591007 (v. 1.0 dated 04 Jul 2022) during the reporting interval.

[40] One interim CSR was issued for Substudy D of Study C4591031 (v. 1.0 on 10 June 2022) and 2 were issued for Substudy E (v. 1.0 dated 16 July 2022 and v 1.0 dated 27 October 2022) during the reporting interval.

[41] Last subject last visit occurred during the reporting interval for the following studies: BNT162-01 (13 Apr 2022); BNT162-04 (07 Feb 2022); BNT162-06 (09 Jan 2022).

Bivalent vaccine

– C4591031[40]: *A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.*

– C4591044: *An interventional, randomized, active-controlled, phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b RNA-based vaccine candidates as a booster dose in COVID-19 vaccine-experienced healthy individuals.*

– C4591048: *A master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA-based vaccine candidate(s) in healthy children.*

– BNT162-21: *An exploratory Phase I, randomized, observer-blind, active controlled dose escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults.* This trial uses IMP BNT 162b4 as investigational IMP and BNT162b2 Bivalent as investigational and active comparator.

No clinically important new safety information has emerged from ongoing clinical trials.

Remaining Trials

There were 3 ongoing clinical trials:

Original vaccine

– C4591030: *A phase 3, randomized, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.*

– BNT162-17: *A Phase II trial to evaluate the safety and immunogenicity of SARS-CoV-2, monovalent and multivalent RNA-based vaccines in healthy subjects.*

Bivalent vaccine

– C4591036: *Low-interventional cohort study of myocarditis/pericarditis associated with COMIRNATY in persons less than 21 years of age.*

No clinically important new safety information has emerged from these ongoing clinical trials.

7.3. Long-term Follow-up

There is no new significant safety information with regards to long-term follow-up of clinical trial participants for this reporting period.

7.4. Other Therapeutic Use of Medicinal Product

BNT162b2 was also administered as study vaccine in another Pfizer-sponsored clinical development program (C526). The study C5261001 "*A phase 1 randomized study to evaluate the safety, tolerability, and immunogenicity of combined modified RNA vaccine candidates against COVID-19 and influenza in healthy individuals*" was ongoing during the reporting period.

There was no new clinically important safety information identified for this reporting period.

7.5. New Safety Data Related to Fixed Combination Therapies

BNT162b2 is not used in fixed or multi-drug combination with other compounds.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Reference is made to the response of the MHPD dated 15 November 2022, where the following request was made: *Given the status of the information provided from these (C4591010, C4591021 and C4591022) interim reports, the MHPD recommends that moving forward these reports be presented and discussed in the future PSURs/PBRER, unless a safety issue is identified that requires immediate regulatory action.*

Response

Please refer to Appendix 5.5.2.1. through Appendix 5.5.2.3. for the interim reports of studies C4591010, C4591021 and C4591022 submitted in the reporting period.

During the reporting period, there were 11 ongoing sponsor-initiated non-interventional studies, and one non-interventional study (C4591019) was completed.

8.1. Completed Non-Interventional Studies

Safety studies

Neither PASS nor other studies where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product were completed during the reporting period.

Other studies

During the reporting period, the study C4591019[42] was completed. No new safety information emerged from this non-interventional study; the summary of results from this study is provided in Table 44.

[42] Study C4591019 was a commitment to the Japanese regulatory. The full CSR in Japanese was finalised in July 2022 and the abstract CSR in English was finalised in October 2022.

Table 44. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591019	Special investigation of COMIRNATY Intramuscular Injection (Investigation of Patients with Underlying Disease Considered to be at High Risk of Aggravation of COVID-19).	Vaccination with Comirnaty is well-tolerated in the population with underlying disease considered to be at high risk of aggravation of COVID-19. Based on the results of this study, there are no new risks that may require additional pharmacovigilance activities at this time.

8.2. Ongoing Non-Interventional Studies

Safety Studies (see Appendix 4.4 for a list of ongoing non-interventional safety studies and their protocol titles):

PASS[43]: Non-interventional studies C4591008,[44] C4591009,[45] C4591010,[46] C4591012,[45] C4591021[45] and C4591022[45] are PASS. No clinically important information has emerged from PASS. Summary of the interim reports of the NIS C4591010, C4591021 and C4591022 submitted during the reporting period are available in Appendix 5.5.2.1, Appendix 5.5.2.2 and Appendix 5.5.2.3, respectively.

Other studies where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.

Other Studies

There were 5 ongoing non-interventional studies:

- *C4591006,[47] General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).*

[43] During the reporting period, interim CSRs were issued for the studies C4591008 (23 June 2022), C4591009 (24 October 2022), C4591010 (23 August 2022), C4591012 (24 June 2022), C4591021 (20 September 2022).

[44] Study C4591008 is a voluntary study; it is included in the US-PVP as post-authorisation safety study addressing the important potential risk of VAED/VAERD.

[45] Studies C4591009, C4591012, C4591021 and C4591022 are commitments to the US FDA and are Category 3 commitments in the EU-RMP v.9.0.

[46] Study C4591010 is Category 3 commitment in the EU-RMP v. 9.0.

[47] Study C4591006 is a commitment to the Japanese regulatory.

- *C4591014,[48] Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- *C4591025,[49] A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.*
- *C4591034, Patient-Reported Health-Related Quality of Life Associated With COVID-19: A Prospective Survey Study on Symptomatic Adults Confirmed With RT-PCR From Outpatient Settings in the US.*
- *C4591042, Patient characteristics, healthcare resource utilization and costs among patients with COVID-19 in England.*

During the reporting period, no new significant safety information has emerged from the non-interventional studies.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

During the reporting interval, there were 14 cases originating from non-Pfizer and non-BNT clinical trials. Among them, in 6 cases BNT162b2 (Original), BNT162b2 Omi and/or BNT162b2 and BNT162b2 Omi BA.4/BA.5 (Bivalent) vaccines were study drugs, while in 8 cases the vaccines were co-administered with the study medications.

Eight (8) cases originated from the following non-Pfizer and non-BNT trials:

- EPOC1703 - Multicentre, proof-of-concept, phase II study evaluating the efficacy and safety of combination therapy with binimetinib, encorafenib and cetuximab in patients with BRAF non-V600E mutated metastatic colorectal cancer (1 case reporting the SAE Dehydration and the non-serious AE Overdose).

- NCT04816019 - A Phase I Study to Determine Safety, Tolerability and Immunogenicity of Intranasal Administration of the COVID Vaccine ChAdOx1 nCOV-19 in Healthy UK Adults (3 cases, all reporting the SAEs COVID-19, Drug ineffective and Interchange of vaccine products)

- 2021-002348-57 - A Randomized, Parallel Group, Single-Blind, Phase 2 Study to Evaluate the immune response of two classes of SARS-Cov-2 Vaccines employed As Second Boost in Patients under current Rituximab Therapy and no humoral response after standard mRNA vaccination (1 case reporting the SAEs COVID-19 and Drug ineffective).

[48] PAM-MEA-013.

[49] Study C4591025 is a committed study, which was requested by the Ministry of Food and Drug Safety in Korea.

- UX007-IST214 - Safety and efficacy of UX007 (triheptanoin) in Korean patients with long-chain fatty acid oxidation disorders (LC-FAOD) (1 case reporting the SAE Myalgia).

- CAMG334ADE03 - Assessment of Prolonged Safety and tOLerability of in Migraine Patients in a Long-term OpeN-label Study (APOLLON) (1 case reporting the SAE Enteritis and the non-serious AEs Abdominal pain upper, Dyspnoea, Muscle spasms, Vomiting, and Incorrect route of product administration).

- BOSTON-1 - Efficacy + Safety of Liposome Cyclosporine A to Treat Bronchiolitis Obliterans Post Single Lung Transplant (1 case reporting the SAE Thrombocytopenia).

The AEs reported in these 8 cases were assessed as related to BNT162b2 by the investigator, and the MAH concurred with the causality assessment, except for the SAE Dehydration, for which it was considered that there was not a reasonable possibility that the event was related to vaccine administration, based on the lack of a plausible pathophysiological mechanism for the event.

Six (6) originated from the following non-Pfizer and non-BNT trials:

- 22-0004 - Phase 2 Clinical Trial to Optimize Immune Coverage of SARS-CoV-2 Existing and Emerging Variants (5 cases reporting the following SAEs: Sickle cell anaemia with crisis [2], Meningitis aseptic, Pyelonephritis, and Seizure [1 each]).

- VAC31518COV3001 - A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older (1 case reporting the SAE Death).

The investigator’s assessment for Death was not provided; the MAH considered that there was not enough evidence to reasonably attribute the participant’s death to the vaccine due to the long latency (more than one year) between vaccination and the death.

For all the remaining SAEs, both the investigator and the MAH assessed the causality unrelated to the vaccine.

During this reporting period, there was no new significant safety information reported from other non-Pfizer, non-BNT sponsored clinical trials/studies.

9.2. Medication Errors

In the response to the Rapporteur's preliminary AR and updated AR on the request for supplementary information regarding EMEA/H/C/005735/II/0140, the following request was made: *With launch of the modified vaccines the MAH is requested to commit to again carefully monitor Medication errors and inform the Rapporteur immediately in case of unexpected findings or trends.*

Response

Please refer to the analysis of the safety database in this Section.

The following request was included in the Health Canada Assessment of the abbreviated monthly summary #6: *Poor quality product administered was amongst the most frequently reported Preferred Terms in those who received a booster dose, and in those 5 to 11 years of age. Please provide an analysis of potential quality issues in the next PSUR, and discuss if additional risk minimization measures should be put into place.*

Response

Please refer to Section 6.3.1.3.5 *Product Quality Analysis* for case summary in the interval period.

Analysis of the safety database

Cases potentially indicative of medication errors[50] that occurred in the reporting period are summarised below.

[50] Medication errors search criteria: MedDRA (version 25.1): *HLTs (All paths):* Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product prescribing errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR *PTs:* Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Contraindication to vaccination; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

Of the 58,188 cases, 1323 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Off-label use or intentional use rather than medication error was reported in 1035 cases[51];
- Cases consisted of questions or requests for information about the scheduling of the 2 doses of BNT162b2 or the second dose (not administered yet at the time of reporting) or scheduling outside the prescribed dosing window were reported in 283 cases;
- The subject intentionally refused to be vaccinated or was not able to receive the scheduled BNT162b2 in 5 cases.

Clinical Trial Data

- Number of cases: No cases indicative of potential medication errors during the reporting period, compared to 2 cases (0.3%) retrieved in the PSUR #3.

Post-Authorisation Data

From the global safety database, 56,865 cases reporting 75,032 events (20.1% of 282,992 cases, the total PM dataset) indicative of potential medication errors were retrieved during the reporting period compared to 66,764 relevant cases (13.1%) analysed in the PSUR #3.

The 56,865 relevant medication error cases originated (≥2% of cases) from the following countries: Austria (18,747), the US (11,022), Sweden (8885), Japan (6693), Germany (3098), New Zealand (1573).

The most frequently reported (≥2%) medication error PTs included Inappropriate schedule of product administration (33,797), Poor quality product administered (16,440), Product temperature excursion issue (7455), Product administration error (6726), Wrong product administered (2205), Product storage error (2185), Expired product administered (1941).

In some instances, clusters of medication errors were reported. During the reporting interval, 3 different types of medication error cases (>1000) were identified and coded to the PTs Product temperature excursion issue, Poor quality product administered, and Product storage error.

All cases demonstrated no-harm and had no co-reported events:

- in 4484 cases, BNT162b2 was given at 2-8°C after taking it out of the deep freezer;
- in 4298 cases, BNT162b2 was refrozen and re-thawed before use;

[51] Among the 1035 cases, 48 cases involved 6 months to 4 years and 87 cases involved 5 through 11 years.

- in 3140 cases, subjects vaccinated with vaccine stored at an incorrect temperature.

9.2.1. Medication Errors Categorisation

Among the medication error cases (56,865 cases), compared to 66,764 medication errors in the PSUR #3, the following scenarios, categorised according to the EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014) were described:

- Medication errors associated with harm [i.e., resulting in adverse reaction(s)]: 1670 cases (2.9%) compared to 1326 cases (2.0%) in the PSUR #3.
- Medication errors without harm [i.e. not resulting in adverse reaction(s)]: 55,167 cases (97.0%) compared to 65, 350 (97.9%) in the PSUR #3.
- Potential medication errors: 39 cases (0.1%) compared to 87 cases (0.1%) in the PSUR #3.
- Intercepted medication errors: 3 cases (0.01%) compared to 1 case (0.001%) in the PSUR #3.

Of note, some cases involved more than one medication error.

9.2.2. Medication Errors in the 6 Months through 4 Years Age Group

- Number of relevant cases: 269
- Country/region of incidence: the US (266), [redacted] (1 each)
- Number of relevant events: 408.
- Relevant event seriousness: non-serious (407), serious (1).
- Relevant PTs (≥20) included Poor quality product administered (102), Product administration error (76), Product preparation error (47), Product preparation issue (41), Inappropriate schedule of product administration (40), Product administered at inappropriate site (32), Product temperature excursion issue (20).

Table 45 describes for each ME category the top 3 medication errors by primary and booster series in individuals 6 months through 4 years.

Table 45. Medication Error Categories: Top 3 Primary and Booster Dose Medication Errors in 6 Months through 4 Years

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Primary series**	Product administered at inappropriate site	0	1	1
	Booster series	-	0	0	0

Table 45. Medication Error Categories: Top 3 Primary and Booster Dose Medication Errors in 6 Months through 4 Years

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Mediation Errors without harm	**Primary series**	Poor quality product administered	0	92	92
		Product administration error	0	66	66
		Product preparation error	0	41	41
	Booster series	Inappropriate schedule of product administration	0	25	25
		Product administration error	0	11	11
		Poor quality product administered	0	11	11
Potential Error	**Primary series**	Circumstance or information capable of leading to medication error	0	2	0
	Booster series	-	0	0	0
Intercepted Error	**Primary series**	-	0	0	0
	Booster series	-	0	0	0

9.2.3. Medication Errors in the 5 through 11 Years Age Group

- Number of cases: 2303
- Country/region of incidence (≥2%): the US (1747), Japan (193), Spain (76), Canada (75).
- Number of relevant events: 3540.
- Relevant event seriousness: non-serious (3532), serious (8).
- Relevant PTs (>20) indicative of medication error included Poor quality product administered (950), Expired product administered (802), Product administration error (687), Product preparation error (301), Product temperature excursion issue (213), Inappropriate schedule of product administration (159), Wrong product administered (116), Product label issue (91), Vaccination error (65), Product preparation issue (38), Underdose (30), Product expiration date issue (22), Incorrect dose administered (21).

Table 46 describes for each ME category the top 3 medication errors occurred by primary and booster series in individuals 5 through <12 years.

Table 46. Medication Error Categories: Top 3 Primary and Booster Dose Medication Errors in 5 through <12 Years

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
	Primary series	Inappropriate schedule of product administration	0	29	29

Table 46. Medication Error Categories: Top 3 Primary and Booster Dose Medication Errors in 5 through <12 Years

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Booster series**	Product preparation error	0	2	2
Mediation Errors without harm	**Primary series**	Poor quality product administered	0	862	862
		Expired product administered	0	647	647
		Product administration error	0	628	628
	Booster series	Expired product administered	1	159	160
		Product preparation error	4	126	130
		Poor quality product administered	2	90	92
Potential Error	**Primary series**	Circumstance or information capable of leading to medication error	0	1	1
	Booster series	Circumstance or information capable of leading to medication error	0	1	1
Intercepted Error	**Primary series**	-	0	0	0
	Booster series	-	0	0	0

9.2.4. Medication Errors in the 12 Years and Older Age Group

- Number of cases: 38,032
- Country/region of incidence (≥2%): Austria (18,719), Sweden (8856), Germany (2518), the US (2139), Japan (788), Norway (772).
- Number of relevant events: 40,450.
- Relevant event seriousness: non-serious (40,196), serious (254).
- Relevant PTs (>118): Inappropriate schedule of product administration (33,291), Poor quality product administered (1870), Product administration error (1426), Wrong product administered (956), Vaccination error (593), Incorrect route of product administration (590), Product temperature excursion issue (415), Expired product administered (361), Incorrect dose administered (221), Underdose (169), Accidental underdose (119).

Table 47 below describes for each ME category the top 3 medication errors occurred by primary and booster series in individuals 12 years and older age group.

Table 47. Medication Error Categories: Top 3 Primary and Booster Dose Medication Errors in 12 Years and Older

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Primary series**	Inappropriate schedule of product administration	0	1549	1549
		Incorrect route of product administration	0	21	21
		Vaccination error	0	9	9
	Booster series	Wrong product administered	0	12	12
		Incorrect dose administered	0	6	6
		Incorrect route of product administration	0	5	5
Mediation Errors without harm	**Primary series**	Inappropriate schedule of product administration	0	30347	30347
		Wrong product administered	3	769	772
		Poor quality product administered	1	654	655
	Booster series	Wrong product administered	15	861	876
		Poor quality product administered	1	665	666
		Product administration error	0	527	527
Potential Error	**Primary series**	Circumstance or information capable of leading to medication error	0	1	1
	Booster series	Circumstance or information capable of leading to medication error	0	8	8
Intercepted Error	**Primary series**	-	0	0	0
	Booster series	Intercepted product administration error	0	2	2

9.2.5. Medication Errors in the Unknown Age Group

- Number of cases: 16,259
- Country/region of incidence (≥2%): US (6868), Japan (5712), New Zealand (1570), Canada (572), Germany (553), Australia (413).
- Number of relevant events: 30,631.
- Relevant event seriousness: non-serious (30,613), serious (18).
- Relevant PTs (>117): Poor quality product administered (13,517), Product temperature excursion issue (6807), Product administration error (4536), Product storage error (2166), Wrong product administered (1119), Expired product administered (761), Product preparation error (409), Underdose (387), Inappropriate schedule of product administration (307), Product preparation issue (130), Product packaging confusion (118).

Table 48 below describes for each ME category the top 3 medication errors occurred by primary and booster series when the vaccine presentation is unknown.

Table 48. Medication Error Categories: Top 3 Primary and Booster Medication Errors in Unknown Age Group

ME Categories	Type of Vaccines	Medication error PTs	Total
Medication errors with harm	**Primary series**	Inappropriate schedule of product administration	4
		Medication error	1
		Product administered at inappropriate site	1
	Booster series	Incorrect dose administered	3
		Wrong product administered	2
		Incorrect route of product administration	1
Mediation Errors without harm	**Primary series**	Poor quality product administered	10986
		Product temperature excursion issue	4720
		Product administration error	4087
	Booster series	Poor quality product administered	3134
		Product temperature excursion issue	2261
		Wrong product administered	1777
Potential Error	**Primary series**	Circumstance or information capable of leading to medication error	21
	Booster series	Circumstance or information capable of leading to medication error	6
Intercepted Error	**Primary series**	Intercepted medication error	1
		Intercepted product administration error	1
	Booster series	-	0

Conclusion

Overall, among the 56,865 relevant medication error PM cases, 1670 cases (0.6% of the total interval cases, 2.9% of total relevant medication error cases) were considered harmful because they were accompanied by clinically relevant co-reported events.

The potential for medication errors with all vaccine presentations are mitigated through the information in the vaccine labelling and available educational materials for the HCPs administering the vaccine.

Some medication errors are expected to occur despite written instructions for handling the vaccine (thawing, dilution, preparation) and educational activities for the HCPs or due to national or regional recommendations regarding dosing schedules that may differ from recommendations in the product labelling. The number and seriousness of the reported medication errors events do not indicate there is the need for any additional mitigation activity to prevent harm.

10. NON-CLINICAL DATA

During the reporting period, no new nonclinical safety findings were identified.

11. LITERATURE

In the AR of the 13th SMSR / 2nd SBSR (EMA/PRAC/202255/2022), the following request was made: *The MAH is requested in future SSRs and PSURs to present all relevant literature concerning the safety of Comirnaty (also besides the database Medline and Embase) that is published during the reporting period.*

Response

Please refer to the content of this Section and to Appendix 5.4.3 for the abstracts of the relevant literature papers evaluated.

Nonclinical (Published)

A search of the Medline and Embase databases identified no nonclinical studies that presented important new safety findings for BNT162b2.

Clinical (Published)

A search of the Medline and Embase databases identified no clinical trials that presented important new safety findings for BNT162b2. However, there were 18 literature articles (of which 1 [Hause et al., 2023] published after DLP) that contained new safety findings for myocarditis. These are presented in the table below grouped as follows: a) Booster; b) Special patient population; c) Clinical characteristics, severity, investigations and d) Long-term data.

Please refer to Appendix 5.9 for the abstracts. Full publications are available upon request.

Table 49. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

Citation/*Comment*
a) Booster *There were several literature publications that evaluated myocarditis occurrence after the 3rd or 4th dose (first or second booster) of the vaccine.* *Mervorach et al analysed almost 4 million booster dose administrations in Israel and found that there was a mild decrease in the occurrence of vaccine-associated myocarditis after the third vaccine relative to the second, although the overall incidence is still low. In the 3 944 797 individuals (48.7% male) who received a booster dose, the myocarditis risk estimates in the 30 days after the booster in male patients were 1.42 per 100 000 overall and 6.44 per 100 000 and 5.21 per 100 000 for male individuals 16 to 19 and 20 to 24 years of age, respectively. Compared with vaccine dose 2, for male individuals, the overall RD per 100 000 was −2.72 (95% CI, 3.67 to −1.73), driven mainly by male individuals 16 to 19 years of age (RD, −8.45 [95% CI, −15.30 to −0.44]); for female individuals, the overall RD was −0.48. The clinical presentation was mild, with resolution of post-booster myocarditis in all cases, as judged by clinical symptoms, inflammatory markers, and troponin levels, ECG, echocardiogram normalization if abnormal (<55% ejection fraction), and a relatively short hospital stay.* *In the Yechezkel et al retrospective cohort study from Israel, none of the 17 814 recipients of the second booster dose were diagnosed with myocarditis or pericarditis within 42 days following the second booster. For individuals who were eligible to receive the second booster, authors also extended the analysis to examine whether these events were associated with the primary series (ie, first and second doses) or the first booster. Among the 44 003 eligible individuals, five individuals were diagnosed with myocarditis following inoculation with the primary series (risk difference 1·14 [95% CI 0·23 to 2·27]) and two after the first booster (risk difference –0·68 [–1·82 to 0·46]); 12 were diagnosed with pericarditis following the primary series (1·59 [–0·23 to 3·41]), and seven following the first booster (–0·23 [–2·05 to 1·59]).* *In a population of >42 million vaccinated individuals aged 13 years or older in England, Patone et al found that the risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine. Specifically for BNT162b2, authors found the risk of myocarditis at 1 to 28 days similar after a second (IRR, 1.57 [95% CI, 1.28–1.92]) and booster dose of BNT162b2 (IRR, 1.72 [95% CI, 1.33–2.22]). Authors estimated that after a booster dose of BNT162b2, an additional 2 (95% CI, 1–3) myocarditis events per million people would be anticipated, compared with an additional 35 (95% CI, 34–36) myocarditis events per million people in the 1 to 28 days after a SARS-CoV-2–positive test before vaccination.* *In Canada, Naveed et al conducted an observational population-based cohort study to estimate observed to expected rates of myocarditis after SARS-COV-2 vaccination in British Columbia. Authors found that, using a 7-day risk window, overall myocarditis rates were lower after the third dose than after the second dose (0.76, 95% CI 0.45–1.20 v. 1.90, 95% CI 1.50–2.39) and among those aged 12–17 years who received BNT162b2 vaccines, myocarditis rates after the second and third doses were similar (males: 6.7, 95% CI 3.1–12.8 v. 7.0, 95% CI 1.4–20.5; females: 1.5, 95% CI 0.2–5.5 v. 0, 95% CI 0–8.2).* *Regarding the administration of the bivalent booster doses in the US, Hause et al reviewed adverse events and health impacts reported after receipt of bivalent approx. 14.4 million individuals aged ≥12 years who received a bivalent Pfizer-BioNTech booster doses during August 31–October 23, 2022. Authors found that reporting rates of myocarditis following COVID-19 mRNA primary series and monovalent booster vaccination were highest among adolescent and young adult males; myocarditis rates after monovalent booster dose in these early data are similar to or lower than those after primary series doses.* *The systematic review and meta-analysis by Chang et al included a total of 1,604,254,833 people who received 2,575,129,450 doses of COVID-19 vaccine in the 42 analysed studies. Authors found that a risk of myocarditis was observed after COVID-19 vaccination, but it was much lower than that following the SARS-CoV-2 infection. No significant increased risk of myocardial infarction or arrhythmia was found after COVID-19 vaccination. The overall incidence rate of myocarditis after COVID-19 vaccination was 14.80 (12.96–16.65) events per million persons, 8.84 (7.77–9.91) events per million doses, and for each dose, incidence rate per 1000,000 doses was 5.51 (2.78–8.24) for first dose, 13.66 (10.39–16.9) for second dose and 5.92 (1.77–10.06) for third dose.*

Table 49. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

Citation/*Comment*
1. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 COVID-19 third booster vaccine in Israel.[a]
2. Yechezkel M, Mofaz M, Painsky A, et al. Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study.[b]
3. Patone M, Mei XW, Handunnetthi L, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex.[c]
4. Naveed Z, Li J, Spencer M, et al. Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: a population-based cohort study.[d]
5. Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among persons aged ≥12 years - United States, August 31-October 23, 2022.[e]
6. Chang Y, Lv G, Liu C, et al. Cardiovascular safety of COVID-19 vaccines in real-world studies: a systematic review and meta-analysis.[f]
b) Special Patients Population *Hause et al reported in the US Morbidity and Mortality Weekly report in September that an analysis of the vaccine safety of the 599,457 children aged 6 months–4 years who received the Pfizer-BioNTech vaccine between June 18, 2022–August 21, 2022 found no cases of myocarditis reported after vaccination.* *Malden et al report an observational study using US RWD of children aged 5–11 years vaccinated with Pfizer-BioNTech COVID-19 mRNA vaccine. Of the approx. 7,000 participants recruited, authors found there was no indication of myocarditis or pericarditis diagnoses in the EHR within the 21 days following vaccination.* *In a publication issued after the DLP of the PSUR, Hause et al report that no reports of myocarditis were recorded in VAERS by 1 January 2023 for the 861,251 children aged 5–11 years who received a bivalent Pfizer-BioNTech booster in the United States in the same period.*
7. Hause AM, Marquez P, Zhang B, et al. COVID-19 mRNA vaccine safety among children aged 6 months-5 years - United States, June 18, 2022-August 21, 2022.[g]
8. Malden DE, Gee J, Glenn S, et al. Reactions following Pfizer-BioNTech COVID-19 mRNA vaccination and related healthcare encounters among 7,077 children aged 5-11 years within an integrated healthcare system.[h]
9. Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023.[i]
c) Clinical characteristics, severity, investigations *Pillay et al conducted a living evidence syntheses and review of incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following COVID-19 vaccination. Authors found that adolescent and young adult men are at the highest risk of myocarditis after mRNA vaccination. Incidence of myocarditis in children aged 5-11 years is very rare but certainty was low. In adolescents and adults, most (>90%) myocarditis cases involved men of a median 20-30 years of age and with symptom onset two to four days after a second dose (71-100%), with most people being admitted to hospital (≥84%) for a short duration (two to four days). Data for clinical risk factors were very limited, and the clinical course of mRNA related myocarditis appeared to be benign, although longer term follow-up data were limited. Several hypothesised mechanisms were reviewed, but all had limited direct supporting or refuting evidence.* *Kato et al conducted a literature search and meta-analysis to evaluate the imaging characteristics of myocarditis after mRNA vaccination on CMR. Authors identified 12 articles, including 274 patients with mRNA vaccine-related myocarditis, with the majority of patients being young male recipients after the 2nd dose of the mRNA vaccine (median age: 17 years, male: 91.6%, after 2nd dose: 91.4%). The analysis found that more than 80% of the patients had LGE on the LV myocardium, mainly located at the epicardial side of the lateral wall; abnormal T1 was found in 63%, and abnormal T2 was found in 79%; Lake Louise criteria were positive for 87% of the patients. However, with respect to severity, authors found that the*

Table 49. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

Citation/*Comment*
severity of imaging findings is not severe, as reflected by low LGE volume (1–3.9%) and concluded that the short-term outcome of vaccine-related myocarditis is favourable.
10. Pillay J, Gaudet L, Wingert A, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review.[j]
11. Kato S, Horita N, Utsunomiya D. Imaging characteristics of myocarditis after mRNA-based COVID-19 vaccination: a meta-analysis.[k]
d) Long term data *Several publications described longer term follow up (3-6 months) of patients with myocarditis that described clinical resolution and observations of residual LGE on CMR in some patients. The largest study was Krakalick et al follow up surveillance study of VAERS that collected data for 519 (62%) of 836 eligible patients who were at least 90 days post-myocarditis onset. The study found that after at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, most individuals in the cohort were considered recovered by health-care providers, and quality of life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age. Most patients had improvements in cardiac diagnostic marker and testing data at follow-up, including normal or back-to-baseline troponin concentrations (181 [91%] of 200 patients with available data), echocardiograms (262 [94%] of 279 patients), electrocardiograms (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients). An abnormality was noted among 81 (54%) of 151 patients with follow-up cardiac MRI; however, evidence of myocarditis suggested by the presence of both late gadolinium enhancement and oedema on cardiac MRI was uncommon (20 [13%] of 151 patients). At follow-up, most patients were cleared for all physical activity (268 [68%] of 393 patients). The other publications were smaller studies or case series which similarily found clinical improvement/resolution, and the LGE extent showed decreases compared with acute episode. In their case series of 13 patients, Manno et al found the persistence of CMR lesions associated with higher troponin levels at admission.* *Lai et al compared the prognosis of post-mRNA vaccine myocarditis with viral infection-related myocarditis over 180 days using RWD in Hong Kong. Authors found that the postvaccination myocarditis group had a 92% lower mortality risk (adjusted HR: 0.08; 95% CI: 0.01-0.57) compared with viral myocarditis. No significant differences in other prognostic outcomes were seen.*
12. Krupickova S, Voges I, Mohiaddin R, et al. Short-term outcome of late gadolinium changes detected on cardiovascular magnetic resonance imaging following coronavirus disease 2019 Pfizer/BioNTech vaccine-related myocarditis in adolescents.[l]
13. Shiyovich A, Plakht Y, Witberg G, et al. Myocarditis following COVID-19 vaccination in adolescents: Cardiac magnetic resonance imaging study.[m]
14. Hadley SM, Prakash A, Baker AL, et al. Follow-up cardiac magnetic resonance in children with vaccine-associated myocarditis.[n]
15. Mustafa Alhussein M, Rabbani M, Sarak B, et al. Natural history of myocardial injury after COVID-19 vaccine-associated myocarditis.[o]
16. Manno EC, Amodio D, Cotugno N, et al. Higher troponin levels on admission are associated with persistent cardiac magnetic resonance lesions in children developing myocarditis after mRNA-Based COVID-19 vaccination.[p]
17. Kracalik I, Oster ME, Broder KR, et al. Myocarditis outcomes after mRNA COVID-19 vaccination investigators and the CDC COVID-19 Response Team. Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study.[q]
18. Lai FTT, Chan EWW, Huang L, et al. Prognosis of myocarditis developing after mRNA COVID-19 vaccination compared with viral myocarditis.[r]

All Other Published Sources

A search of the Medline and Embase databases identified no new information that presented important new safety findings for BNT162b2.

Unpublished manuscripts

During the reporting period, no new safety findings were identified.

12. OTHER PERIODIC REPORTS

During the reporting period, the MAH did not submit another PSUR for BNT162b2.

The list of periodic reports prepared and submitted by the MAH during the reporting period is provided below.

Table 50. List of Periodic Reports submitted in the Reporting Period

Periodic Report Type	No.	Reporting Period
Abbreviated SMSR[a]	6	16 June 2022 through 15 July 2022
	7	16 July 2022 through 15 August 2022
	8	16 August 2022 through 15 September 2022
	9	16 September 2022 through 15 October 2022
	10	16 October 2022 through 15 November 2022
	11	16 November 2022 through 15 December 2022
Summary Bridging Report for Comirnaty Original/Omicron BA.1 for UK	1	16 August 2022 through 15 November 2022
Summary Bridging Report for Comirnaty Original in Pediatric Individuals 6 months to < 5 years/Comirnaty Original/Omicron BA.4/BA.5 for Canada	1	16 September 2022 through 15 December 2022

a. Submitted to non-EEA countries.

During the reporting period, no new significant safety findings were identified for BNT162b2 in other periodic reports prepared by the MAH.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting period, no lack of efficacy information from clinical trials was identified.

14. LATE-BREAKING INFORMATION

After the DLP,

- an updated CDS (version 19.0) was made effective on 22 December 2022. In this version updated clinical data after 2 doses for children 5 to <12 years of age was added; diarrhea was added as ADR in children 5 to <12 years of age in Section 4.8 *Undesirable effects*; efficacy data after 2 doses in children 5 to <12 years of age efficacy and efficacy and immunogenicity data in 6 months through <5 years of age after 3 doses were added in Section 5.1 *Pharmacodynamic properties*. Efficacy in infants and in children after 3

doses was deleted in Section 5.1 *Pharmacodynamic properties.* Updated frequency values in 5 through <12 years of age were included in Table A-3 of Appendix A; Angioedema and Night sweats were added as rare ADR Diarrhea was reclassified from "Common" to "Very Common" ADR in 5 through <12 years of age in Table B-3 of Appendix B.

- a new signal (Myositis) was opened based upon a signal assessment report EMA PRAC;

- The following action was taken for safety reasons. In Switzerland the bivalent Omi BA.1 is not approved for individuals 12 to less than 18 years because there was no clinical data available for that population. As country-specific packaging is not yet available, Switzerland is receiving EU packaging that has the age on the carton (12+ as per EU MA). Therefore, an information Letter (in English) explaining the discrepancy between information on the carton and indication approved by Swissmedic is provided with each shipment. In addition, the MAH provides electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

- The literature article "Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023" (Hause et al.) including important safety information about the use of bivalent vaccines and young children has been included in Section 11 *Literature.*

The following 2 requests will be addressed in a separate supplemental document:

- In the preliminary AR for the Type II variation EMEA/H/C/005735/II/0139 to update on six-month post (booster) dose 3 interim report data in patients aged 16 years of age and above from studies C4591001 and C4591031 substudy A, the following request was made: *To ascertain whether the SmPC text in 4.4 and 4.8 currently covers these severe cases adequately, with the next PSUR, the MAH was requested to present an in-depth cumulative review of all myocarditis and pericarditis cases with fatal outcome that have been reported with the vaccine. Based on cases identified in clinical trials, narrative descriptions from postmarketing sources, O/E analysis (if possible to perform) and literature review, the MAH is requested to evaluate whether a further update of the SmPC section 4.4 and/or 4.8 is warranted (issue pursued in the next PSUR).*

- The PRAC Rapporteur requested a review on the outcome of myocarditis/pericarditis cases following Comirnaty exposure. The review should include not only case reports, but also any data from (observational) studies and published literature. Furthermore, please provide the MAH's position on whether the current PI wording remains appropriate or if an update of the PI is warranted, in which case please provide a PI update proposal.

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

Signal Overview

New signals for BNT162b2 during the reporting interval are presented below in Table 51 along with the ongoing signals and signals closed during the reporting interval.

It should be noted that review of safety topics and evaluation of signals also take into consideration safety data available for original and bivalent presentations of BNT162b2.

Appendix 3 provides a summary of the safety signals that were new, ongoing, or closed during the reporting interval. See Section 16.2.1 *Evaluation of Closed Signals* for evaluation of signals that were closed during the reporting interval and Section 16.3 *Evaluation of Risks and New Information* for evaluation of new information for previously known risks not considered to constitute a newly identified signal.

Table 51. Overview of Signals (at DLP 18 December 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Pemphigus and Pemphigoid	New and ongoing	Enquiry from a competent authority (EMA PRAC)	Not applicable	EPITT No. 19859
Dizziness	New and closed	Enquiry from a competent authority (EMA PRAC)	Adverse reaction (i.e., identified risk)	EMEA/H/C/PSUSA/00010898/202112
Haemophagocytic lymphohistiocytosis (HLH)	New and closed	Other: Routine safety surveillance	No risk	-
Dermatomyositis	New and closed	Other: Routine safety surveillance	No risk	-
Histiocytic necrotizing lymphadenitis (HNL)	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	EMA/PRAC/689208/2022 EPITT: no: 19835
Genital (vulvovaginal) ulceration	New and closed	Enquiry from a competent authority (Australia TGA and EMA PRAC)	No risk	EPITT No. 19840
IgA nephropathy	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	-
Acquired haemophilia	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	-
Hearing loss	New and closed	Enquiry from a competent authority (Health Canada and EMA PRAC)	No risk	-

* Reflects the MAH position in the MAH signal log. This may differ from the position of the competent authority.

Other Safety Topics Not Considered Signals

EMA requested or recommended in assessment reports, the continued monitoring or cumulative review of the following safety topics that neither EMA nor the MAH considered to be validated safety signals. Factors considered in this categorization included one or more of the following:

- Whether the AE is new for the product;
- Seriousness, severity, increased frequency or medical significance of the data;
- High or rapidly increasing statistical disproportionality score;
- Potential public health impact;
- Factors suggestive of a relationship to the drug when considering disease knowledge, biological plausibility, mechanism of action of the drug or the drug class, alternative aetiologies based on clinical and scientific experience, and temporal clustering of events.

The safety topics monitored or reviewed are the following:

- Multisystem Inflammatory Syndrome (Appendix 5.6.1);
- Dyspnoea; Palpitations, Tachycardia/Heart Rate Increase (Appendix 5.6.2);
- Subacute thyroiditis[52] (Appendix 5.6.3).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 52 summarises the important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU-RMP version 5.0 adopted on 10 March 2022 (Procedure number: EMEA/H/C/005735/II/0087).

Table 52. Ongoing Safety Concerns at the Beginning of the Reporting Period

Important identified risks	Anaphylaxis[a]
	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

[52] Cumulative review of subacute thyroiditis was requested by Australian TGA.

Table 52. Ongoing Safety Concerns at the Beginning of the Reporting Period

a. After DLP of the PSUR #3, the important identified risk of anaphylaxis was removed from the list of safety concerns in RMP version 5.1 (procedure EMEA/H/C/005735/X/0138). Therefore, MAH's proposal was accepted to remove the important identified risk of anaphylaxis from the list of safety concerns for the next PSUR reporting period (4th PSUR), because anaphylaxis is a known risk of vaccines that is adequately being managed by HCPs who administer vaccines and the vaccinees in daily practice.

During the reporting period, the MAH submitted the following versions of the EU-RMP:

1. Version 5.1 submitted on 08 July 2022 (Procedure Number: EMEA/H/C/005735/X/0138) and approved on 19 October 2022:

    - to include 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 of COMIRNATY® 3 µg Concentrate for dispersion for injection for infants and children between 6 months to 4 years of age;

    - to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received on March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087).

2. Version 6.0 submitted on 19 July 2022 (Procedure Number: EMEA/H/C/005735/II/0140) and approved on 01 September 2022:

    - To support the extension of the indication to ≥12 years of age to receive an additional booster (fourth) dose of bivalent Omicron-modified vaccine (Comirnaty Original/ Omicron BA.1 [15/15µg]).

3. Version 7.0 submitted on 15 August 2022 (Procedure Number: EMEA/H/C/005735/II/0143) and approved on 12 September 2022:

    - To support the extension of the indication to ≥12 years of age to receive a booster dose of bivalent Omicron-modified vaccine (Comirnaty Original/Omicron BA.4/BA.5 [15/15 µg]), given ≥4 months after the third dose.

4. Version 7.2 submitted on 15 August 2022 (Procedure Number: EMEA/H/C/005735/II/0147) and approved on 10 November 2022:

    - To support the extension of the indication to 5-11 years of age to receive a booster dose of bivalent Omicron-modified vaccine (Comirnaty Original/Omicron BA.4-5 [5/5 µg]) given at least 4 months after a primary vaccination course against COVID-19.

5. Version 8.0 submitted on 15 August 2022 (Procedure Number: EMEA/H/C/005735/X/0138) and approved on 19 October 2022:

    - To consolidate the EU-RMP version by merging EU-RMP v 5.1 and 7.1

6. Version 9.0 submitted on 03 November 2022 (Procedure number: EMEA/H/C/005735/X/0147):

    - To consolidate the EU-RMP version by merging EU-RMP v 7.2 and 8.0.

    - To address the PRAC preliminary assessment request to remove Myocarditis and Pericarditis, and Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) as safety concerns in study C4591048.

    - To reclassify the clinical trials C4591001 and C4591007 from category 2 to category 3 studies following the renewal approval with cMA conversion to standard MA (R-0137, EC decision: 10 October 2022).

Please refer to Section 16.4 *Characterisation of Risks*, for the MAH proposal to update the list of the safety concerns in the EU-RMP.

16.2. Signal Evaluation

Please refer to Table 51 for signals that were ongoing and closed during the reporting interval.

Signals assessed in an EMA regulatory procedure during the reporting period

In accordance with the core PSUR19 guidance,[53] the conclusions of the evaluations of Dizziness, Histiocytic necrotizing lymphadenitis (HNL) and Vulval ulceration are briefly reported below. Full reviews are available in Appendix 5.3.1 and Appendix 5.3.3, respectively.

Following review of the totality of available information, including the relatively low number of post-authorization reports for these events in the context of >2 billion BNT162b2 doses administered, and the approximately 1.7 million BNT162b2 adverse event cases in the safety database,

- Based on the review of the clinical trial data and of the post-marketing setting, it has been determined that dizziness should be considered an ADR to BNT162b2 (Section 4.8 of the company CDS has been updated accordingly). Subsequent changes to local labels, including the SmPC, have taken place per Pfizer process. The favourable benefit risk profile of Comirnaty for authorized age groups is unchanged by this information.

- the lack of clear mechanism by which the vaccine could cause HNL, a condition which in and of itself does not have a clear pathogenesis, and the available data do not allow a conclusion that Comirnaty causes HNL. The latency (days to months) from vaccination is noted but is not sufficient information from which to conclude causality. Based on this

[53] https://www.ema.europa.eu/en/documents/scientific-guideline/consideration-core-requirements-psurs-COVID-19-vaccines_en.pdf

and in the context of the individual and public health benefits of vaccination, there is no need to update the labelling or risk management documents at this time and routine signal detection activities will continue.

- Overall, there remains insufficient evidence to conclude a causal association between vulvovaginal ulcerations and Comirnaty. Therefore, no updates to the PI or labelling are warranted at this time. The topic will continue to be monitored by routine pharmacovigilance.

Signals not assessed in an EMA regulatory procedure

Please refer to Section 16.2.1 and to Section 16.2.2 for the detailed evaluation of HLH, dermatomyositis, IgA nephropathy, acquired haemophilia and hearing loss.

16.2.1. Evaluation of Closed Signals

Table 53 provides the summary evaluations of the signals closed during the reporting period. Routine signal detection continues.

Table 53. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined not to be risks	
Haemophagocytic lymphohistiocytosis (HLH)	HLH was identified as a signal during the reporting period based on routine signal detection that identified the report of this serious adverse event in 1 participant in a pivotal Pfizer-run COVID-19 vaccine clinical trial C4591001 (assessed by investigator as not related) and in a participant of a dermatomyositis study who reported receiving BNT162b2 vaccine. The participant in the COVID-19 vaccine clinical trial had HLH 9 months following dose three and was found to have EBV. There were no other reports of HLH in C4591001 nor in the paediatric pivotal clinical trial C4591007 in participants <12 years of age. There were no relevant literature publications regarding HLH and BNT162b2. The Pfizer safety database search through 22 Sep 2022 for all BNT162b2 reports of PT Haemophagocytic lymphohistiocytosis (MedDRA v. 25.0) retrieved 103 reports, the overwhelming majority of which (99) had insufficient information, confounding factors, alternative causes or questionable diagnoses of HLH. Age-stratified O/E analyses were conducted using 21- and 42-day risk intervals and the age bands of 12-17 and 18-4 had O/E >1 (respectively: 1.082 [0.351-2.526] and 1.7 [0.693-3.549]) but the interpretation is severely limited by the small number of cases. A causal mechanism is not evident. Overall, based on the totality of available information, a causal association between HLH and BNT162b2 was not concluded.
Dermatomyositis	Dermatomyositis was identified as a signal during the reporting period based on awareness from Pfizer colleagues about a participant in a Pfizer-sponsored non-vaccine placebo-controlled clinical trial of an IMP for the treatment of dermatomyositis who attributed [redacted] dermatitis to BNT162b2. In C4591001, the pivotal Pfizer-run clinical trial for ages 12 and older, there were no reports of dermatomyositis or of flares of dermatomyositis in the placebo-controlled periods or in those participants with 6 months of follow-up after 2 doses. Of note, 1 participant in the BNT162b2 group and 2 in the placebo group had medical histories of dermatomyositis. In study C4591024 (Phase 2b open label study of BNT162b2 in immunocompromised participants), a [redacted]-year-old participant with a

Table 53. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	medical history of dermatomyositis had a flare requiring hospitalization and treatment, however this occurred approximately 2.5 months following dose 2 of BNT162b2. The literature review retrieved 20 relevant publications, mainly case reports, and 1 retrospective study in 402 COVID-19 vaccinated subjects with autoimmune skin disease. The authors noted that self-reports of flares requiring escalation in treatment in <7% of the subjects did not alter the favourable benefit/risk of vaccination in subjects with autoimmune diseases. The Pfizer safety database search through 13 Sep 2022 for all BNT162b2 reports of PT Dermatomyositis (MedDRA v. 25.0) retrieved 127 reports, comprised of 64 cases of alternative potential causes and risks for dermatomyositis and 49 cases with insufficient detail for assessment; 14 cases had with no obvious aetiology for the event. A causal mechanism is not evident. Age and sex stratified O/E analyses were conducted for 21- and 42-day risk window and ratios were all well below 1. Overall, based on the totality of available information, there was not adequate evidence to support a causal association between dermatomyositis and BNT162b2.
Histiocytic necrotizing lymphadenitis (HNL)	HNL was identified as a signal during the reporting period following notification from EMA PRAC. Please refer to Appendix 5.3.1.
Genital (vulvovaginal) ulceration	Genital (vulvovaginal) ulceration was initially reviewed and concluded not to be a valid signal by the MAH prior to notification from the EMA PRAC on 02 September 2022 via a signal assessment report and a request for a cumulative review of information. At the request of EMA PRAC, a cumulative review (DLP 15 August 2022) was conducted. There were no relevant cases in placebo-controlled periods of the Pfizer-conducted pivotal adult and paediatric clinical trials C4591001 and C4591007. The medical literature was reviewed and consisted of case reports of this rare condition. The Pfizer safety database search through 15 August 2022 for all BNT162b2 reports of PT Genital ulceration, Vulval ulceration, Vaginal ulceration, Vulvovaginal ulceration or Vulvar erosion (MedDRA v. 25.0) retrieved 165 reports, 3 of which were in males, 6 with alternative explanations for the occurrence of genital ulceration, 13 confounded by either medical history of previous ulcerating disorders, 21 without a reported latency from vaccination, and 45 with insufficient clinical detail for adequate assessment or incomplete infectious work-ups for the most common causes of genital ulcerations. The event has a poorly understood aetiology and pathophysiology and is a diagnosis of exclusion and there were a very small number of cases with a high certainty of the correct diagnosis and temporality with vaccination. Overall, there was insufficient evidence to conclude a causal association with BNT162b2 vaccine. The PRAC Rapporteur endorsed the position that there is not sufficient evidence to conclude a causal association between vulval ulceration and Comirnaty exposure and requested for the next PSUR a review of additional cases from 16 August 2022, medical literature and O/E analyses if applicable. Please see Appendix 5.3.3. for this updated information.
IgA nephropathy	In the Assessment Report for PSUR #2, EMA/PRAC requested a cumulative review of cases reporting IgA nephropathy. The review was submitted with PSUR #3 and described a brief history of the previous surveillance and reviews on glomerulonephritis and nephrotic syndrome conducted for Comirnaty. The Pfizer safety database search through 30 June 2022 for all BNT162b2 reports of PT IgA nephropathy and for cases with a medical history of IgA nephropathy coded with PT Condition aggravated (MedDRA v. 25.0) retrieved 103 reports, the majority of which reported new onset IgA nephropathy rather than an aggravation of IgA nephropathy in the context of a medical history of the same. Latency varied from 2 to 263 days and was reported after the 1st, 2nd and 3rd doses of vaccine. Eliminating the group of reports with insufficient information on latency, history and clinical

Table 53. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	details, left fewer cases for review and only 28 where a biopsy was mentioned and fewer still where biopsy results provided a definitive diagnosis. The age, sex and dose-stratified O/E analyses using 7-, 14- and 21-day risk windows were unsupportive of the event being higher than expected. Overall, this information considered with the lack of signal in the clinical trials, literature publications comprising mainly case reports and one small prospective study in patients with IgA nephropathy suggesting no impact of vaccination on clinical course and no clear mechanism, there was insufficient evidence to conclude a causal association.
Acquired haemophilia	In the Assessment Report for PSUR #2, EMA/PRAC requested a cumulative review of cases reporting acquired haemophilia to be submitted with PSUR #3. The Pfizer safety database search through 18 June 2022 for all BNT162b2 reports of PTs under the HLT of Coagulation factor deficiencies (MedDRA v. 25.0) retrieved 68 reports, equally divided between males and females and occurring after the 1st, 2nd, and 3rd doses of vaccine. The majority of cases were in elderly patients (>65 years) and contained insufficient information surrounding the event and diagnosis or elements (such as medical conditions or concomitant medications) confounding the interpretation of the role of vaccine. There were no relevant published literature articles and no cases in the clinical trials. The age-stratified O/E analysis using 21- and 42-day risk windows were not supportive of the event being higher than expected. Overall, the totality of available information did not support a causal association between vaccination and acquired haemophilia.
Hearing loss	In the Assessment Report for the Summary Bimonthly Safety Report #3, both EMA/PRAC and Health Canada requested a cumulative review of hearing loss to be submitted with PSUR #3. The Pfizer safety database search through 18 June 2022 for all BNT162b2 reports of the following PTs: Conductive deafness, Deafness, Deafness bilateral, Deafness neurosensory, Deafness occupational, Deafness permanent, Deafness transitory, Deafness unilateral, Hypoacusis, Mixed deafness, Neurosensory hypoacusis, Sudden hearing loss (MedDRA v. 25.0); 3177 cases were retrieved and >97% of cases where age was reported were in adults. Of >2000 cases describing a latency of 0-21 days post vaccination, 433 had medical conditions representing potential alternative causes of decreased hearing. Others described use of concomitant or co-suspect medication potentially confounding assessment of the cases. Of the cases that were medically confirmed, the same was true while there were a minority of cases in which no alternative reason for the development of hearing loss was evident. In the placebo-controlled period of pivotal clinical trial C4591001 (DLP 13 March 2021), there were 12 participants who reported hearing loss events; 9/23,037 (0.04%) were in the placebo group and 3/23,040 (0.01%) were in the BNT162b2 group. In the placebo-controlled period of clinical trial C4591007 (DLP 06 September 2021), there were 3/750 participants who reported hearing loss events in the placebo group; there were none reported in the BNT162b2 group (1518 participants). Excepting case reports, the few published retrospective observational studies do not show a clear correlation between COVID-19 vaccination and hearing loss. The age and sex-stratified O/E analyses using 21- and 42-day risk windows were all <1. Overall, the totality of available information was not supportive that there is a causal association between Comirnaty and hearing loss.
Risks Not Categorized as Important	
Dizziness	Dizziness outside of the context of vaccination anxiety/stress-related reactions was identified as a signal and cumulatively reviewed. The Pfizer safety database search through 18 June 2022 for all BNT162b2 reports of PT Dizziness (MedDRA v. 25.0) retrieved 96,959 reports, most of which were non-serious and occurred on the day of (Day 0) or after (Day 1) of vaccination. There were 5563 reports of dizziness that

Table 53. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	occurred with a time to onset of 2-21 days, mostly in the 32–64-year-old age groups. Serious events of dizziness were most frequently co-reported with events largely consistent with systemic reactogenicity events. In the pivotal clinical trial (C4591001) placebo-controlled portion, dizziness was uncommonly reported and there was no imbalance between the placebo group and vaccination group. At the time of assessment, approximately 6% of spontaneously reported AE reports for BNT162b2 were cases of dizziness. Focus on the most clinically important cases shows a similar pattern with most events occurring within a few days of vaccination and co-reported with events that are recognized reactogenicity events and stress-related responses to the vaccination process. Based on the totality of the data, the MAH determined that dizziness should be considered an adverse reaction of BNT162b2 (Appendix 1.1).

16.2.2. Signal Evaluation Plan for Ongoing Signals

The table below provides the evaluation plan for signals in which the evaluation was still ongoing (i.e., not closed) at the cut-off date of this PSUR.

Table 54. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Pemphigus and Pemphigoid	Following receipt of an EMA PRAC adopted recommendation (EMA/PRAC/868335/2022) for this signal on 01 December 2022, it was under evaluation by the MAH at the cut-off date of this PSUR (18 December 2022). The requested cumulative review and response to the list of questions will be submitted to EMA in a 60-day timetable.

16.3. Evaluation of Risks and New Information

Evaluation of new information for previously recognised important identified and important potential risks, other risks (not categorised as important), special situations, and special patient populations for BNT162b2 is provided below in Section 16.3.1, Section 16.3.2, Section 16.3.3, Section 16.3.4 and Section 16.3.5, respectively.

16.3.1. Evaluation of Important Identified Risks

In the PRAC AR of the PSUR #3 (EMEA/H/C/PSUSA/00010898/202206), the following request was made: *The MAH should focus the analysis of myocarditis/pericarditis cases on aspects of these ADRs not fully known or addressed in the Comirnaty product information (myocarditis/pericarditis is already an ADR stated in section 4.8), and if the warning in section 4.4 regarding myocarditis/pericarditis is "still in line with current knowledge. Therefore, the myocarditis/pericarditis analysis should focus more on information concerning the course, outcome, and possible risk factors of the myocarditis/pericarditis cases following Comirnaty exposure.*

In the AR of the type II variation EMEA/H/C/005735/II/0140, *the MAH is expected to continue monitor and better quantify the risk of myocarditis and pericarditis in the 5-11*

years of age group and following the booster dose(s) and discuss any relevant findings in the upcoming PSUR. The Rapporteur should be notified immediately in case of unexpected findings or trend.

Response

Please refer to Section 16.3.1.1.1 and Section 16.3.1.1.2, respectively.

After DLP,

- in the preliminary AR for variation EMEA/H/C/005735/II/0139, EMA requested the MAH to *present a cumulative review of all myocarditis and pericarditis cases with fatal outcome that have been reported with the vaccine*;
- the PRAC Rapporteur requested *a review on the outcome of myocarditis/pericarditis cases following Comirnaty exposure. The review should include not only case reports, but also any data from (observational) studies and published literature.*

The MAH is requested to evaluate whether the current PI/SmPC wording remains appropriate or if an update of the PI/SmPC is warranted.

Response

The MAH will provide this review in a separate supplemental document.

Evaluation of incremental data for the important identified risks Myocarditis and Pericarditis is provided below.

16.3.1.1. Important Identified Risks – Myocarditis and Pericarditis

There were 1951 potentially relevant cases of Myocarditis and Pericarditis: 1287 cases reported myocarditis and 796 cases reported pericarditis (in 132 of these 1951 cases, both myocarditis and pericarditis were reported).

For the incremental evaluation of Myocarditis and Pericarditis cases, please refer to Section 16.3.1.1.1 and Section 16.3.1.1.2, respectively.

Literature Data

During the reporting period significant information on myocarditis was reviewed. Please refer to Section 11 *Literature* for details.

Risk Assessment of New Information

Based on the interval data, no new safety information was identified pertaining to the risk of myocarditis and pericarditis with BNT162b2.

This risk is communicated in the BNT162b2 CDS, in

– Section 4.4, General recommendations, which includes information on appropriate action to be taken, as follows: "Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients".[54]

– Section 4.8, Undesirable effects as adverse drug reaction in the post-authorisation experience.

This risk will continue to be monitored through routine pharmacovigilance.

16.3.1.1.1. Important Identified Risks – Myocarditis

Search criteria[55] - PTs: Autoimmune myocarditis; Carditis; Chronic myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Myopericarditis.

Overall – All Ages

Clinical Trial Data

- Number of cases: none, compared to 1 case of BNT162b2 (0.15%) retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 1287 (original [1251], original + Omi BA.1 [17], original + Omi BA.4/BA.5 [19]) (0.5% of 282,992 cases of the total PM dataset), compared to 5422 cases (1.1%) retrieved in the PSUR #3.
- Country/region of incidence (≥10): Germany (394), Canada (124), Japan (90), Australia (86), United States (73), United Kingdom (70), France (57), Austria (51), Italy (38), Poland, Sweden (32 each), Taiwan, Province of China (27), Hong Kong (26), Malaysia, New Zealand (17 each), Greece (14), Israel (13), Netherlands (12), Denmark (11), Slovakia (10). The remaining 93 cases were distributed among 29 countries.

[54] Myocarditis and pericarditis are listed in Section 4.8 of the EU-SmPC.

[55] The SMQ (narrow) Noninfectious myocarditis/pericarditis that became available upon the up-versioning to MedDRA v. 25.0 is used as search criteria. In the up-versioning to MedDRA to 25.1, a new PT was added to the SMQ (Immune-mediated pericarditis) and is now included in the evaluation of pericarditis.

- MC (723), NMC (564).
- Subjects' gender: female (431), male (787) and unknown (69).
- Subjects' age in years: n = 1116, range: 6 – 96, mean: 38.3, median: 35.0.
- Medical history (n = 449); the most frequently (≥10) reported medical conditions included Hypertension (62), Seasonal allergy (47), Asthma (36), Obesity (33), Drug hypersensitivity, Myocarditis (21 each), Depression (19), Type 2 diabetes mellitus (19), Hypersensitivity (18), Mite allergy (17), Non-tobacco user (16), Tobacco user (15), Autoimmune thyroiditis (12), Ex-tobacco user (11).
- COVID-19 Medical history (n = 59): COVID-19 (43), Suspected COVID-19 (13), Coronavirus infection (2), COVID-19 pneumonia, SARS-CoV-2 test positive (1 each).
- Co-suspect medications (>2): elasomeran (18), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine (3 each).
- Number of relevant events: 1329.
- Relevant event seriousness: serious (1329).
- Reported relevant PTs: Myocarditis (1062), Myopericarditis (246), Carditis, Eosinophilic myocarditis (6 each), Immune-mediated myocarditis (4), Giant cell myocarditis, Hypersensitivity myocarditis (2 each), Chronic myocarditis (1).
- Relevant event outcome[56]: fatal (46), resolved/resolving (482), resolved with sequelae (65), not resolved (314), unknown (424).
- Risk factors: Of the 1287 cases reporting events indicative of myocarditis, 723 cases (56.1%) were medically confirmed. Of the 1287 cases, in 239 cases (18.6% of the cases reporting myocarditis related events) the events were confounded by subject' s relevant medical history such as cardiac disorders, neoplasms, COVID-19, immune disorders, embolic disorders etc and/or relevant co-suspect medications. Of the total 1287 cases, in 346 cases (26.9 %) the cases were confounded by co-reported events indicative of an alternate etiology, such as neoplasms, ischaemic cardiomyopathy/coronary artery disease, infections, or the long time to onset of the myocarditis event post-vaccination (>21 days) did not match a suspected vaccine induced event. Of the 1287 cases, in 956 cases (74.3%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

[56] Multiple episodes of the same event were reported with different clinical outcomes within some cases hence the sum of the event outcomes exceed the total number of events.

Age-stratified data[57]

Subjects aged less than 5 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Subjects aged 5 – 11 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 18 (original [18]) (0.01 % of 282,992 cases of the total PM dataset, 0.4 % of the 4991 subjects aged 5-11 years), compared to 48 cases (0.01 %) retrieved in the PSUR #3.
- Country/region of incidence: Canada (5), Taiwan, Province of China (3), Hong Kong, Hungary (2 each), [redacted] (1 each).
- Subjects' age in years: n = 14, range: 6 – 11, mean: 9.1, median: 9.0.
- Medical history (n = 1): Bronchopulmonary dysplasia, Congenital hypothyroidism, Eosinophilia, Feeding disorder, Fracture, Inguinal hernia, Low birth weight baby, Osteopenia, Premature baby, Renal tubular dysfunction, Retinopathy of prematurity, Surgery (1 each).
- COVID-19 Medical history (n = 1): Suspected COVID-19 (1).
- Co-suspect medications: None.
- Most frequently co-reported PTs (>1): Chest pain (5), Chest discomfort (4), Product administered to patient of inappropriate age, Pyrexia (3 each), Dyspnoea, Overdose (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised the table below.

[57] Cases where the age was reported as:
- "Child" (4 cases) were evaluated in the overall and in the 5-11 years of age groups,
- "Adolescent" (11 cases) were evaluated in the overall and in the 16-17 years of age groups,
- "Adult" (63 cases) were evaluated in the overall and in the Age Unknown group; and
- "Elderly" (3 cases) were evaluated in the overall and in the ≥ 40 years of age groups.

Table 55. Myocarditis in Subjects aged 5 – 11 Years (N=18)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	6	2
	No	2	5	1
Relevant PT[a]	Myocarditis	3	9	3
	Myopericarditis	1	3	0
Hospitalisation required/prolonged	Yes	1	7	0
	No	3	4	3
Relevant suspect dose	Dose 1	2	2	0
	Dose 2	2	9	0
	Unknown	0	0	3
Original		4	11	3
Original + Omi BA.4/BA.5		0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=12	≤ 24 hours	2	3	0
	1-5 days	0	3	0
	6-13 days	1	1	0
	>14 days	0	2	0
	Unknown	1	3	3
Event Outcome	Fatal	1	0	0
	Not resolved	0	1	0
	Resolved	2	7	
	Resolving	0	3	0
	Unknown	1	1	3
Duration of event[b]	Unknown	2	7	0

a. All serious occurrences.
b. For those cases where the event resolved; there were no events which resolved with sequelae.

Fatal case (1)

An [redacted] subject, dose 2, medically confirmed, [redacted]

- Medical History: No relevant medical history
- Co-suspect medications: None reported
- PTs with fatal outcome: Myocarditis, Altered state of consciousness, Cardiac arrest
- Time to onset (myocarditis): 0 days
- Causes of death: suspected myocarditis. Autopsy performed, reported cause of death as suspected myocarditis, no further details
- Comment: The subject was initially discharged from hospital for unknown reasons and re-admitted 3 days later in cardiac arrest. The subject received cardiac pulmonary cerebral resuscitation, extracorporeal membrane oxygenation (ECMO), continuous venovenous hemofiltration and was admitted in ICU. The brain CT showed diffuse brain

swelling, laboratory tests showed metabolic acidosis and cardiac enzyme elevation, and subject was diagnosed with fulminant myocarditis (BC level 1). Viral tests were negative. It was reported that subject was 'kept on antibiotics', namely vancomycin and ceftazidime, however the reasons for antibiotic administration were not provided. The fatal outcome occurred upon family agreement to discontinue ECMO. Autopsy reported the cause of death as suspected myocarditis, but no further information on histopathological findings was provided. There are important data regarding the clinical context that are missing in this case, such as the reasons for the original hospitalization or rationale for antibiotic administration; until such information becomes available, on a conservative approach, the role of vaccine in inducing the myocarditis event, and the event leading to fatal outcome cannot be ruled out.

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 88 (original [85], original + Omi BA.1 [2], original + Omi BA.4/BA.5 [1]) (0.03 % of 282,992 cases of the total PM dataset, 2.2 % of the 3977 subjects aged 12-15 years), compared to 366 cases (0.07%) retrieved in the PSUR #3.
- Country/region of incidence (≥2): Japan (15), Taiwan, Province of China (14), Germany (8), Canada (7), Hong Kong, Malaysia (6 each), United States (5), Latvia (4), Italy, Poland, Sweden (3 each), France, Philippines (2 each). The remaining 10 cases were distributed among 10 countries.
- Subjects' age in years: n = 88, range: 12 – 15, mean: 13.8, median: 14.0.
- Medical history (n = 20); the most frequently (≥2) reported medical conditions included Mite allergy, Seasonal allergy (3 each), Allergy to metals, Dermatitis contact, Hypersensitivity, Rhinitis allergic (2 each).
- COVID-19 Medical history: None.
- Co-suspect medications: colecalciferol (2), azathioprine, ivabradine, metoprolol, pantoprazole, prednisolone (1 each).
- Most frequently co-reported PTs (≥5): Chest pain (35), Pyrexia (28), Dyspnoea (17), Headache (13), Chest discomfort (9), Dizziness (8), Electrocardiogram ST segment elevation, Malaise, Palpitations, Pericarditis, Vomiting (6 each), Fatigue, Tachycardia (5 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 56 below.

Table 56. Myocarditis in Subjects aged 12 – 15 Years (N=88)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	7	15	0
	No	14	51	1
Relevant PT[a]	Myocarditis	19	54	1
	Myopericarditis	2	17	0
Hospitalisation required/prolonged	Yes	11	50	0
	No	10	16	1
Relevant suspect dose	Dose 1	3	6	0
	Dose 2	10	19	1
	Dose 3	3	30	0
	Dose 4	0	1	0
	Dose Unknown	5	10	0
Original		21	63	1
Original + Omi BA.1		0	2	0
Original + Omi BA.4/BA.5		0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=54	≤ 24 hours	1	6	0
	1-5 days	2	29	0
	6-13 days	3	2	0
	14-25 days	2	3	0
	26-229 days	3	3	0
	Unknown	10	29	1
Event Outcome	Fatal	0	0	0
	Not resolved	1	7	0
	Resolved	6	33	1
	Resolved with sequelae	2	1	0
	Resolving	5	16	0
	Unknown	7	14	0
Duration of event[b] n=14, median=8 days	Up to 3 days	0	2	0
	4-6 days	0	2	0
	7-25 days	0	7	0
	26-230 days	1	2	0

a. All serious occurrences.
b. For those cases where the event resolved/resolved with sequelae.

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 79 (original [78], original + Omi BA.1 [1] (0.03 % of 282,992 cases of the total PM dataset, 2.6 % of the 3093 subjects aged 16-17 years), compared to 345 cases (0.07%) retrieved in the PSUR #3.

- Country/region of incidence (≥3): United States (11), Germany (10), Canada (8), Japan, Taiwan, Province of China (6 each), Israel, Poland (5 each), Australia, Hong Kong, Italy (4 each), Brazil, Denmark (3 each). The remaining 10 cases were distributed among 7 countries.
- Subjects' age in years: n = 68, range: 16 – 17, mean: 16.5, median: 17.0.
- Medical history (n = 24); the most frequently (≥2) reported medical conditions included Obesity (6), Asthma, Chest pain (3 each), Drug hypersensitivity, Hospitalisation, Hypersensitivity, Mite allergy, Myocarditis, Seasonal allergy (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: doxycycline, triheptanoin (1 each).
- Most frequently co-reported PTs (>2): Chest pain (22), Pyrexia (16), Dyspnoea (9), Palpitations (7), Headache (5), Chest discomfort, Dizziness, Pericarditis, Troponin increased (4 each), Asthenia, Fatigue, Hyperhidrosis, Myocardial necrosis marker increased, Nausea (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 57 below.

Table 57. Myocarditis in Subjects aged 16 – 17 Years (N=79)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	8	53	2
	No	3	13	0
Relevant PT[a]	Myocarditis	7	49	2
	Myopericarditis	4	21	0
Hospitalisation required/prolonged	Yes	6	53	2
	No	5	13	0
Relevant suspect dose	Dose 1	1	8	0
	Dose 2	5	35	1
	Dose 3	3	13	1
	Dose Unknown	2	10	0
Original		11	65	2
Original + Omi BA.1		0	1	0
Original + Omi BA.4/BA.5		0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=38	≤24 hours	4	2	
	1-5 days	2	18	1
	6-80 days	1	4	1
	81-334 days	0	3	0
	Unknown	4	43	0
Event Outcome	Fatal	0	1	0
	Not resolved	2	6	0
	Resolved	3	35	0
	Resolved with sequelae	1	1	0
	Resolving	3	7	2
	Unknown	2	20	0

Table 57. Myocarditis in Subjects aged 16 – 17 Years (N=79)

Duration of event[b] n=8, median= 6 days	Up to 3 days	0	2	0
	4-6 days	0	3	0
	7-28 days	0	1	0
	29-168 days	1	1	0

a. All serious occurrences.
b. For those cases where the event resolved/ resolved with sequelae.

Fatal case (1)

A [redacted] subject, dose 1, non-medically confirmed, [redacted]:

- Medical history: No relevant medical history
- Co-suspect medications: None
- PTs with fatal outcome: Infection, Pulmonary Oedema, Myocarditis
- Time to onset (myocarditis): 4 months
- Causes of death: myocarditis. Autopsy performed, reports lymphocytic myocarditis, no further details
- Comment: Limited information reported – the subject who received one dose of vaccine 4 months prior to event, collapsed at a soccer game. In spite of CPR, the subject expired. Myocarditis is assessed as BC level 1 due to autopsy report. In view of long latency from the vaccination and the concurrent infection and pulmonary oedema, the role of the vaccine in inducing myocarditis is unlikely. Death unlikely related or a consequence to myocarditis event alone, given concurrent events at the time of death.

Subjects aged 18 – 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 199 (original [197], original + Omi BA.1 [1], original + Omi BA.4/BA.5 [1]) (0.07 % of 282,992 cases of the total PM dataset, 1.1 % of the 18410 subjects aged 18-24 years), compared to 968 cases (0.2%) retrieved in the PSUR #3.
- Country/region of incidence (≥5): Germany (55), United States (18), Austria (14), Australia, Japan (13 each), France (11), Poland (10), United Kingdom (8), Canada, Hong Kong (7 each), Israel, Sweden (5 each). The remaining 33 cases were distributed among 18 countries.
- Subjects' age in years: n = 199, range: 18 – 24, mean: 20.9, median: 21.0.
- Medical history (n = 51): the most frequently (≥2) reported medical conditions included Asthma, Seasonal allergy (8 each), Non-tobacco user (7), Myocarditis, Obesity, Tobacco

user (3 each), Abstains from alcohol, Allergy to animal, Coeliac disease, Dust allergy, Food allergy, Hypertension, Mite allergy (2 each).

- COVID-19 Medical history (n = 6): COVID-19 (4), Suspected COVID-19, SARS-CoV-2 test positive (1 each).
- Co-suspect medications: elasomeran (4), belimumab (1).
- Most frequently co-reported PTs (>5): Chest pain (42), Dyspnoea (28), Fatigue (27), Pyrexia (22), Chest discomfort (18), Asthenia, Interchange of vaccine products (13 each), Headache (11), Pericarditis, Tachycardia, Troponin increased (11 each), Arrhythmia, Dizziness (10 each), Angina pectoris, Exercise tolerance decreased, Off label use, Palpitations (9 each), Cardiac failure, Malaise, Pericardial effusion (7 each), Pain (6).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 58 below.

Table 58. Myocarditis in Subjects aged 18 – 24 Years (N=199)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	17	96	8
	No	16	56	6
Relevant PT[a]	Myocarditis	25	114	14
	Myopericarditis	8	37	0
	Hypersensitivity myocarditis	0	2	0
	Immune-mediated myocarditis	1	0	0
Hospitalisation required/prolonged	Yes	12	97	6
	No	21	55	8
Relevant suspect dose	Dose 1	5	31	4
	Dose 2	11	65	4
	Dose 3	11	35	1
	Dose 4	1	1	1
	Dose Unknown	5	20	4
Original		32	151	14
Original + Omi BA.1		0	1	0
Original + Omi BA.4/BA.5		1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n= 98	≤24 hours	3	6	0
	1-5 days	3	35	6
	6-13 days	3	8	0
	14-21 days	1	5	0
	22-60 days	4	6	0
	61-120 days	1	7	0
	121-365 days	3	7	0
	Unknown	16	80	8
Event Outcome	Fatal	1	3	0
	Not resolved	9	21	1
	Resolved	5	47	3
	Resolved with sequelae	2	5	0
	Resolving	4	22	4
	Unknown	13	55	6

Table 58. Myocarditis in Subjects aged 18 – 24 Years (N=199)

Duration of event[b] n= 8, median= 10 days	Up to 3 days	1	1	0
	4-6 days	0	1	0
	7-25 days	0	3	0
	26-126 days	0	2	0

a. All serious occurrences.
b. For those cases where the event resolved/resolved with sequelae.

Fatal cases (4)

[redacted] subject, dose 3 (with dose 2 being a vector vaccine), medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: Not reported
- PTs with fatal outcome: Myocarditis, Off-label use, Interchange of vaccine products
- Time to onset (myocarditis): 87 days
- Causes of death: suspected myocarditis. Autopsy performed, results not provided
- Comment: Limited information provided, myocarditis BC level 4. In view of long latency from the vaccination, the role of the vaccine in inducing myocarditis is unlikely.

[redacted] subject, dose 2, non-medically confirmed, [redacted]

- Medical history: No relevant medical history
- Co-suspect medications: None
- PTs with fatal outcome: Cardiac arrest, Cardiac failure, Coronary artery thrombosis, Myocarditis
- Time to onset (myocarditis): Unknown
- Causes of death: Cardiac arrest, Cardiac failure, Coronary artery thrombosis, Myocarditis. Autopsy not reported
- Comment: Limited information provided in this consumer report. The case reveals the subject experienced a thromboembolic event (‘blood clots in [redacted] heart’), heart failure and was placed on waiting list for a heart transplantation. During this wait time, the subject experienced a cardiac arrest which was successfully resuscitated and [redacted] was undergoing cardiac rehabilitation and treatment with unspecified medicines. Given the concurrent embolic event and heart failure, a vaccine induced myocarditis cannot be confirmed (BC level 5). Although the circumstances of the case are unclear, the statement ‘Died on the flight and they brought [redacted] back’ suggests that the case did not result in a fatal outcome.

A [redacted] subject, dose unknown, medically confirmed, [redacted]

- Medical history: No data
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): No data
- Causes of death: No data
- Comment: This media report only includes a statement regarding a [redacted] who died from myocarditis (BC level 4). In view of the limited information reported, an assessment of the role of the vaccine in inducing the myocarditis event precluded.

A [redacted] subject, dose 3, medically confirmed, [redacted]

- Medical history: No relevant medical history
- Co-suspect medications: None
- PTs with fatal outcome: Interchange of vaccine products, Myocarditis, Circulatory collapse, Sudden death
- Time to onset (myocarditis): 3 days
- Causes of death: Circulatory collapse, myocarditis. Autopsy found inflammation and necrosis in myocardial tissue, as well as atrophy and fibrosis in cardiac tissue. Parvovirus B19 test was positive
- Comment: The subject received first 2 doses with Moderna mRNA vaccine, and dose 3 with Comirnaty. After dose 3, the subject experienced malaise, pain, pyrexia and 3 days later, the subject was found deceased. The autopsy confirmed myocarditis (BC level 1), identified lesions suggestive of a pre-existing disorder (fibrosis and atrophy), and Parvovirus B19 was positive in lung and submandibular gland. Given the known role of parvovirus in inducing myocarditis and the cardiac findings suggestive of pre-existing injury, a role of the vaccine in inducing myocarditis is unlikely.

Subjects aged 25 – 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 108 (original [105], original + Omi BA.1 [1], original + Omi BA.4/BA.5 [2]) (0.04% of 282,992 cases of the total PM dataset, 0.5 % of the 21841 subjects aged 25-29 years), compared to 519 cases (0.1%) retrieved in the PSUR #3.

- Country/region of incidence (≥2): Germany (50), Australia (8), Sweden, UK (6 each), Austria, France and Italy (5 each), Japan, Poland and US (3 each), Hong Kong (2). The remaining 12 cases were distributed among 12 countries.
- Subjects' age in years: n = 108, range: 25 – 29, mean: 27.4, median: 28.0.
- Medical history (n = 35); the most frequently (≥2) reported medical conditions included Depression, Seasonal allergy (5 each), Myocarditis (4), Atrial septal defect, Attention deficit hyperactivity disorder, Crohn's disease, Ex-tobacco user, Hypothyroidism, Migraine, Mite allergy (3 each), Antiphospholipid syndrome, Anxiety, Arthritis, Asthma, Autoimmune thyroiditis, Barrett's oesophagus, Deep vein thrombosis, Pulmonary embolism (2 each).
- COVID-19 Medical history (n = 9): COVID-19 (7), Suspected COVID-19 (2).
- Co-suspect medications: COVID-19 vaccine (2), influenza vaccine inact SPLIT 4V (1).
- Most frequently co-reported PTs (≥5): Chest pain (22), Dyspnoea (18), Fatigue, Pericarditis (16 each), Tachycardia (15), Palpitations (14), Dizziness, Pyrexia (11 each), Headache (10), Chest discomfort (9), Angina pectoris (8), Arrhythmia, Asthenia, Malaise, Pericardial effusion (7 each), Inappropriate schedule of product administration (6), COVID-19, Exercise tolerance decreased, Influenza, Pain in extremity (5 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 59 below.

Table 59. Myocarditis in Subjects aged 25 – 29 Years (N=108)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	9	37	3
	No	18	38	3
Relevant PTs[a]	Myocarditis	20	67	6
	Myopericarditis	8	9	0
	Eosinophilic myocarditis	0	2	0
Hospitalisation required/prolonged	Yes	11	34	2
	No	16	41	4
Relevant suspect dose	Dose 1	5	14	0
	Dose 2	13	24	4
	Dose 3	6	19	1
	Dose 4	0	1	0
	Dose Unknown	3	17	1
Original		26	73	6
Original + Omi BA.1		1	0	0
Original + Omi BA.4/BA.5		0	2	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n= 67	≤ 24 hours	3	4	0
	1-5 days	1	17	2
	6-13 days	3	5	0
	14-21 days	2	4	0
	22-31 days	4	3	1

Table 59. Myocarditis in Subjects aged 25 – 29 Years (N=108)

	32-60 days	2	3	0
	61-365 days	2	11	0
	Unknown	11	32	3
Event Outcome	Fatal	0	3	0
	Not resolved	12	16	0
	Resolved	4	15	1
	Resolved with sequelae	0	6	0
	Resolving	4	14	0
	Unknown	8	25	5
Duration of event[b] n=6, median= 120 days	Up to 3 days	0	1	0
	4-6 days	0	1	0
	7-198 days	1	3	0

a. All serious occurrences.
b. For those cases where the event resolved/ resolved with sequelae.

Fatal cases (3)

[redacted], dose unknown, medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): Not known
- Causes of death: Myocarditis. Autopsy not reported
- Comment: Limited information provided in this case that precludes an assessment of role of the vaccine or an assessment of the event and circumstances leading to the reported fatal outcome.

A [redacted] subject, dose unknown, non-medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): Not known
- Causes of death: reported as myocarditis. Autopsy not reported
- Comment: Limited information provided in this consumer report that precludes an assessment of with the role of the vaccine or an assessment of the event and circumstances leading to the reported fatal outcome.

[redacted] subject, dose 2, medically confirmed, [redacted]

- Medical history: COVID-19, Depression, Anxiety, Insomnia, Apathy, Asthenia, Chest discomfort
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): 5 days
- Causes of death: reported as 'ventricular arrhythmia secondary to myocarditis/severe progressive cardiac dilation and secondary arrhythmias such as ventricular fibrillation'. Autopsy found large cardiac / ventricular dilatation with probable histological myocarditis
- Comment: The subject experienced COVID-19 infection prior to vaccination, and seizures after the first vaccine dose. Regarding myocarditis, the case reports that myocarditis arose after COVID-19 infection, and evolved after the first vaccine dose and led to fatal outcome through progressive dilatation and secondary ventricular arrhythmia. The outcome occurred outside hospital and the subject could not be resuscitated. Based on the information reported, it is reasonable to consider that myocarditis development is related to prior COVID-19 disease.

Subjects aged 30 – 39 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 162 (original [156], original + Omi BA.1 [2], original + Omi BA.4/BA.5 [4]) (0.06 % of 282,992 cases of the total PM dataset, 0.3 % of the 50039 subjects aged 30-39), compared to 983 cases (0.2%) retrieved in the PSUR #3.
- Country/region of incidence (≥3): Germany (61), Australia (14), France (12), Canada, United Kingdom (10 each), Austria, Japan, United States (7 each), Poland (6), Slovakia (4), Sweden (3). The remaining 21 cases were distributed among 15 countries.
- Subjects' age in years: n = 162, range: 30 – 39, mean: 34.5, median: 35.0.
- Medical history (n = 50); the most frequently (≥2) reported medical conditions included Seasonal allergy (10), Asthma, Myocarditis (5 each), Drug hypersensitivity, Hypersensitivity (4 each), Ex-tobacco user, Mite allergy, Obesity (3 each), Allergy to plants, Cardiovascular disorder, Dyslipidaemia, Epilepsy, Epstein-Barr virus infection, Essential hypertension, Non-tobacco user, Overweight, Pericarditis, Tobacco user (2 each).
- COVID-19 Medical history (n = 13): COVID-19 (10), Suspected COVID-19 (2), Coronavirus infection, COVID-19 pneumonia (1 each).

- Co-suspect medications: elasomeran (5), clozapine, influenza vaccine, ramipril (1 each).
- Most frequently co-reported PTs (>5): Chest pain (53), Dyspnoea (36), Fatigue (25), Palpitations (20), Arrhythmia (19), Chest discomfort (18), Dizziness (17), Headache (16), Pericarditis (14), Asthenia, Pyrexia, Tachycardia (13 each), Dyspnoea exertional (10), Heart rate increased, Interchange of vaccine products (9 each), Malaise, Pain in extremity, Performance status decreased, Pericardial effusion, Troponin increased (8 each), Syncope (7), Exercise tolerance decreased, Inappropriate schedule of product administration, and Off label use (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 60 below.

Table 60. Myocarditis in Subjects aged 30 – 39 Years (N=162)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	22	55	6
	No	33	45	1
Relevant PT[a]	Myocarditis	48	91	7
	Myopericarditis	8	8	0
	Carditis	1	0	0
	Chronic myocarditis	0	1	0
	Eosinophilic myocarditis	0	1	0
	Giant cell myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	15	48	3
	No	40	52	4
Relevant suspect dose	Dose 1	17	24	4
	Dose 2	17	38	1
	Dose 3	17	18	1
	Dose 4	1	4	0
	Dose Unknown	3	16	1
Original		54	95	7
Original + Omi BA.1		0	2	0
Original + Omi BA.4/BA.5		1	3	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=90	≤24 hours	1	2	1
	1-5 days	9	19	2
	6-13 days	3	11	1
	14-21 days	2	6	1
	22-60 days	4	6	0
	61-120 days	2	6	0
	121-220 days	3	6	0
	221-365 days	2	3	0
	Unknown	31	43	2
Event Outcome	Fatal	0	5	0
	Not resolved	27	32	1
	Resolved	11	13	0
	Resolved with sequelae	1	7	0
	Resolving	2	16	0

Table 60. Myocarditis in Subjects aged 30 – 39 Years (N=162)

	Unknown	16	29	6
Duration of event[b] n=7, median=2 days	Up to 3 days	1	1	0
	4-25 days	0	2	0
	26-164 days	1	2	0

a. All serious occurrences.
b. For those cases where the event resolved/ resolved with sequelae.

Fatal cases (5)

[redacted] subject, dose 1, non-medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Cardiac discomfort; Myopericarditis
- Time to onset (myocarditis): 1 day
- Causes of death: Myocarditis. Autopsy not reported
- Comment: Limited information provided in this case that precludes an assessment of with the role of the vaccine or an assessment of the event and circumstances leading to the reported fatal outcome.

[redacted] subject, dose unknown, medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): Not known
- Causes of death: Myocarditis. Autopsy not reported
- Comment: Limited information provided in this media report that precludes an assessment of with the role of the vaccine or an assessment of the event and circumstances leading to the reported fatal outcome.

A [redacted] subject, dose 3 (first 2 Moderna vaccine), Non-medically confirmed, [redacted]

- Medical history: Hypertension, Asthma, Hypersensitivity, ECG abnormal
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis, Sarcoidosis, Interchange of vaccine products
- Time to onset (myocarditis): 239 days

- Causes of death: Autopsy showed granulomatous myocarditis and multiple findings in other organs consistent with sarcoidosis
- Comment: The subject was diagnosed with granulomatous myocarditis and sarcoidosis post-mortem. The case also reports that after last vaccine dose, the subject started to experience syncopal episodes during sport (rowing) or domestic activities and underwent cardiology consultation and tests that found severe concentric left ventricular hypertrophy, low ejection fraction (55%) and dilated atria with mitral valve prolapse; there is no reference to identification of myocarditis in these examinations post-vaccination. Given the cardiac abnormalities that are likely pre-existing, e.g., atrial dilatation, ventricular hypertrophy, and considering that subject was reportedly an athlete (rower), the role of the vaccine in inducing myocarditis is unlikely. There is no information regarding the circumstances around the fatal episode to enable a meaningful clinical assessment.

A [redacted] subject, dose 2, medically confirmed, [redacted]:

- Medical history: Not reported; unspecified ECG abnormality reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): Not known/ 4 days between vaccination and fatal outcome
- Causes of death: Autopsy found macrophage and T-lymphocyte infiltration in left ventricle and part of right ventricle.
- Comment: The subject was found deceased 4 days after vaccination and myocarditis found in autopsy examination. There is limited information regarding circumstances of the myocarditis event and clinical situation before the fatal outcome; until such information becomes available, on a conservative approach, the role of vaccine in inducing the myocarditis event, and the event leading to fatal outcome cannot be ruled out.

A [redacted] subject, dose 1, medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis, Ischaemic stroke
- Time to onset (myocarditis): 2 days
- Causes of death: Reported as ischaemic stroke and myocarditis, however the autopsy did not find myocarditis.
- Comment: The subject experienced out of hospital cardiac arrest 2 days after vaccination. The cardiologic examination revealed atrial fibrillation, severe left ventricular dysfunction with global hypokinesia, and apical thrombus. The CT with

angiography found acute ischaemic stroke which resulted in death. The reported originally suspected a post-vaccine myocarditis as the trigger of the stroke, however the autopsy did not find myocarditis, thus making a role of the vaccine unlikely.

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none, compared to 1 case of BNT162b2 (0.15%) retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 480 (original [460], original + Omi BA.1 [9], original + Omi BA.4/BA.5 [11]) (0.2 % of 282,992 cases of the total PM dataset, 0.3 % of the 149203 subjects ≥ 40 years), compared to 1752 cases (0.3%) retrieved in the PSUR #3.
- Country/region of incidence (≥5): Germany (188), Australia (39), UK (38), Japan (28), France (26), Austria, Canada (21 each), Sweden (14), US (13), Italy, New Zealand (12 each), Greece (8), Finland, Malaysia, Netherlands (5 each). The remaining 45 cases were distributed among 20 countries.
- Subjects' age in years: n = 477, range: 40 – 96, mean: 57.7, median: 55.0.
- Medical history (n = 229); the most frequently (>5) reported medical conditions included Hypertension (55), Seasonal allergy, Type 2 diabetes mellitus (19 each), Obesity (17), Asthma (14), Drug hypersensitivity (13), Depression (12), Chronic obstructive pulmonary disease, Tobacco user (9 each), Diabetes mellitus, Hypersensitivity (8 each), Atrial fibrillation, Autoimmune thyroiditis, Cardiac failure, Clinical trial participant, Hyperlipidaemia, Myocarditis (7 each), Breast cancer, Chemotherapy, Dyslipidaemia, Gastrooesophageal reflux disease, Hypercholesterolaemia (6 each).
- COVID-19 Medical history (n = 27): COVID-19 (21), Suspected COVID-19 (5), Coronavirus infection (1).
- Co-suspect medications (>1): elasomeran (9), COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19) (3), influenza vaccine, influenza vaccine inact SAG 4V, nivolumab, alverine (2 each).
- Most frequently co-reported PTs (>10): Dyspnoea (111), Fatigue (91), Arrhythmia (73), Chest pain (72), Pericarditis (55), Palpitations (50), Dizziness (44), Tachycardia (42), Chest discomfort (38), Cardiac failure (37), Pyrexia (36), Asthenia, Headache, Interchange of vaccine products (35 each), Malaise, Off label use (31 each), Atrial fibrillation (30), Pericardial effusion (29), Myalgia (28), Troponin increased (27), Hypertension (23), Cough, Nausea (22 each), Arthralgia (20), Dyspnoea exertional, Immunisation, Pain (19 each), Inappropriate schedule of product administration (18), Angina pectoris (15), Paraesthesia (14), Condition aggravated, Myocardial infarction, Syncope (13 each), Limb discomfort (12), Back pain, Disturbance in attention, Heart rate increased (11 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 61 below.

Table 61. Myocarditis in Subjects aged ≥40 Years (N=480)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	117	113	3
	No	133	113	1
Relevant PTs[a]	Myocarditis	211	194	4
	Myopericarditis	40	32	0
	Carditis	2	3	0
	Eosinophilic myocarditis	1	2	0
Hospitalisation required/prolonged	Yes	106	105	4
	No	144	121	0
Relevant suspect dose	Dose 1	63	48	1
	Dose 2	67	61	1
	Dose 3	62	74	1
	Dose 4	32	13	0
	Dose 5	1	3	0
	Dose Unknown	25	27	1
Original		237	219	4
Original + Omi BA.1		6	3	0
Original + Omi BA.4/BA.5		7	4	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=266	≤24 hours	19	6	0
	1-5 days	35	30	0
	6-13 days	20	20	0
	14-21 days	17	18	0
	22-31 days	12	10	2
	32-60 days	14	14	0
	61-220 days	13	25	0
	221-365 days	4	7	0
	Unknown	120	101	2
Event Outcome	Fatal	12	17	0
	Not resolved	80	66	0
	Resolved	26	35	1
	Resolved with sequelae	16	21	1
	Resolving	47	30	0
	Unknown	73	63	2
Duration of event[b] n=27, median=85 days	Up to 3 days	0	1	0
	4-6 days	1	1	0
	7-25 days	1	2	0
	26-180 days	4	9	0
	181-607 days[c]	5	3	0

a. All serious occurrences.
b. For those cases where the event resolved/ resolved with sequelae.
c. Of the 8 cases that reported long duration of myocarditis (from 181-607 days), in 2 cases the event resolved without any complications. Of the remaining 6 cases where the relevant event resolved with sequelae, 3 cases reported development of cardiac failure, 2 cases reported arrhythmia and the remaining case reported development of pericardial effusion along with myocarditis.

Fatal cases (29)

A [redacted] subject, dose 1, medically confirmed, [redacted]

- Medical history: Arterial hypertension
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): 0 days
- Causes of death: Myocarditis. Autopsy reports inflammatory infiltration of the myocardium, pulmonary congestion, alveolar oedema, nephrosclerosis and adrenal adenoma.
- Comment: The case reports a subject who was found deceased 12 hours after vaccination; a witness described 'rattling breath' prior to the event. The autopsy describes myocardial infiltrations, and excluded other plausible causes of death (e.g., pulmonary embolism, myocardial infarction) or COVID-19 infection. Overall, apart from the autopsy report, there is too limited information available regarding the clinical circumstances in this case to enable a meaningful assessment of the role of the vaccine in inducing myocarditis in this subject.

A [redacted] subject, dose 4, medically confirmed, [redacted]

- Medical history: Not reported
- Co-suspect medications: No data
- PTs with fatal outcome: Myocarditis, sudden death, cardio-respiratory arrest
- Time to onset (myocarditis): 2 days
- Causes of death: Myocarditis as revealed by autopsy report which documents lymphocyte and macrophage infiltrates in myocardium.
- Comment: It is reported that the subject experienced gastrointestinal symptoms the day of vaccination and two days later was found deceased. The autopsy documented myocardial inflammation and elevation of troponin, CK and CRP. There is important information missing regarding the medical history, the clinical circumstances and the gastrointestinal pathology that limit the assessment of the vaccine role in this case.

An [redacted] subject, dose 4, medically confirmed, [redacted]

- Medical history: Osteoporosis, Scleroderma, Autoimmune disease (NOS)
- Co-suspect medications: No data
- PTs with fatal outcome: Arrhythmia; Blood pressure decreased; Cardio-respiratory arrest; autopsy reported Dyspnoea; Intestinal dilatation; Myocarditis
- Time to onset (myocarditis): 0 days

- Causes of death: reported by HCP as cardiac failure, arrhythmia and myocarditis; Autopsy reports bilateral pulmonary congestion and distended bowel, but no mention of myocarditis
- Comment: This [redacted] subject experienced dyspnoea and syncope the day of vaccination, followed by cardiac arrest which was resuscitated; and was followed by placing a pacemaker for bradycardia due to complete AV block, but experienced a second cardiorespiratory arrest that resulted in a fatal outcome. Myocarditis fulminant was suspected by the reporter due to 'blood examination', presumably troponin, which is reported to be high, yet not in the range of a fulminant myocarditis (0.154 ng/ml). The case also reports endotracheal intubation and suction of sputum, and in autopsy, there are findings of pulmonary congestion and distended bowel. Given the advanced age of the subject, limited information on myocarditis and extra-cardiac pathology, a role of the vaccine in inducing myocarditis is unlikely.

In 19 cases reported in subjects over 40 years of age, there were important confounders or other factors reported in the case that make the role of the vaccine in inducing myocarditis to be unlikely, such as: myocardial infarction/coronary artery disease (3 cases), other severe conditions (valvular disease [1 case], sarcoidosis [2 cases], capillary leak syndrome [1 case], cancer [1 case], pre-existing cardiac dilatation or failure [3 cases], COPD with severe emphysema [1 case]), infection (sepsis [2 cases], pneumonia [3 cases], HHV6 [1 case], atypical mycobacterial infection [1 case]).

In other 3 cases, the long time to onset (>21 days, 3 cases) does not support a temporal relationship with the vaccination.

In the remaining 4 cases, there was limited information precluding the clinical assessment of the myocarditis event and/or fatal outcome (4 cases).

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 153 (original [152], original + Omi BA.1 [1]) (0.05 % of 282,992 cases of the total PM dataset, 0.5 % of the 30605 subjects with unknown age), compared to 441 cases (0.08%) retrieved in the PSUR #3.
- Country/region of incidence (>1): Canada (65), Germany (22), Japan (17), US (15), Italy (9), Australia, UK (6 each), Turkey (4), Netherlands (3). The remaining 6 cases were distributed among 6 countries.
- Subjects' age in years: Unknown.
- Medical history (n = 39); the most frequently (≥2) reported medical conditions included Autism spectrum disorder, Non-tobacco user (4 each), Anxiety, Asthma, Hypertension,

Obesity (3 each), Arthritis, Attention deficit hyperactivity disorder, Cardiac murmur, Chest pain, Oedema, Polycystic ovaries, Thyroidectomy (2 each).

- COVID-19 Medical history (n = 2): Suspected COVID-19 (2)
- Co-suspect medications: triheptanoin (1).
- Most frequently co-reported PTs (>5) included Chest pain (55), Dyspnoea (34), Pericarditis (24), Pyrexia (19), Fatigue, Palpitations (18 each), Chest discomfort (15), Dizziness (12), Malaise, Tachycardia (10 each), Asthenia (8), Angina pectoris, Cardiac disorder, Chills, Headache, Myalgia (7 each), Arrhythmia (6).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 62 below.

Table 62. Myocarditis in Subjects of Unknown Age (N=153)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	16	58	24
	No	14	33	8
Relevant PT[a]	Myocarditis	19	66	29
	Myopericarditis	15	31	2
	Immune-mediated myocarditis	0	3	0
	Giant cell myocarditis	0	0	1
Hospitalisation required/prolonged	Yes	5	43	2
	No	25	48	30
Relevant suspect dose	Dose 1	9	17	4
	Dose 2	17	34	0
	Dose 3	1	20	3
	Dose 4	0	1	1
	Dose 5	0	1	0
	Dose Unknown	3	18	24
Original		30	90	32
Original + Omi BA.1		0	1	0
Original + Omi BA.4/BA.5		0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=67	≤24 hours	8	0	2
	1-5 days	5	29	0
	6-13 days	6	3	0
	14-21 days	1	5	0
	22-60 days	2	2	0
	61-364 days	1	3	0
	Unknown	11	59	30
Event Outcome	Fatal	0	1	2
	Not resolved	16	16	0
	Resolved	8	38	1
	Resolved with sequelae	0	1	0
	Resolving	2	4	2
	Unknown	8	40	27

Table 62. Myocarditis in Subjects of Unknown Age (N=153)

Duration of event[b]	Up to 3 days	0	1	0
n=3, median=1 day	3-91 days	2	0	0

a. All serious occurrences.
b. For those cases where the event resolved/resolved with sequelae.

Fatal cases (3)

There were 3 cases where subject age was unknown. Of them, one case reported a concurrent myocardial infarction that confounds the myocarditis diagnosis, and the other two cases presented too limited information precluding assessment.

Subjects with booster dose

Clinical Trial Data

- Number of cases: none, compared to 1 case (0.15%) retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 411 (original [375], original + Omi BA.1 [17], original + Omi BA.4/BA.5 [19]) (0.1 % of 282,992 cases of the total PM dataset, 1.4 % of the 62,302 subjects who received a booster dose), compared to 1682 cases (0.3%) retrieved in the PSUR #3.
- Country /region of incidence (≥10): Germany (151), Japan (52), Canada (26), France (25), UK (24), US (17), Austria, Taiwan, Province of China (16 each), Hong Kong (14), Italy (10); the remaining 60 cases were distributed among 23 countries.
- MC (213), NMC (198).
- Subjects' gender: female (147), male (253), and unknown (11).
- Subjects' age in years: n = 381, range: 12 – 96, mean: 43.4, median: 42.0.
- Medical history (n = 177); the most frequently (>4) reported medical conditions included Hypertension (29), Seasonal allergy (20), Asthma (11), Hypersensitivity, Obesity (10 each), Depression, Type 2 diabetes mellitus (9 each), Myocarditis (8), Drug hypersensitivity (7), Ex-tobacco user, Hypercholesterolaemia, Mite allergy (6 each), Prostate cancer (5).
- COVID-19 Medical history (n = 17): COVID-19 (12), Suspected COVID-19 (3), Coronavirus infection, SARS-CoV-2 test positive (1 each).
- Co-suspect medications (>1): elasomeran, influenza vaccine inact SAG 4V, influenza vaccine inact SPLIT 4V, nivolumab (2 each)
- Number of relevant events: 428.
- Relevant event seriousness: all serious.

- Reported relevant PTs: Myocarditis (349), Myopericarditis (73), Carditis, Eosinophilic myocarditis (2 each), Hypersensitivity myocarditis, Immune-mediated myocarditis (1 each).
- Relevant event outcome: fatal (21), resolved/resolving (163); resolved with sequelae (24), not resolved (115), unknown (105).
- Most frequently co-reported PTs (>20): Chest pain (306), Dyspnoea (255), Fatigue (186), Pyrexia (148), Pericarditis (131), Palpitations (125), Arrhythmia (117), Chest discomfort (115), Dizziness (106), Headache (98), Tachycardia (97), Asthenia (81), Malaise (71), Interchange of vaccine products (67), Pericardial effusion (57), Troponin increased (57), Cardiac failure (54), Off label use (52), Myalgia (47), Angina pectoris (45), Nausea (44), Dyspnoea exertional (40), Inappropriate schedule of product administration, Pain (40 each), Atrial fibrillation (35), Cough (34), Hypertension (32), Arthralgia, Exercise tolerance decreased (31 each), Chills (30), Heart rate increased, Pain in extremity, Vomiting (29 each), Paraesthesia (28), Syncope (27), Hyperhidrosis, Performance status decreased (26 each), Disturbance in attention (22), Diarrhoea, Immunisation, Limb discomfort, Myocardial infarction (21 each).

The number of myocarditis cases occurred after a booster dose in each age group is reported in Table 63 below by gender.

Table 63. Myocarditis in Subjects who Received a Booster Dose

Characteristics		Original Booster No. of Cases			Original +Omi BA.1 No. of Cases			Original +Omi BA.4/BA.5 No. of cases		
		F	M	U	F	M	U	F	M	U
Age group	0 to 17 years	6	42	1	0	3	0	0	1	0
	18 to 24 years	12	36	2	0	1	0	1	0	0
	25 to 29 years	5	21	1	1	0	0	0	2	0
	30 to 39 years	17	17	1	0	2	0	1	3	0
	40 years and older	90	95	1	6	3	0	7	4	0
	Unknown	1	22	5	0	1	0	0	0	0
	Total	131	233	11	7	10	*0*	9	10	*0*

F=female; M=male; U=unknown

During the reporting period there were 122 cases of medically confirmed myocarditis with a latency 21 days or less in subjects receiving booster dose. Of the 122 cases, 93 cases were assessed as serious due to hospitalisation. In 100 cases myocarditis occurred within 1 week post vaccine administration. In most of these cases, the insufficient description of cardiovascular and/or non-cardiovascular medical history and the lack of diagnostic tests confirming the aetiologies of myocarditis preclude a clear causality assessment on an individual case basis.

16.3.1.1.2. Important Identified Risks – Pericarditis

Search criteria[55,58] - PTs: Autoimmune pericarditis; Immune-mediated pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Overall – All Ages

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 796 (original [776], original + Omi BA.1 [8], original + Omi BA.4/BA.5 [12]) (0.3% of 282,992 cases of the total PM dataset), compared to 4156 cases (0.8%) retrieved in the PSUR #3.
- Country/region of incidence: Canada (137), Australia (135), France (109), Germany (91), Italy (61), UK (43), US (32), New Zealand (23), Japan (21), Norway (17). The remaining 127 cases were distributed among 27 countries.
- MC (450), NMC (346).
- Subjects' gender: female (410), male (362) and unknown (24).
- Subjects' age in years: n = 683, range: 6 – 95, mean: 44.2, median: 43.0.
- Medical history (n = 297); the most frequently (≥10) reported relevant medical history included Hypertension (43), Pericarditis (34), Asthma (17), Seasonal allergy (16), Drug hypersensitivity, Tobacco user (15 each), Atrial fibrillation, Depression (14 each), Hypothyroidism (13), Obesity (11), Dyslipidaemia, Gastrooesophageal reflux disease, Nontobacco user (10 each).
- COVID-19 Medical history (n = 59): COVID-19 (50), Suspected COVID-19 (6), COVID-19 pneumonia, Post-acute COVID-19 syndrome (2 each), Coronavirus infection, SARS-CoV-2 test positive (1 each).
- Co-suspect medications (n=19 cases); relevant co-suspect medications included COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (3), COVID-19 vaccine, influenza vaccine inact SAG 4V (2 each), brodalumab, COVID-19 vaccine NRVV AD26 (JNJ 78436735), COVID-19 vaccine prot. Subunit (NVX COV 2373), elasomeran, infliximab, influenza vaccine inact SPLIT 4V, ixekizumab, mepolizumab (1 each).
- Number of relevant events: 798.
- Relevant event seriousness: serious (798).

[58] In the upversioning to MedDRA to 25.1, a new PT was added (Immune-mediated pericarditis) which is now included in the evaluation of pericarditis.

- Reported relevant PTs: Pericarditis (787), Pleuropericarditis (6), Pericarditis constrictive (4), Autoimmune pericarditis (1).
- Relevant event outcome[56]: fatal (4), resolved/resolving (303), resolved with sequelae (29), not resolved (249), unknown (218).

Cumulatively, there were 10,727 cases of pericarditis which constitute 0.6% of the overall PM dataset (1,766,357). During the current reporting period, there were 796 cases that reported pericarditis which constitute 0.3% of 282,992 cases of the total PM dataset, and majority (92.5%) of these cases were spontaneously reported. Of these 796 cases, the majority of the cases (400 cases; 50.3%) were reported from adult population with the age group ranging from 30 to 64 years of age, where the female subjects (223 cases; 55.8%) were reported higher than the male subjects (170 cases; 42.5%). In the majority (776 cases; 97.5%) of the cases, the event of pericarditis was reported after the original booster dose and relatively less after the bivalent booster doses (original + Omi BA.1 or original + Omi BA.4/BA.5) (2.5%).

Upon review of these 796 cases, in 319 cases, the pericarditis events were confounded by co-suspect vaccines/medications (such as COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine inact SAG 4V, brodalumab, elasomeran, infliximab), or subject' s relevant medical history (e.g., COVID-19, hypertension, pericarditis, asthma) or co-reported conditions/events indicative of infections, neoplasms, thromboembolic or myocardial infarction events or the long time to onset of the pericarditis event post-vaccination (>21 days) that did not match a suspected vaccine induced events. There were 59 other cases involving elderly subjects which might be attributed to the subjects' age factor. When reported, in the majority (332) of the pericarditis events, the outcome was reported as either resolved, resolved with sequelae or resolving at the time of reporting. There were 4 cases reporting pericarditis events with a fatal outcome which are discussed in the age-stratified data.

Based on the review of these cases reporting pericarditis events, there was no new significant safety information identified during the current reporting period. Hence, no label update is warranted based on the analysis of these cases.

Age-stratified data[59]

Subjects aged less than 5 years

Clinical Trial Data

- Number of cases: none, no cases were retrieved in the PSUR #3.

[59] Cases where the age was reported as
- "Adolescent" (2 cases) were evaluated in the overall and in the 16-17 years of age groups,
- "Adult" (52 cases) were evaluated in the overall and in the Age Unknown group; and
- "Elderly" (7 cases) in the overall and in the ≥ 40 years of age groups.

Post-Authorisation Data

- Number of cases: none, compared to 1 case retrieved in the PSUR #3.

Subjects aged 5 – 11 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 6 (original [6]) (0.002 % of 282,992 cases of the total PM dataset, 0.1% of the 4991 subjects aged 5-11 years), compared to 30 cases (0.006%) retrieved in the PSUR #3.
- Country/region of incidence: Canada (3), [redacted] (1 each).
- Subjects' age in year: n = 6, range: 6 – 11, mean: 8.5, median: 8.5.
- Medical history: Bronchitis, Dermatitis atopic, Suffocation feeling (1 each).
- COVID-19 Medical history: Suspected COVID-19 (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain (4), Pyrexia (3), Abdominal pain, Palpitations (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below table.

Table 64. Pericarditis in Subjects aged 5-11 years (N=6)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	1	0
	No	1	2	0
Relevant PT[a]	Pericarditis	3	3	0
Hospitalisation required/prolonged	Yes	0	1	0
	No	3	2	0
Relevant suspect dose	Dose 1	2	2	0
	Dose 2	1	0	0
	Dose 3	0	1	0
Original		3	3	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=6	1-5 days	1	0	0
	14-21 days	1	1	0
	32-60 days	1	0	0
	Unknown	0	2	0
Event Outcome	Resolved	2	1	0
	Resolving	0	0	0

Table 64. Pericarditis in Subjects aged 5-11 years (N=6)

	Unknown	1	2	0
Duration of event[b] n=1, median: NA	4-6 days	1	0	0

a. All serious occurrences.
b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 15 (original [14], original + Omi BA.4/BA.5 [1]) (0.005 % of 282,992 cases of the total PM dataset, 0.4 % of the 3997 subjects aged 12-15 years), compared to 118 cases (0.02%) retrieved in the PSUR #3.
- Country/region of incidence: Canada (3), Australia, Denmark, Japan, Taiwan, province of China (2 each), [redacted] (1 each).
- Subjects' age in years: n = 15, range: 12.0 – 15.0, mean: 13.9, median: 14.0.
- Medical history (n = 3): Adenotonsillectomy, Dermatitis atopic, Familial risk factor, Headache, Hypersensitivity, Injection site pain, Long QT syndrome, Migraine, Mite allergy, Parasite stool test positive, Pneumonia, (1 each).
- COVID-19 Medical history: None.
- Co-suspect medications: None.
- Most frequently co-reported PTs (≥2): Chest pain, Myocarditis (6 each), Chest discomfort, Dyspnoea, Headache (3 each), Abdominal pain, Pyrexia, Tachycardia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 65.

Table 65. Pericarditis in Subjects aged 12-15 years (N=15)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	1	7	0
	No	3	4	0
Relevant PT[a]	Pericarditis	4	11	0
Hospitalisation required/prolonged	Yes	1	6	0
	No	3	5	0
Relevant suspect dose	Dose 1	1	2	0
	Dose 2	1	5	0
	Dose 3	2	3	0

Table 65. Pericarditis in Subjects aged 12-15 years (N=15)

	Unknown	0	1	0
Original		4	10	0
Original + Omi BA.4/BA.5		0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=15	1-5 days	0	7	0
	6-13 days	1	1	0
	32-60 days	0	1	0
	61-180 days	0	1	0
	181-365	1	0	0
	Unknown	2	1	0
Event Outcome	Not resolved	0	1	0
	Resolved	2	6	0
	Resolving	1	2	0
	Unknown	1	2	0
Duration of event[b] n=5, median: 20	7-10 days	0	2	0
	11-26 days	1	0	0
	27-57 days	0	1	0
	181-365 days	0	1	0

a. All serious occurrences.
b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 11 (original [11]) (0.003 % of 282,992 cases of the total PM dataset, 0.4% of the 3093 subjects aged 16-17 years), compared to 106 cases (0.02%) retrieved in the PSUR #3.
- Country/region of incidence: Australia, Canada, Japan, Taiwan, province of China (2 each), [redacted]1 each).
- Subjects' age in years: n = 9, range: 16 – 17, mean: 16.7, median: 17.0.
- Medical history (n = 3): Allergic respiratory disease, Depression, Food allergy, Hypersensitivity, Obesity, Orthostatic intolerance (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: None.
- Most frequently co-reported PTs (≥2): Chest pain (5), Chest discomfort, Chills, Fatigue, Headache, Hyperhidrosis, Myocarditis, Myopericarditis, Pyrexia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 66.

Table 66. Pericarditis in Subjects aged 16-17 years (N=11)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	5	0
	No	2	1	0
Relevant PT[a]	Pericarditis	5	6	0
Hospitalisation required/prolonged	Yes	1	3	0
	No	4	3	0
Relevant suspect dose	Dose 1	2	0	0
	Dose 2	2	2	0
	Dose 3	1	3	0
	Unknown	0	1	0
Original		5	6	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=11	≤ 24 hours	1	1	0
	1-5 days	1	2	0
	14-21 days	0	1	0
	22-31 days	1	0	0
	61-180 days	1	0	0
	Unknown	1	2	0
Event Outcome	Resolved	3	2	0
	Resolved with sequelae	0	1	0
	Resolving	2	2	0
	Unknown	0	1	0
Duration of event[b] n=1, median: NA	58-180 days	0	1	0

a. All serious occurrences.
b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 18 – 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 67 (original [67]) (0.02 % of 282,992 cases of the total PM dataset, 0.4% of the 18,410 subjects aged 18-24 years), compared to 479 cases (0.09%) retrieved in the PSUR #3.
- Country/region of incidence: Australia (17), France (14), Germany (8), Canada, New Zealand, US (4 each), Hong Kong, Italy (3 each), Sweden (2), [redacted] (1 each).
- Subjects' age in years: n = 67, range: 18 – 24, mean: 21.4, median: 22.0.
- Medical history (n = 15): Allergy to animal (2), Abdominal pain, Asthma, Autism spectrum disorder, Autoimmune thyroiditis, Back pain, Body mass index, Body surface area, Childhood asthma, Colitis ulcerative, Depression, Dermatitis atopic, Diarrhoea, Eosinophilic oesophagitis, Fibromyalgia, Food allergy, Fracture, Gilbert's syndrome, HELLP syndrome, Histamine intolerance, Hormonal contraception, Hypersensitivity, Hypothermia, Milk allergy, Movement disorder, Neck pain, Pericardial disease, Physiotherapy, Polycystic ovaries, Road traffic accident, Seasonal allergy, Tobacco user, Vitiligo (1 each).
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications (n= 1 case): ethinylestradiol/levonorgestrel (1).
- Most frequently co-reported PTs (≥2): Chest pain (24), Dyspnoea (17), Myocarditis (10), Fatigue (9), Palpitations (8), Dizziness, Pericardial effusion (7 each), Tachycardia (6), Asthenia (5), Arrhythmia, Chest discomfort, Insomnia, Paraesthesia, Pyrexia (4 each), Angina pectoris, Malaise, Pleurisy (3 each), Abdominal pain, Anxiety, Cough, Decreased appetite, Dyspnoea exertional, Electrocardiogram abnormal, Exercise tolerance decreased, Haematuria, Headache, Hypoaesthesia, Influenza like illness, Lip swelling, Loss of personal independence in daily activities, Lymphadenopathy, Myalgia, Nausea, Pain in extremity, Periorbital swelling, Peripheral swelling, Presyncope, Rash, Sinus tachycardia, Troponin increased (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 67.

Table 67. Pericarditis in Subjects aged 18-24 years (N=67)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	14	26	0
	No	10	16	0
Relevant PT[a]	Pericarditis	24	42	0
Hospitalisation required/prolonged	Yes	5	16	1
	No	19	26	0
Relevant suspect dose	Dose 1	9	16	0
	Dose 2	6	13	0
	Dose 3	9	9	0
	Unknown	0	4	1
Original		24	42	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=67	≤ 24 hours	2	3	0
	1-5 days	5	11	0
	6-13 days	4	2	0
	14-21 days	1	4	0
	22-31 days	0	2	0
	32-60 days	1	0	0
	61-180 days	2	2	0
	181-365 days	1	2	0
	Unknown	8	16	1
Event Outcome	Not resolved	6	12	0
	Resolved	3	9	0
	Resolved with sequelae	2	1	0
	Resolving	6	5	0
	Unknown	7	15	1
Duration of event[b] n=5, median: 34	7-10 days	0	1	0
	27-57 days	2	1	0
	58-180 days	1	0	0

a. All serious occurrences.
b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 25 – 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 79 (original [79]) (0.03 % of 282,992 cases of the total PM dataset, 0.4% of the 21,841 subjects aged 25-29 years), compared to 417 cases (0.08%) retrieved in the PSUR #3.
- Country/region of incidence: Australia (30), France, Germany (11 each), UK (4), Canada, Italy, Sweden (3 each), Japan (2), [redacted] (1 each).
- Subjects' age in years: n = 79, range: 25 – 29, mean: 26.8, median: 27.0.
- Medical history (n = 24): the medical conditions reported more than once included Seasonal allergy (4), Acne, Anorexia nervosa, Antiphospholipid syndrome, Arthritis, Deep vein thrombosis, Drug hypersensitivity, Endometriosis, Myocarditis, Ovarian cyst ruptured, Pericarditis, Pulmonary embolism (2 each).
- COVID-19 Medical history (n = 8): COVID-19 (6), Suspected COVID-19 (2).
- Co-suspect medications (n= 4 cases): COVID-19 vaccine, escitalopram, influenza vaccine inact SPLIT 4V, ixekizumab (1 each).
- Most frequently co-reported PTs (≥2): Chest pain (31), Dyspnoea (25), Myocarditis (16), Palpitations (14), Chest discomfort, Fatigue (13 each), Pericardial effusion (8), Dizziness (7), Pain, Pyrexia (6 each), Angina pectoris (5), Arrhythmia, Arthralgia, Cough, COVID-19, Drug ineffective, Heart rate increased, Pain in extremity, Pulmonary embolism (4 each), Asthenia, Back pain, Chills, Dyspepsia, Electrocardiogram abnormal, Exercise tolerance decreased, Feeling abnormal, Headache, Malaise, Nausea, Pain in jaw, Pleural effusion, Syncope, Tachycardia, Tremor (3 each), Adjusted calcium increased, Anion gap increased, Anxiety, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood albumin increased, Blood calcium increased, Blood lactate dehydrogenase increased, Blood pressure increased, Burning sensation, Cardiac disorder, Concomitant disease aggravated, Depression, Diarrhoea, Emotional distress, Extrasystoles, Haematocrit increased, Human chorionic gonadotrophins decreased, Hypoaesthesia, Inappropriate schedule of product administration, Lethargy, Lymphadenopathy, Mitral valve incompetence, Oxygen saturation decreased, Panic attack, Paraesthesia, Presyncope, Protein total increased, Pruritus, Pulmonary valve incompetence, Red blood cell count increased, Sinus rhythm, Tinnitus, Tricuspid valve incompetence, Troponin increased (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 68.

Table 68. Pericarditis in Subjects aged 25-29 years (N=79)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	29	18	1
	No	16	13	2
Relevant PT[a]	Pericarditis	45	31	3
	Pleuropericarditis	1	0	0
Hospitalisation required/prolonged	Yes	8	4	1
	No	38	27	2
Relevant suspect dose	Dose 1	21	10	0
	Dose 2	13	11	1
	Dose 3	8	5	0
	Dose 4	1	0	0
	Unknown	2	5	2
Original		45	31	3
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=81[b]	≤ 24 hours	4	1	0
	1-5 days	9	7	0
	6-13 days	11	5	1
	14-21 days	0	2	0
	22-31 days	3	1	0
	32-60 days	2	4	0
	181-375 days	4	2	0
	Unknown	13	10	2
Event Outcome[b]	Not resolved	17	9	0
	Resolved	8	9	0
	Resolved with sequelae	0	2	0
	Resolving	6	3	1
	Unknown	15	9	2
Duration of event[c] n=4, median: 184	Up to 3 days	1	0	0
	27-57 days	1	0	0
	181-365 days	0	2	0

a. All serious occurrences.
b. Event(s) reported more than one TTO and/or clinical outcome.
c. For those cases where the event resolved or resolved with sequelae.

Subjects aged 30 – 39 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 133 (original [131], original + Omi BA.1 [2]) (0.05 % of 282,992 cases of the total PM dataset, 0.3% of the 50,039 subjects aged 30-39), compared to 940 cases (0.2%) retrieved in the PSUR #3.
- Country/region of incidence: Australia (32), Canada (26), France (22), Germany (13), Italy (10), UK (7), Austria, Belgium, Denmark, Malaysia (3 each).
- Subjects' age in years: n = 133, range: 30 – 39, mean: 34.6, median: 35.0.
- Medical history (n = 39): the medical conditions reported more than once included the PTs Pericarditis (8), Seasonal allergy, Tobacco user (5 each), Endometriosis (3), Autoimmune disorder, Autoimmune thyroiditis, Caesarean section, Mite allergy (2 each).
- COVID-19 Medical history (n = 15): COVID-19 (13), Suspected COVID-19 (2).
- Co-suspect medications (n=2): COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (2 each).
- Most frequently co-reported PTs (≥2%): Chest pain (51), Dyspnoea (32), Fatigue (27), Palpitations (17), Pericardial effusion (13), Chest discomfort, Myocarditis (12 each), Tachycardia (10), Pain (9), Asthenia (8), Headache, Myalgia, Off label use (7 each), Dizziness, Lymphadenopathy, Malaise, Pain in extremity, Pyrexia (6 each), Cough, Inappropriate schedule of product administration (5 each), Dyspnoea exertional, Exercise tolerance decreased, Heart rate increased, Hyperhidrosis, Immunisation, Interchange of vaccine products, Paraesthesia (4 each), Angina pectoris, Anxiety, Arrhythmia, Arthralgia, Back pain, Chills, Electrocardiogram abnormal, Electrocardiogram ST segment elevation, Hypothermia, Loss of personal independence in daily activities, Post-acute COVID-19 syndrome, Postural orthostatic tachycardia syndrome, Troponin increased (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in below Table 69.

Table 69. Pericarditis in Subjects aged 30-39 years (N=133)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	40	36	2
	No	22	31	2
Relevant PT[a]	Pericarditis	61	67	4
	Pleuropericarditis	1	0	0
Hospitalisation required/prolonged	Yes	18	14	1
	No	44	54	3
Relevant suspect dose	Dose 1	26	29	2
	Dose 2	18	19	1
	Dose 3	10	10	0
	Dose 4	2	4	0
	Unknown	6	5	1
Original		61	66	4
Original + Omi BA.1		1	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=135[b]	≤ 24 hours	2	8	0
	1-5 days	14	13	0
	6-13 days	9	8	0
	14-21 days	5	4	1
	22-31 days	0	1	0
	32-60 days	3	2	0
	61-180 days	2	5	0
	181-365 days	0	4	0
	≥ 366 days	0	1	0
	Unknown	28	22	3
Event Outcome[b]	Not resolved	20	34	0
	Resolved	12	10	0
	Resolved with sequelae	6	1	0
	Resolving	12	10	0
	Unknown	13	13	4
Duration of event[c] n=5, median: 65	4-6 days	0	1	0
	11-26 days	0	1	0
	58-180 days	1	1	0
	181-365 days	1	0	0

a. All serious occurrences.
b. Event(s) reported more than one TTO and/or clinical outcome.
c. For those cases where the event resolved or resolved with sequelae.

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 381 (original [365], original + Omi BA.1 [6], original + Omi BA.4/BA.5 [10]) (0.1 % of 282,992 cases of the total PM dataset, 0.3% of the 149,203 subjects ≥ 40 years), compared to 1756 cases (0.3%) retrieved in the PSUR #3.

- Country/region of incidence: France (57), Germany (50), Australia (47), Italy (42), Canada (39), UK (24), New Zealand, Norway (16 each), US (15), Greece (11), Japan, Sweden (10 each), Denmark (9), Austria, Netherlands (7 each), Portugal (5), Brazil, Poland (3 each), Belgium, Spain (2 each), [redacted] (1 each).

- Subjects' age in years: n = 374, range: 40 – 95, mean: 57.9, median: 55.0.

- Medical history (n = 171): the medical conditions reported more than 5 times included PTs Hypertension (39), Pericarditis (14), Atrial fibrillation (13), Hypothyroidism (11), Asthma, Dyslipidaemia (10 each), Depression, Gastrooesophageal reflux disease, Non-tobacco user (9 each), Diabetes mellitus, Drug hypersensitivity, Obesity (8 each), Tobacco user, Type 2 diabetes mellitus (7 each), Hypercholesterolaemia, Osteoporosis, Seasonal allergy (6 each).

- COVID-19 Medical history (n = 28): COVID-19 (25), COVID-19 pneumonia, Post-acute COVID-19 syndrome (2 each), Coronavirus infection, Suspected COVID-19 (1 each).

- Co-suspect medications (n= 12): duloxetine, influenza vaccine inact SAG 4V (2 each), apixaban, brodalumab, COVID-19 vaccine, COVID-19 vaccine NRVV AD26 (JNJ 78436735), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), COVID-19 vaccine Prot. Subunit (NVX COV 2373), elasomeran, infliximab, mepolizumab (1 each).

- Most frequently co-reported PTs (≥2%): Chest pain (121), Dyspnoea (81), Pericardial effusion (63), Fatigue (59), Myocarditis (50), Palpitations (47), Chest discomfort (43), Pyrexia (30), Tachycardia (27), Asthenia (25), Dizziness, Off label use, Pleural effusion (21 each), Interchange of vaccine products, Myalgia, Nausea, Pain (19 each), Malaise (17), Dyspnoea exertional, Headache, Pain in extremity (16 each), Cough, Paraesthesia (15 each), Arthralgia, Atrial fibrillation, Immunisation (14 each), Disturbance in attention, Inappropriate schedule of product administration (13 each), Arrhythmia, General physical health deterioration (12 each), Influenza like illness (11), Back pain, Hyperhidrosis, Syncope (10 each), Feeling abnormal, Pleurisy, Pneumonia (9 each), Angina pectoris, Anxiety, Cardiac failure, C-reactive protein increased, Hypertension, Muscular weakness, Myopericarditis, Tremor, Vomiting (8 each), Abdominal pain upper, Blood pressure increased, Condition aggravated, Exercise tolerance decreased, Heart rate

increased, Impaired work ability, Insomnia (7 each), Chills, Decreased appetite, Dyspepsia, Gait disturbance, Loss of personal independence in daily activities, Lymphadenopathy, Memory impairment, Tinnitus (6 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 70 below.

Table 70. Pericarditis in Subjects aged ≥ 40 years (N=381)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	128	89	3
	No	90	71	0
Relevant PT[a]	Autoimmune pericarditis	1	0	0
	Pericarditis	214	156	3
	Pericarditis constrictive	0	4	0
	Pleuropericarditis	4	0	0
Hospitalisation required/prolonged	Yes	68	60	2
	No	151	100	1
Relevant suspect dose	Dose 1	58	38	1
	Dose 2	59	43	1
	Dose 3	61	52	0
	Dose 4	18	11	0
	Dose 5	2	1	0
	Dose 6	1	0	0
	Unknown	19	15	1
Original		208	154	3
Original + Omi BA.1		4	2	0
Original + Omi BA.4/BA.5		6	4	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=385[b]	≤ 24 hours	15	7	0
	1-5 days	29	25	0
	6-13 days	29	15	0
	14-21 days	17	9	0
	22-31 days	10	8	2
	32-60 days	11	8	1
	61-180 days	11	16	0
	181-365 days	13	10	0
	≥ 366 days	1	1	0
	Unknown	83	64	0
Event Outcome[b]	Fatal	2	2	0
	Not resolved	77	47	0
	Resolved	34	39	1
	Resolved with sequelae	10	6	0
	Resolving	45	32	0
	Unknown	51	37	2
Duration of event[c] n= 22, median: 100	Up to 3 days	0	0	1
	4-6 days	0	1	0
	7-10 days	0	2	0
	11-26 days	1	0	0

Table 70. Pericarditis in Subjects aged ≥ 40 years (N=381)

	27-57 days	1	3	0
	58-180 days	1	3	0
	181-365 days	5	2	0
	≥ 366 days	1	1	0

a. All serious occurrences.
b. Event(s) reported more than one TTO and/or clinical outcome.
c. For those cases where the event resolved or resolved with sequelae.

Fatal cases in elderly (> 75 years of age) (4)

- Cases medically confirmed (2):

[redacted].

  - Medical history: Unknown.
  - Co-suspect medications : None.
  - PTs with fatal outcome: Concomitant disease aggravated, Hyperhidrosis, Myocarditis, Pericarditis, Pleuritic pain, Pneumonia.
  - Time to onset (pericarditis): 14 days after dose 1.
  - Causes of death: All the above events.

[redacted]

  - Medical history: Unknown.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Aortic dissection, Arteritis, Cardiac tamponade, Pericarditis, Vascular fragility.
  - Time to onset (pericarditis): Unspecified days after dose 3.
  - Causes of death: All the above events.

- Cases non-medically confirmed (2):

[redacted]

  - Medical history: Scleroderma/surgery.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Atrial fibrillation, Gangrene, Myocardial infarction, Pericarditis, Pleural effusion, Pulmonary fibrosis, Pulmonary hypertension, Scleroderma, Thyroiditis.
  - Time to onset (pericarditis): 22 days after dose 3.
  - Causes of death: All the above events.

[redacted]

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Chest discomfort, Dyspnoea, Fatigue, Insomnia, Pericarditis, Syncope.
- Time to onset (pericarditis): 119 days after dose 3.
- Causes of death: Due to all the above events.

Of 4 pericarditis events reported with a fatal outcome, one also reported a myocarditis event and was discussed in the myocarditis section. In the remaining 3 cases, there were important confounders or other factors reported in the case that make the role of the vaccine in inducing pericarditis to be unlikely, such as: myocardial infarction/coronary artery disease, sarcoidosis, and aortic dissection.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 104 (original [103], original + Omi BA.1 [1]) (0.04 % of 282,992 cases of the total PM dataset, 0.3% of the 30,605 subjects with unknown age), compared to 309 (0.06%) cases retrieved in the PSUR #3.

- Country/region of incidence: Canada (57), Germany, US (9 each), UK (6), Australia, France, Japan (4 each), Israel (3), Italy, Slovakia, Switzerland (2 each), [redacted] (1 each).
- Subjects' age in years: Unknown.
- Medical history (n = 41): the medical conditions reported more than once included PTs Pericarditis (10), Asthma, Drug hypersensitivity, Hypertension (4 each), Anxiety, Attention deficit hyperactivity disorder, Thyroidectomy (3 each), Depression, Obesity, Surgery (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (3), SARS-CoV-2 test positive (1).
- Co-suspect medications: None.
- Most frequently co-reported PTs (≥2%): Chest pain (52), Dyspnoea (30), Chest discomfort, Myopericarditis, Palpitations (15 each), Myocarditis (14), Fatigue (12), Pyrexia (9), Asthenia (7), Angina pectoris, Cough, Dizziness, Malaise, Tachycardia (6 each), Dyspnoea exertional, Nausea, Pleural effusion (5 each), Pericardial effusion (4), Arrhythmia, Arthralgia, Autoimmune disorder, Cardiac disorder, Headache, Pain, Pleuritic pain (3 each), Atrial fibrillation, Chills, Condition aggravated, Disturbance in attention, Hyperhidrosis, Inappropriate schedule of product administration, Insomnia,

Interchange of vaccine products, Mental impairment, Migraine, Nasopharyngitis, Off label use, Pneumonia, Weight increased (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 71.

Table 71. Pericarditis in Subjects with Unknown Age (N=104)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	18	18	8
	No	31	24	5
Relevant PT[a]	Pericarditis	49	42	13
Hospitalisation required/prolonged	Yes	9	7	2
	No	40	35	11
Relevant suspect dose	Dose 1	17	14	5
	Dose 2	20	20	0
	Dose 3	4	7	1
	Dose 4	0	0	1
	Unknown	8	1	6
Original		48	42	13
Original + Omi BA.4/BA.5		1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=105[b]	≤ 24 hours	3	0	0
	1-5 days	10	10	0
	6-13 days	2	3	0
	14-21 days	1	1	0
	22-31 days	1	4	0
	32-60 days	0	0	2
	61-180 days	2	0	0
	≥ 366 days	1	1	0
	Unknown	29	24	11
Event Outcome	Not resolved	16	9	1
	Resolved	14	16	0
	Resolving	5	0	1
	Unknown	14	17	11
Duration of event[c] n=30, median: NA	Unknown	14	16	0

a. All serious occurrences.
b. Event(s) reported more than one TTO and/or clinical outcome.
c. For those cases where the event resolved or resolved with sequelae.

Subjects with booster dose

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 249 (original [229], original + Omi BA.1 [8], original + Omi BA.4/BA.5 [12]) (0.09% of 282,992 cases of the total PM dataset, 0.4% of the 62,302 subjects who received a booster dose), compared to 1216 cases (0.2%) in the PSUR #3.
- Country/region of incidence: France (44), Germany (40), Canada (23), Italy (21), UK (19), New Zealand (14), Japan (12), US (10), Denmark (9), Austria, Netherlands (7 each), Greece, Norway (6 each), Australia, Belgium, Hong Kong (4 each), Brazil, Spain, Sweden, Taiwan, Province of China (3 each), Luxembourg (2), [redacted] (1 each).
- MC (130), NMC (119).
- Subjects' gender: female (132), male (114), and unknown (3).
- Subjects' age in year: n = 229, range: 8 – 95, mean: 50.0, median: 52.0
- Medical history (n = 117): the medical conditions reported more or equal to 5 times included the PTs Hypertension (23), Pericarditis (9), Atrial fibrillation (7), Asthma, Depression, Dyslipidaemia, Endometriosis, Hypothyroidism, Non-tobacco user, Obesity (6 each), Anxiety, Gastrooesophageal reflux disease, Seasonal allergy, Tobacco user (5 each).
- COVID-19 Medical history (n = 14): COVID-19 (12), Suspected COVID-19 (2).
- Co-suspect medications (n=5): influenza vaccine inact SAG 4V (2), apixaban, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), duloxetine (1 each).
- Number of relevant events: 250.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Pericarditis (245), Pleuropericarditis (5)
- Relevant event outcome: fatal (3), resolved/resolving (103), resolved with sequelae (10), not resolved (78), unknown (58).
- Most frequently co-reported PTs (≥3%): Chest pain (77), Dyspnoea (55), Pericardial effusion (46), Fatigue (42), Myocarditis (39), Chest discomfort (32), Palpitations (28), Off label use (25), Pyrexia (23), Interchange of vaccine products (22), Immunisation, Tachycardia (19 each), Asthenia, Cough, Pleural effusion (15 each), Malaise (13), Headache, Myalgia (12 each), Dyspnoea exertional, Pain (11 each), Arrhythmia, General physical health deterioration (10 each), Atrial fibrillation, Back pain, Hyperhidrosis (8 each), Dizziness, Myopericarditis, Pain in extremity, Pleurisy (7 each), Arthralgia, Chills, Condition aggravated, C-reactive protein increased, Disturbance in attention, Heart rate increased (6 each).

The number of pericarditis cases occurred after a booster dose in each age group is reported in the below Table 72 by gender.

Table 72. Pericarditis in Subjects who Received a Booster Dose

Characteristics		Original Booster No. of Cases			Original +Omi BA.1 No. of Cases			Original +Omi BA.4/BA.5 No. of cases		
		F	M	U	F	M	U	F	M	U
Age group	0 to 17 years	3	6	0	0	0	0	0	0	0
	18 to 24 years	9	10	0	0	0	0	0	0	0
	25 to 29 years	9	6	0	0	0	0	0	0	0
	30 to 39 years	12	14	0	1	1	0	0	0	0
	40 years and older	82	62	1	4	2	0	6	4	0
	Unknown	5	8	2	0	0	0	1	0	0
	Total	*120*	*106*	*3*	*5*	*3*	*0*	*7*	*5*	*0*

F=female; M=male; U=unknown

During the reporting period there were 130 cases of medically confirmed pericarditis who received booster dose. Of these 130 cases, there were 70 cases with a latency of 21 days or less, and 54 cases with a latency of 7 days or less in subjects receiving booster dose. All cases were assessed as serious due to hospitalisation and/or medically significant (110) or due to disability or life-threatening (19). One case reported a fatal outcome which is reviewed above in the age stratified section. In most of these cases, the insufficient description of cardiovascular and/or non-cardiovascular medical history and the lack of diagnostic tests confirming the aetiologies of pericarditis preclude a clear causality assessment on an individual case basis.

O/E Analysis

O/E analysis was performed for Myocarditis/Pericarditis (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*). For myocarditis in the US, O/E ratios were above 1 for all stratifications in either the 21-day or 42-day risk window except males <5, males 50+, females <5, females 60+ years, and overall bivalent BA.4/5 using the low background rate. O/E ratios were above 1 for males 12-24 years, overall monovalent dose 2, and overall all doses, processed cases using the mid background rate and either the 21-day or 42-day risk window, as well as for males 12-17 years and overall all doses, processed cases using the high background rate and either the 21-day or 42-day risk window. Recent increases in O/E ratios for the younger age groups may have been influenced by increased reporting of cases after the release of a Dear Healthcare Provider letter in late July 2021. For myocarditis/pericarditis, the O/E ratios were above 1 in at least one risk window for the 12-24 years age groups in males, the 12-59 years age groups in females, overall monovalent doses 1, 2, and 3+, and overall all doses in the EEA. All O/E ratios were below 1 for myocarditis/pericarditis in the US except for males and females 12-17 years.

Conclusion

Evaluation of Myocarditis and Pericarditis did not reveal any significant new safety information for this interval. Considering the accumulating data from post-authorisation use

of the vaccine, including the consistent findings from passive and active surveillance databases of increased occurrences of myocarditis and pericarditis following vaccination with BNT162b2, myocarditis and pericarditis were added as ADRs in section 4.8, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022.

16.3.2. Evaluation of Important Potential Risks

The Republic of Korea MFDS requested the MAH to provide: *Safety evaluation for the second booster vaccination. Up-to-date safety information (post-marketing safety information, etc.) related to booster vaccination-related adverse reactions of special interest (AESI) and vaccine related exacerbated diseases (VAED including VAERD.) The MAH self-committed to provide this information in the current PSUR.*

Response

The MAH has implemented a search for the administration of booster doses of BNT162b2 original and BNT162b2 bivalent vaccines. Please refer to the subsection "Second Booster Analysis" for the analysis of cases occurred after the second booster in Section 16.3.2.1 for analysis of cases occurred after the second booster.

16.3.2.1. VAED/VAERD

Evaluation of incremental data for the important potential risk VAED/VAERD is provided below.

Search criteria:

1. PTs Vaccine associated enhanced respiratory disease OR Vaccine associated enhanced disease OR

2. Standard Decreased Therapeutic Response Search (Drug ineffective OR Vaccination failure) AND 1 among the following PTs: Abdominal pain; Acute hepatic failure; Acute kidney injury; Acute myocardial infarction; Acute respiratory distress syndrome; Altered state of consciousness; Arrhythmia; Cardiac failure; Cardiogenic shock; Cerebrovascular accident; Chillblains; COVID-19 pneumonia; Deep vein thrombosis; Diarrhoea; Disseminated intravascular coagulation; Dyspnoea; Encephalopathy; Erythema multiforme; Hypoxia; Jaundice; Meningitis; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children; Myocarditis; Peripheral ischaemia; Pulmonary embolism; Renal failure; Respiratory failure; Seizure; Shock; Tachypnoea; Thrombocytopenia; Vasculitis; Vomiting.

VAED is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection.[60]

As noted by the Brighton Collaboration, there is currently no uniformly accepted definition of VAED (or VAERD) and the BC working group considers that a definitive case of VAED (Level 1 diagnostic certainty) cannot be ascertained with current knowledge of the mechanisms of pathogenesis of the condition; they have provided guidance on levels of diagnostic certainty of VAED cases based on various laboratory and clinical findings.

An expected rate of VAED is difficult to establish so a meaningful O/E analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continue to accrue.

Of note, there were 9 cases reporting the PTs Vaccine associated enhanced disease (4), and Vaccine associated enhanced respiratory disease (5). Of these 9 cases, 2 met the criteria to be considered potential VAED cases (PTs Vaccine associated enhanced respiratory disease [2]). Both cases were considered confirmed cases of COVID-19.

- In 1 case, the event (along with PTs Acute respiratory distress syndrome, Respiratory failure, Multiple organ dysfunction syndrome, hypotension, Acute kidney injury and Shock) were reported as fatal in a [redacted] subject. An autopsy was performed and revealed COVID-19 infection, focal acute and proliferative phases of diffuse alveolar damage, and pulmonary embolism. The subject also had a history of immunization with the BNT162b2 mRNA pre-hospitalization, possible infection with COVID-19 suggested by IgM and IgG antibodies (unclear if produced against the spike protein or nucleocapsid protein of the virus), and a CT consistent with COVID-19 despite persistently negative SARS-CoV-2 PCR tests.

- In the 2nd case, [redacted] subject was administered 3 doses of the BNT162b2 vaccine. [redacted] experienced bilateral pneumonia due to SARS-CoV-2 (infection confirmed via positive PCR test) with severe respiratory failure. Despite treatment, [redacted] condition worsened, and [redacted] was admitted to the Intensive Care Unit. At the time of the report, the subject was reported as recovering, with a subsequent nosocomial pneumonia due to Aspergillus niger.

Clinical Trial Data

There were no cases reporting COVID-19 infection associated to one of the PTs to identify potential severe or atypical cases of COVID-19.

[60] Munoz FM, Cramer JP, Dekker CL, et al. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021;39(22):3053-66.

Post-Authorisation Data

Of the 403 cases retrieved based on search strategy, 4 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- In 2 cases the PT indicative of lack of efficacy did not refer to BNT162b2 vaccine.
- In 2 cases the subjects developed SARS-CoV-2 infection during the early days from the 1st dose (days 1 – 13); therefore, the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable, even if severe, cannot be considered a potential case of enhanced disease.

Overview

- Number of cases: 399 (original [397], original + Omi BA.1, original + Omi BA.4/BA.5 [2 each]) (0.1% of 282,992 cases, the total PM dataset), compared to 1268 (0.2%) retrieved in the PSUR #3. All cases are serious.
- MC cases (288), NMC cases (111).
- Country/region of incidence: Spain (72), US (64), France (55), Germany (35), UK (31), Japan (19), Estonia (18), Italy (13), Canada (12), Philippines (10); the remaining 70 cases originated from 24 different countries.
- Gender: female (209), male (173), and unknown (17).
- Age in years (n = 367), range: 2 – 100, mean: 61.6, median: 67.0.
- Relevant event seriousness: 415 serious, 119 non-serious.
- Reported relevant PTs by organ system:
    - Respiratory system PTs (145): Dyspnoea (103), Respiratory failure (20), Pulmonary embolism (10), Hypoxia (6), Tachypnoea (4), and Acute respiratory distress syndrome (2).
    - Gastrointestinal system PTs (105): Diarrhoea (44), Vomiting (37), and Abdominal pain (24).
    - Cardiovascular system PTs (41): Arrhythmia (16), Myocarditis (15), Cardiac failure (8), and Acute myocardial infarction (2).
    - Renal and urinary system PTs (11): Acute kidney injury (6) and Renal failure (5).
    - Nervous system PTs (15): Cerebrovascular accident (7), Seizure (6), and Altered state of consciousness (2).
    - Vascular system PTs (9): Shock (5), Vasculitis (2), Deep vein thrombosis, and Peripheral ischaemia (1 each).
    - Blood and lymphatic system PTs (5): Disseminated intravascular coagulation (3) and Thrombocytopenia (2).

- Immune system PTs (12): Vaccine associated enhanced respiratory disease (5), Vaccine associated enhanced disease (4), and Multisystem inflammatory syndrome in children (3).

- Other PTs (191): COVID-19 pneumonia (172), Jaundice (7), Multiple organ dysfunction syndrome, Meningitis (5 each), and Erythema multiforme (2).

- Case outcome: fatal (46), not resolved (76), resolved/resolving (185), resolved with sequelae (12), and unknown (80).

COVID-19 positivity and severity of events

- Suspected COVID-19 infection: 61 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (58 cases) or to Vaccination failure (1 case); 2 cases reported Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease (1 each).
- Confirmed COVID-19 infection: 338 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (191 cases) or Vaccination failure (142 cases)]; 5 cases reported Vaccine associated enhanced disease (3) or Vaccine associated enhanced respiratory disease (2).
- Seriousness criteria for the total 399 cases:
  - Medically significant: 168 (6 cases reported with disability);
  - Hospitalisation required (non-fatal/non-life threatening): 161 (6 cases reported with disability);
  - Life threatening: 24 (2 cases reported with disability);
  - Death: 46 (1 case reported with disability).

Seriousness criteria: medically significant (168)

- In 127 of 168 cases where the seriousness criterion was “medically significant”, the subjects had a confirmed COVID-19 infection after vaccination, while 41 subjects had suspected COVID-19 infection. These 41 subjects did not require hospitalisation.

- In the 127 confirmed COVID-19 cases, subjects’ age ranged from 5 to 90 years (n = 122, mean: 52.4 years, median: 55.5 years) (7 paediatrics, 72 adults, 44 elderly, 4 unknown); gender was reported as female (79), male (43), and unknown (5).

- Time to event onset of the COVID 19 infection was reported for 87 of these 127 cases:
  - Day 73 to 442 after dose 1 (13 cases);
  - Day 1 to 483 after dose 2 (20 cases);
  - Day 0 to 304 after dose 3 (35 cases);
  - Day 0 to 297 after dose 4 (13 cases);
  - Day 38 to 353 after vaccination [dose number not reported] (6 cases).

- These 127 cases reported 177 relevant events.[61] The most commonly (>15) reported relevant PTs Dyspnoea (31), Diarrhoea (30), COVID-19 pneumonia (29), Vomiting (23), and Abdominal pain (16).

- The outcome of the COVID-19 infection related events reported in these 127 cases was: resolved/resolving (53), resolved with sequelae (1), not resolved (17), and unknown (106).

Seriousness criteria: hospitalisation (non-fatal, non-life threatening) (161)

- Hospitalisation occurred in 161 subjects, for 14 of them the COVID-19 infection was not confirmed.

- In the 147 COVID-19 confirmed cases, subjects' age (n = 145) ranged from 11 to 100 years, (mean: 72.3 years, median: 75.0 years) (1 paediatric, 33 adults, 111 elderly, 2 unknown); gender was reported as female (71), male (74), and unknown (2).

- Time to event onset of the COVID-19 infection was reported for 118 of these 147 cases.
  - Day 14 to 331 after dose 1 (7 cases);
  - Day 21 to 466 days after dose 2 (24 cases);
  - Day 16 to 382 days after dose 3 (72 cases);
  - Day 27 to 238 days after dose 4 (10 cases);
  - Day 5 to 341 after vaccination [dose number not reported] (5 cases).

- These 147 cases reported 197 relevant events. The most commonly (≥5) reported relevant PTs COVID-19 pneumonia (101), Dyspnoea (42), Diarrhoea, Vomiting (9 each), Myocarditis, and Respiratory failure (5 each).

- The outcome of the COVID-19 infection related events reported in these 147 cases was: resolved/resolving (114), not resolved (17), resolved with sequelae (6), and unknown (60).

Seriousness criteria: life-threatening (non-fatal) (24)

- In 19 of the 24 cases as life-threatening, the subjects had a confirmed COVID-19 infection after vaccination, while 5 subjects had suspected COVID-19 infection.

- In these 19 confirmed COVID-19 cases, subject's age ranged from 17 to 91 years (n = 16), (mean: 55.3 years, median: 60.0 years), (1 paediatric, 9 adults, 7 elderly, 2 unknown); gender was reported as female (9), male (8), and unknown (2).

[61] PTs included in the search strategy excluding Drug ineffective and Vaccination failure.

- Time to event onset of the COVID-19 infection was reported for 8 of these 19 cases.
  - Day 35 after dose 1 (1 case);
  - Day 57 to 182 after dose 2 (5 cases);
  - Day 243 after dose 3 (1 case);
  - Day 264 after vaccination [dose number not reported] (1 case).

- These 19 cases reported 21 relevant events. The most commonly (≥2) reported relevant PTs COVID-19 pneumonia (9), Dyspnoea (4), Myocarditis, and Pulmonary embolism (2 each).

- The outcome of the COVID-19 infection related events reported in these 21 cases was: resolved/resolving (8), not resolved (3), resolved with sequelae (3), and unknown (8).

Seriousness criteria: Death (46 cases)

Forty-six subjects died, of which COVID-19 was not confirmed in 1 case; the remaining 45 confirmed cases are described below.

- Age: 39 to 91 years (n = 42), Mean = 74.4 years, Median = 77.5 years.

- Country/region of incidence: Spain (15), Estonia, France (5 each), Germany, Italy, US (3 each), Australia, Hungary, Japan (2 each), [redacted] (1 each).

- Gender: female (17), male (26), and unknown (3).

- Medical history (n = 41) included PTs in the following SOCs; Most frequently (≥2) reported PTs by SOC are presented below:
  - Vascular disorders – 19 cases (41.3%): Hypertension (16);
  - Cardiac disorders – 17 cases (37.0%): Atrial fibrillation (10), Myocardial ischaemia (4), Hypertensive heart disease (3), and Cardiac failure congestive (2);
  - Neoplasms benign, malignant and unspecified (incl cysts and polyps) – 16 cases (34.8%): Chronic lymphocytic leukaemia (3), Colon cancer (2);
  - Nervous system disorders – 11 cases (23.9%): Mixed dementia (4), Cognitive disorder (3), Parkinsonism (2);
  - Surgical and medical procedures – 11 cases (23.9%): Nephrectomy (2);
  - Respiratory, thoracic and mediastinal disorders – 10 cases (21.7%): Acute respiratory failure (4), Chronic obstructive pulmonary disease (3), Dyspnoea (2);
  - Metabolism and nutrition disorders – 9 cases (19.6%): Diabetes mellitus (4), Type 2 diabetes mellitus (3), Hyperuricaemia, (2);
  - Infections and infestations – 7 cases (15.2%): Sepsis (3)
  - Musculoskeletal and connective tissue disorders – 6 cases (13.0%): Osteoarthritis (4);

  - Renal and urinary disorders – 6 cases (13.0%): Chronic kidney disease (4), Acute kidney injury (2);
  - General disorders and administration site conditions – 4 cases (8.7%): Lithiasis (2);
  - Social circumstances – 4 cases (8.7%): Tobacco user (2);
  - Endocrine disorders – 3 cases (6.5%): Hypothyroidism (2);
  - Reproductive system and breast disorders – 3 cases (6.5%): Benign prostatic hyperplasia (3);
  - Blood and lymphatic system disorders – 2 cases (4.3%): Anaemia (2);
  - Other medical histories were reported under the following SOCs: Gastrointestinal disorders, Investigations (2 each), Congenital, familial and genetic disorders, Immune system disorders, Injury, poisoning and procedural complications, Psychiatric disorders, and Skin and subcutaneous tissue disorders (1 each).

- Latency of the COVID-19 occurrence was reported in 31 of the 46 cases:
  - Day 0 to 585 after dose 2 (8 cases);
  - Day 40 to 395 after dose 3 (20 cases);
  - Day 2 after dose 4 (1 case);
  - Day 0 and 125 after vaccination [dose number not reported] (2 cases).
- The most frequently (>1) reported causes of death in these 46 cases included COVID-19 pneumonia (25), COVID-19 (17), Vaccination failure (11), Drug ineffective (9), Respiratory failure (6), Dyspnoea, Multiple organ dysfunction syndrome (5 each), Sepsis (3), Cardiac failure, Cardio-respiratory arrest, Cardio-respiratory distress, Haemodynamic instability, Hypoxia, Respiratory distress, and SARS-CoV-2 sepsis (2 each).
  - In all 46 fatal cases, drug ineffective or vaccination failure was reported (cross referenced with Section 16.3.4.1 *Death* and Section 16.3.4.2 *Lack of Therapeutic Efficacy*).
  - Thirty-four of these 46 cases involved elderly subjects (aged 65 to 74 years [12] or ≥75 years [22]), including 22 subjects with underlying medical history of clinical significance.
  - Among the remaining 12 cases; 3 of them had concurrent medical histories (51 to 64 years [3]) that could impact the severity and evolution of the COVID-19 infection, including but not limited to immune system disorders (immunodeficiency, immunosuppression), renal disorders (acute kidney injury, chronic kidney disease, end stage renal disease) and respiratory disorders (acute respiratory distress syndrome, acute respiratory failure, chronic respiratory disease, dyspnoea).
  - Of the remaining 9 cases where medical history was not reported, 1 case reported relevant concomitant medications including daratumumab, dexamethasone, and elranatamab. None of the remaining 8 cases reported concomitant medications. The causes of death were reported as COVID-19 (5), Drug ineffective (4), COVID-19 pneumonia, Respiratory failure (3 each), Multiple organ dysfunction syndrome, SARS-CoV-2 sepsis (2 each), Cardio-respiratory distress, Facial paresis, Lung

carcinoma cell type unspecified stage IV, Pulmonary embolism, Pyrexia, and Vaccination failure (1 each). In 5 cases, the latency to onset of COVID-19 infection was not reported; in the remaining 3 cases the latency reported from dose 2 was 0 days, and from dose 3 was 110 and 182 days.

Second Booster Analysis

No cases reported events occurring after administration of a second booster vaccination.

Conclusion

The purpose of this review of subjects with COVID-19 following vaccination is to identify cases of potential vaccine-associated enhanced disease. The nature of spontaneously reported data provides a challenge because of the lack of a comparison group. Further, the background rate of VAED is not known. No cases were reported after administration of a second booster vaccination with BNT162b2 (original or bivalent). Considering the limitations of the review, VAED/VAERD remains a theoretical risk for the vaccine. The MAH is proposing to remove this important potential risk from the list of the safety concerns (Section 16.4 *Characterisation of Risks*).

16.3.3. Evaluation of Other Risks (not categorised as important)

The Republic of Korea MFDS requested the MAH to provide: *Safety evaluation for the second booster vaccination. Up-to-date safety information (post-marketing safety information, etc.) related to booster vaccination-related adverse reactions of special interest (AESI) and vaccine related exacerbated diseases (VAED including VAERD.) The MAH self-committed to provide this information in the current PSUR.*

Response

The MAH has implemented a search for the administration of booster doses of BNT162b2 original and BNT162b2 bivalent vaccines. Please refer for each AESI to the subsection "Second Booster Analysis" for the analysis of cases occurred after the second booster.

In the PRAC AR of the PSUR #3, the PRAC requested that *For future PSURs in the section 'Evaluation of AESIs', the cardiovascular AESIs, haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal*.

Response

Upon review of the incremental data of cases evaluated for all the above mentioned topics, no new safety issues/signals or reporting pattern changes were detected. These topics have been removed from the text of the PSUR.

After responding to the TGA's queries on the Comirnaty SBSR #3 on 20 October 2022 (original seq 0166) - see SCC-REQ-92709 - the PSUR Unit Evaluator provided the following request:

Question 1: The TGA accepts the causality assessments of the sponsor. It is understood that the signal is closed, in line with the EMA PRAC Rapporteur. The sponsor is requested to provide a review of cumulative data on this topic (subacute thyroiditis) in the next SSR (including but not limited to assessment of causation for serious cases).

Response

Conclusions of the cumulative review of the cases in the MAH safety database are provided in Section 16.3.3.1.3.1. *Thyroiditis Subacute – Cumulative Review*. Please refer to Appendix 5.6.3. for more details.

In the PRAC AR of the PSUR #3, the following request was made: *The MAH should continue to closely monitor MIS-C/-A as outlined in PRAC's signal recommendation (EPITT 19732) and all new cases of MIS-C/-A should be reported in the future PSURs.*

Response

Please refer to Appendix 5.6.1 for the review of the cases received in the reporting interval.

A request was made from Canada MHPD on 20 September 2022, following their review of aSMSR #6:

Cases of Guillain-Barre Syndrome (GBS) is not discussed in this abbreviated summary safety report. Please provide an analysis of GBS in the next PSUR including discussion about the international regulatory action from Japan's PMDA (inclusion of GBS in the important precautions section of the Japan package insert updated on 10 June 2022 and inclusion of GBS as an important potential risk in the Japan RMP).

Response

Please refer to Section 16.3.3.1.6.1 *GBS/Miller Fisher Syndrome* for case summary in the interval period.

As part of the approval letter for the emergency use of Tozinameran – COVID-19 mRNA vaccine (nucleoside modified) – COMIRNATY®, the WHO requested the MAH *to provide additional data on vaccine immunogenicity, effectiveness and safety on population groups represented in Low- and Middle-Income Countries (LMICs) including individuals with*

conditions such as malnutrition and populations with existing co-morbidities such as tuberculosis, human immunodeficiency virus (HIV) infection and other high prevalent infectious diseases.

Response

Please refer to Section 16.3.3.1.12. AESIs in subjects with Malnutrition; HIV infection for case summary in the interval period.

There were no other risks that were classified as listed adverse events in which a SMSR or SMSR assessment report recommended/requested continued monitoring in future PSURs and/or risks not categorised as important in which new information has become available during the reporting interval that allows further characterisation of a previously recognised risk.

16.3.3.1. Adverse Events of Special Interest (AESIs)

The company's AESI list takes into consideration the lists of AESIs from several expert groups and regulatory authorities including but not limited to the following: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general. The AESI list includes MedDRA PTs, HLTs, HLGTs or MedDRA SMQs and will be changed as appropriate based on the evolving safety profile of the vaccine.

Overlapping terms among multiple categories were assigned to one category only based on their most clinical relevance.

Please refer to Appendix 5.7 for the observed versus expected analysis for the AESIs.

16.3.3.1.1. Anaphylactic AESIs

Search criteria – PTs: Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock.[62]

Clinical Trial Data

- Number of cases: 1 (BNT162b2) (0.32% of 309 cases of the total CT dataset), compared to 3 cases (0.45%) retrieved in the PSUR #3.

The investigator reported that there was not a reasonable possibility that the events anaphylactic reactions were related to study vaccine (BNT162b2), or clinical trial

[62] According to the search criteria specified for Anaphylaxis in the EU-RMP v 5.0.

procedures. No clinical trial procedures were performed at the time of the event, therefore there was no possibility the event was related to clinical trial procedures. The Sponsor reported that there was not enough evidence to reasonably attribute the case to study vaccine, concomitant drugs or clinical trial procedure based on the latency. Of note, the event reported as an anaphylactic reaction with unknown cause (PT Anaphylactic reaction) occurred approximately 5 months after receiving the booster dose (third dose) of study vaccine (BNT162b2).

Post-Authorisation Data

- Number of cases: 421(BNT162b2 [333], BNT162b2 + BNT162b2 Omi BA.1 [17], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [70]) (0.15% of 282,992 cases, the total PM dataset), compared to 1037 cases (0.20%) retrieved in the PSUR #3.
- MC cases (291), NMC cases (130).
- Country/region of incidence (≥ 10): Japan (130), Poland (81), Germany (48), US (46), Australia (13), Malaysia, UK (11 each), and Greece (10); the remaining 71 cases were distributed among 26 countries.
- Subjects' gender: female (261), male (62) and unknown (98).
- Subjects' age in years: n = 360, range: 3 – 92 years, mean: 43.6, median: 43.0.
- Medical history (n = 162); the most frequently (≥ 8) reported medical conditions included Drug hypersensitivity (33), Asthma, Food allergy (25 each), Hypertension (22), Anaphylactic reaction, Hypersensitivity (14 each), Diabetes mellitus (12), Seasonal allergy (9), Contrast media allergy, and Type 2 diabetes mellitus (8 each).
- COVID-19 Medical history (n = 5): COVID-19 (5)
- Co-suspect medications (n = 18 cases): Relevant co-suspect medications (>1) included varicella zoster vaccine RGE (CHO) (3), elasomeran, macrogol (2 each).
- Number of relevant events: 459.
- Relevant event seriousness: serious (459).
- Reported relevant PTs: Anaphylactic reaction (321), Anaphylactic shock (128), Anaphylactoid reaction (9), Anaphylactoid shock (1).
- Time to event onset[63]: n = 318, range: <24 hours to 234 days, median: 0 days. Immunologic (IgE-mediated) hypersensitivity reactions such as anaphylaxis and non-immunologic (anaphylactoid) reactions generally occur shortly after exposure to exposure, however, for completeness, those events with inconsistent time to onset and/or duration reported are included.
  - <24 hours: 273 events (2 of which had a fatal outcome);

[63] This number does not include the events for which administration dates or event onset dates were partially reported.

- 1 day: 14 events;
- 2-7 days: 15 events;
- 8-14 days: 2 events;
- 15-30 days: 2 events;
- 31-180 days: 10 events;
- 181-234 days: 2 events.

- Duration of relevant events[64]: n = 81, range: <24 hours to 371 days, median 0 day.
  - <24 hours: 42 events;
  - 1 day: 18 events;
  - 2-7 days: 11 events;
  - 8-14 days: 2 events;
  - 15-30 days: 2 events;
  - 31-180 days: 3 events;
  - 181-371 days: 3 events.

- Relevant event outcome: fatal (3), resolved/resolving (211), resolved with sequelae (11), not resolved (27), unknown (207).
- In 3 cases (reporting 3 relevant events with fatal outcomes), the reported cause of death was Anaphylactic reaction (3). Two (2) of the 3 cases involved elderly subjects. Medical history was provided in 1 case and included Autoimmune disorder.

Of the 169 cases reporting medical history/co-suspect medications, 93 cases reported relevant medical history/risk factors (e.g., asthma, drug hypersensitivity, food allergies, autoimmune disorders, hypersensitivity, prior anaphylactic reactions, prior anaphylactic shock, seasonal allergy, contrast media allergy) and/or co-suspect (e.g., varicella zoster vaccine RGE (CHO), adalimumab, influenza vaccine, influenza vaccine inact SPLIT 4V), which may have contributed to the anaphylaxis related events.

Analysis by age group

CT: Paediatric (1).

- A meaningful comparison between different age groups is not possible as there is only 1 paediatric case in the CT dataset.

PM: Paediatric (25), Adults (278), Elderly (58) and Unknown (60).

- No significant difference was observed in the reporting proportion of anaphylaxis relevant PTs between adult and elderly populations. Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

[64] Provided when reported for events with outcome of resolved and resolved with sequelae.

O/E Analysis

O/E analysis was performed for Anaphylaxis (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Second Booster Analysis

Thirty-two (32) cases reported 33 events occurred after administration of a second booster vaccination. In 8 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 24 cases, 15 involved homologous second booster and 9 heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.2. COVID-19 AESIs

Search criteria - SMQ COVID-19 (Narrow and Broad) OR PTs Ageusia; Anosmia; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease.[65]

Cases reporting long COVID (PT: Post-acute COVID-19 syndrome) are reviewed in this section. Please refer also to Section 18.1 *Benefit-Risk Context – Medical Need and Important Alternatives (Complications of COVID-19 and Post-acute COVID).*

Clinical Trial Data

- Number of cases: 4 (BNT162b2 [3], blinded therapy [1]) (1.3 % of 309 cases, the total CT dataset), compared to 7 cases (1.0%) retrieved in the PSUR #3.
- Country/region of incidence: US (3), [redacted] (1).
- Subjects' gender: [redacted] (4).
- Subjects' age in years: n = 4, range: 2-82, mean: 32.8, median: 23.5
- Medical history (n = 2): the reported relevant medical conditions included the PTs Benign prostatic hyperplasia, Chronic obstructive pulmonary disease, Gastrooesophageal reflux disease, Jaundice neonatal, Laryngomalacia, Neuropathy peripheral, Osteoarthritis, Seasonal allergy, Type 2 diabetes mellitus (1 each).
- COVID-19 Medical history: none.

[65] The PTs Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease are evaluated in Section 16.3.2. *Evaluation of Important Potential Risks*, as overlapping terms with the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD).

- Co-suspect medications: none.
- Reported relevant PTs: COVID-19 (3), COVID-19 pneumonia (1). None of the events were related to BNT162b2 or blinded therapy.
- Relevant event outcome: resolved/resolving (4).

Post-Authorisation Data

- Number of relevant cases: 57,462 (original [56,904], original + Omi BA.1 [166], original + Omi BA.4/BA.5 [799]), (20.3% of 282,992 cases, the total PM dataset), compared to 54,335 cases (10.7%) retrieved in the PSUR #3.
- MC cases (45,052); NMC cases (12,410).
- Country/region of incidence (≥ 1%): Austria (40,531), US (5873), France (2511), UK (1493), Netherlands (1381), Germany (1246), Japan (594); the remaining 3833 cases were distributed among 61 countries.
- Subjects' gender: female (32,203), male (24,215) and unknown (1044).
- Subjects' age in years: n = 54,617, range: 1 year – 103.0 years, mean: 45.8, median: 45.0.
- Medical history (n = 7770): the most frequently (≥2%) reported relevant medical conditions included Hypertension (1345), Drug hypersensitivity (981), Asthma (963), Hypersensitivity (459).
- COVID-19 Medical history (n = 1323): COVID-19 (1171), Suspected COVID-19 (98), Post-acute COVID-19 syndrome (37), SARS-CoV-2 test positive (19), Exposure to SARS-CoV-2 (16), Asymptomatic COVID-19, Coronavirus infection (6 each), COVID-19 pneumonia (5), Coronavirus test positive, COVID-19 treatment, SARS-CoV-2 antibody test positive (1 each).
- Co-suspect medications (n = 6947); the most frequently (≥10) reported relevant co-suspect medications included COVID-19 vaccine (3921), elasomeran (1531), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (1240), COVID-19 vaccine NRVV AD26 (JNJ 78436735) (185), adalimumab (131), influenza vaccine (43), COVID-19 vaccine inact (VERO) CZ02 (34), ocrelizumab (31), upadacitinib (19), COVID-19 vaccine NRVV MVA (17), influenza vaccine inact SAG 4V (15)
- Number of relevant events: 57,925.
- Relevant event seriousness: serious (56,525), non-serious (1,402).
- Most frequently reported relevant PTs (≥2%): COVID-19 (54,456), and Suspected COVID-19 (1710).
- Time to event onset[63]: n = 49,091, range: <24 hours to 365 days, median: 136 days.

- <24 hours: 289 events (1 fatal event);
- 1 day: 298 events (3 fatal events);
- 2-7 days: 1008 events (8 fatal events);
- 8-14 days: 819 events (1 fatal event);
- 15-30 days: 1716 events (2 fatal events);
- 31-181 days: 42160 events (33 fatal events);
- ≥ 182 days: 2801 events (33 fatal events).

- Duration of relevant events[64]: n = 900, range: 24 hours to 421 days, median: 9 days:

- <24 hours: 31 events;
- 1 day: 20 events;
- 2-7 days: 303 events;
- 8-14 days: 345 events;
- 15-30 days: 123 events;
- 31-181 days: 54 events;
- 182-365 days: 19 events;
- >365-421 days: 5 events.

- Relevant event outcome[56]: fatal (123), resolved/resolving (3384), resolved with sequelae (137), not resolved (2683), unknown (51,599).

Fatal cases (123)

In 123 cases (reporting 136 relevant events of which 123 relevant events reported a fatal outcome), the reported causes of death (≥10) included COVID-19 (65), Drug ineffective (41), COVID-19 pneumonia (28), Vaccination failure (20), Death, Suspected COVID-19 (10 each). Of note, in 10 cases limited information regarding the cause of death was provided (PT Death [10]). Most (88 of 123 cases) of the fatal cases involved elderly subjects. When the medical history was provided (80 cases), the most frequently (≥ 5) relevant medical conditions included Hypertension (27), Atrial fibrillation (17), Osteoarthritis (7), Chronic kidney disease, Diabetes mellitus, Type 2 diabetes mellitus (6 each), Acute respiratory failure, Asthma, Chronic obstructive pulmonary disease, Cognitive disorder, Hypertensive heart disease, Hypothyroidism, and Myocardial ischaemia (5 each).

LONG COVID

Search criteria: PT Post-acute COVID-19 syndrome.

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of relevant cases: 178 (0.06% of 282,992 cases, the total PM dataset), compared to 200 cases (0.04%) retrieved in the PSUR #3.

- MC cases (67); NMC cases (111).

- Country/region of incidence: Germany (96), Austria (13), France (11), Finland (8), UK (7), Australia, Italy (6 each), Belgium, US (5 each), Netherlands, Sweden (4 each), Switzerland (3), Luxembourg, Norway, Spain (2 each), [redacted] 1 each).

- Subjects' gender: female (114), male (58) and unknown (6).

- Subjects' age in years: n = 159, range: 13 – 83 years, mean: 45.5, median: 44.0. Of these 159 subjects where the subjects' age was provided, there were 3 paediatric, 138 adults, and 18 elderly subjects.

- Medical history (n = 89): the most frequently (≥2%) reported medical conditions included Seasonal allergy (14), Asthma (13) and Hypertension (11).

- COVID-19 Medical history (n = 40): COVID-19 (30), Post-acute COVID-19 syndrome (13), Suspected COVID-19 (4).

Analysis by age group

- CT: Paediatric (2), Adults (1), Elderly (1).

  – Due to low volume of cases, a meaningful comparison between the age groups (paediatric, adults and elderly) is not possible.

- PM: Paediatric (2041), Adults (44,300), Elderly (8562).

  – No significant difference was observed in the reporting proportion of the most frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population.

O/E Analysis

O/E analysis was performed for Ageusia/anosmia (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Second Booster Analysis

There were 2974 cases that reported 7068 events (including 3002 relevant events) which occurred after the administration of a second booster vaccination. In 2173 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 801 cases, 17 involved homologous second booster and 784 heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.3. Immune-mediated/autoimmune AESIs

Search criteria[66]: SMQ Immune-mediated/autoimmune disorders (Narrow and Broad) OR HLGT (All Path) Autoimmune disorders OR PTs Cytokine storm; Hypersensitivity; Thyroiditis subacute; Thrombocytopenia.

Out of 6156 PM cases, 1 case was determined to be non-contributory and was not included in the discussion since this case involved exposure to the vaccine during the mothers' pregnancy.

Clinical Trial Data

- Number of cases: 9 (BNT162b2 [3] and blinded therapy [6] (2.9% of 309 cases, the total CT dataset), compared to 19 cases (2.8%) retrieved in the PSUR #3.
- Country/region of incidence: US (7) and Brazil (2).
- Subjects' gender: female (5) and male (4).
- Subjects' age in years: n = 9, range: 1.58 – 74, mean 28.1, median 4.0.
- Medical history (n = 5): Hypertension (3), Asthma, Type 2 diabetes mellitus, Depression, Colitis ulcerative, Gastrooesophageal reflux disease, Hyperlipidaemia, Back pain, Intervertebral disc protrusion, Hysterectomy, Constipation, Coeliac disease, Neuralgia, Spinal fusion surgery, Urinary incontinence, Uterine leiomyoma, Postmenopause, Patellofemoral pain syndrome, and Spinal nerve stimulator implantation (1 each).
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications: None.
- Number of relevant events: 9.
- Reported relevant PTs: Immune thrombocytopenia (2), Colitis ulcerative, Diabetes mellitus, Haemophagocytic lymphohistiocytosis, Myasthenia gravis, Myelin oligodendrocyte glycoprotein antibody-associated disease, Type 1 diabetes mellitus, and VIth nerve paralysis (1 each). All SAEs were assessed as not related to BNT162b2 or blinded therapy.
- Relevant event outcome: fatal (1), resolved (3), resolved with sequelae (1), not resolved (4).

[66] Eight (8) new PTs have been included in the search strategy due to MedDRA upgrade v. 25.1 (Autoimmune cerebellar ataxia, Food protein-induced allergic proctocolitis, Food protein-induced enterocolitis syndrome, Gluten ataxia, Immune-mediated scleritis, Lichen planus pemphigoides, Paradoxical skin reaction and Polyradiculoneuropathy). Encephalomyelitis, already included in the list of the AESI terms, has been reassigned to Immune mediated (previously in the Neurological).

Post-Authorisation Data

- Number of cases: 6155 (BNT162b2 [6012], BNT162b2 + BNT162b2 Omi BA.1 [68] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [85])[67] (2.2% of 282,992 cases of the total PM dataset), compared to 11,726 cases (2.3%) retrieved in the PSUR #3.

- MC cases (2653), NMC cases (3502).

- Country/region of incidence: Germany (1854), France (584), US (393), Japan (385), Sweden (333), Denmark (299), UK (223), Italy (220), Poland (214), Norway (162), Belgium (159), Austria (141), Australia (136), Netherlands (128), Finland (117), Greece (104), Spain (72), Canada (68), Romania (52); the remaining 511 cases were distributed among 44 countries.

- Subjects' gender: female (3856), male (1951), and unknown (348).

- Subjects' age in years: n = 5574, range: 3 – 97, mean: 50.3, median: 51.0.

- Medical history (n = 2753); the most frequently (≥100) reported relevant medical conditions included Hypertension (448), Seasonal allergy (263), Asthma (201), Drug hypersensitivity (188), Hypersensitivity (162), Psoriasis (133), Hypothyroidism (130), Food allergy (124), and Autoimmune thyroiditis (100).

- COVID-19 Medical history (n = 262): COVID-19 (221), Suspected COVID-19 (30), Post-acute COVID-19 syndrome (5), COVID-19 pneumonia (4), Asymptomatic COVID-19 (3), Exposure to SARS-CoV-2 (2), Coronavirus infection, Coronavirus test positive, and SARS-CoV-2 test positive (1 each).

- Co-suspect medications (n = 319); the most frequently (≥5) reported relevant co-suspect medications included elasomeran (92), adalimumab (75), influenza vaccine (20), influenza vaccine inact split 4V (13), COVID-19 vaccine, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (9 each), upadacitinib (7), influenza vaccine inact SAG 4V, prednisone (6 each), paracetamol, and risankizumab (5 each).

- Number of relevant events: 6788.

- Relevant event seriousness[33]: serious (4423) and non-serious (2366).

- Most frequently (≥2%) reported relevant PTs: Hypersensitivity (1142), Psoriasis (361), Polymyalgia rheumatica (278), Autoimmune disorder (254), Rheumatic disorder, Thrombocytopenia (164 each), Dermatitis (144), Neuralgic amyotrophy (130), Alopecia areata (128), and Autoimmune thyroiditis (125).

[67] Some cases reported more than 1 suspect drug.

- Time to event onset[63]: n = 3319, range: <24 hours to 540 days, median: 9 days.

  - <24 hours: 554 events (3 of which had a fatal outcome);
  - 1 day: 352 events (4 of which had a fatal outcome);
  - 2-7 days: 682 events (4 of which had a fatal outcome);
  - 8-14 days: 396 events (8 of which had a fatal outcome);
  - 15-30 days: 421 events (5 of which had a fatal outcome);
  - 31-181 days: 725 events (9 of which had a fatal outcome);
  - 182-540 days: 189 events (2 of which had a fatal outcome).

- Duration of relevant events[64]: n = 472, range: <24 hours to 549 days, median 33 days.

  - <24 hours: 66 events;
  - 1 day: 29 events;
  - 2-7 days: 65 events;
  - 8-14 days: 29 events;
  - 15-30 days: 40 events;
  - 31-180 days: 108 events;
  - 181-549 days: 135 events.

- Relevant event outcome[56]: fatal (76), resolved/resolving (1777), resolved with sequelae (446), not resolved at the time of reporting (2403), and unknown (2093).

Fatal cases (63)

In 63 cases (reporting 76 relevant events with a fatal outcome), the reported causes of death (≥3) included Interstitial lung disease (11), Multiple organ dysfunction syndrome (9), Pulmonary fibrosis (6), Cerebral infarction, Encephalopathy, Myocarditis, Respiratory failure (4 each), Atrial fibrillation, Cardiac arrest, Cardio-respiratory arrest, Condition aggravated, Cytokine storm, Encephalitis, Pneumonia, Pulmonary embolism, Pulmonary hypertension, and Renal failure (3 each). Most (44 of 61 cases that provided age) of the fatal cases involved elderly subjects. When the medical history was provided (44 cases), significant medical conditions reported in more than 2 cases included Hypertension (18), Diabetes mellitus (6), Tobacco user, Type 2 diabetes mellitus (5 each), Atrial fibrillation, COVID-19 (4 each), Asthma, Cardiac failure, Chronic kidney disease, Gastrooesophageal reflux disease, and Prostate cancer (3 each).

Analysis by age group

- CT: Paediatric (5), Adults (2), and Elderly (2).

  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (206), Adults (4085), Elderly (1327) and Unknown (537).

  – Among the frequently (>2%) reported immune mediated/autoimmune AESIs, it was observed that:

    - PT Polymyalgia rheumatica was reported at a higher frequency in the elderly population when compared to paediatric and adult populations ((none in paediatrics vs 2.4% in adults vs 11.9% in elderly).
    - PT Alopecia areata was reported at a higher frequency in the paediatric population when compared to the adult and elderly populations (6.3% in paediatrics vs 2.2% in adults vs 0.8% in elderly).
    - PTs Rheumatic disorder, Neuralgic amyotrophy, Dermatitis, and Psoriasis were reported at a higher frequency in the adult and elderly populations when compared to the paediatric population (Rheumatic disorder [none in paediatrics vs 2.6% in adults vs 3.1% in elderly], Neuralgic amyotrophy [0.5% in paediatrics vs 2.4% in adults vs 1.8% in elderly], Dermatitis [none in paediatrics vs 2.3% in adults vs 2.6% in elderly], Psoriasis [1.5% in paediatrics vs 6.1% in adults vs 6.3% in elderly]).
    - PT Thrombocytopenia was reported at a higher frequency in the paediatric and elderly population when compared to the adult population (5.3% in paediatrics vs 2.0% in adults vs 4.7% in elderly).
    - PTs Autoimmune thyroiditis and Autoimmune disorder were reported at a higher frequency in the adult population when compared to the paediatric and elderly populations (Autoimmune thyroiditis [1.0% in paediatrics vs 2.6% in adults vs 0.6% in elderly], Autoimmune disorder [1.0% in paediatrics vs 4.0% in adults vs 1.7% in elderly].
    - PT Hypersensitivity was reported at a higher frequency in the paediatric and adult populations when compared to the elderly population (19.9% in paediatrics vs 20.7% in adults vs 10.5% in elderly).

O/E Analysis

O/E analysis was performed for Acute disseminated encephalomyelitis (ADEM), ADEM and encephalitis, Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*). The O/E ratio of ADEM (narrow definition) using the 21-day risk window for the 25-49 years age group was 1.101, however the confidence interval included 1 (95% CI [0.853, 1.398]).

Second Booster Analysis

One hundred and sixty-five (165) cases reported 189 events that occurred after administration of a second booster vaccination. In 81 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 84 cases, 56 involved homologous second booster and 28 heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.3.1. Thyroiditis Subacute – Cumulative Review

Search criteria – PT Thyroiditis subacute.

Please refer to Appendix 5.6.3. *Subacute Thyroiditis* for the cumulative review of the cases in the MAH safety database.

Conclusion

Taking into account the totality of available information, including this review the other routine signal detection activities including observed to expected analyses and review of the medical literature on subacute thyroiditis, there is no change in the MAH's previous assessment that there is insufficient evidence to conclude a causal association between the vaccine and subacute thyroiditis.

16.3.3.1.4. Multisystem Inflammatory Syndrome in Children / Adults

Search Criteria – PTs: Cytokine release syndrome; Distributive shock; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Systemic inflammatory response syndrome.

Please refer to Appendix 5.6.1 *Multisystem Inflammatory Syndrome* for the review of the MIS-C/MIS-A cases received in the reporting interval.

Clinical Trial Data

- Number of cases: 0; no cases were retrieved in the PSUR #3.

Post-Authorisation Data

- Number of relevant cases: 92 (0.03% of 282,992 cases in the total PM dataset), compared to 207 (0.04%) retrieved in PSUR #3. BNT162b2 (85), BNT162b2 + BNT162b2 Omi BA.4/BA.5 (4), BNT162b2 + BNT162b2 Omi BA.1 (3).
- MC cases (73), NMC cases (19).
- Country/region of incidence (≥5): Germany (21), France (15), Japan (12), Australia (8), US (7), Italy (6); the remaining 23 cases were distributed among 12 countries.
- Subjects' gender: female (39), male (47), unknown (6).
- Subjects' age in years: n = 84, range: 13 months – 91, mean: 45.4, median: 44.5.
- Medical history (n = 54); the most frequently (≥3) reported medical conditions included Hypertension (13), Atrial fibrillation (6), Asthma, Chronic obstructive pulmonary

disease, Diabetes mellitus (4 each), Cardiac failure, Chronic kidney disease, Obesity, Pyrexia, Type 2 diabetes mellitus (3 each).

- COVID-19 medical history (n = 7): COVID-19 (6), Coronavirus test positive, Exposure to SARS-CoV-2 (1 each). Of the 7 cases, the COVID infection was past medical history (2), unknown (4).
- Co-suspect medications (n = 8 cases): COVID-19 vaccine (2), acetylsalicylate lysine, clozapine, desogestrel, elasomeran, fluindione, hyoscine, influenza vaccine, influenza vaccine inact SPLIT 4V, loxapine, tropatepine, valproate (1 each).
- Number of relevant events: 94.
- Relevant event seriousness: serious (94).
- Relevant PTs: Multiple organ dysfunction syndrome (43), Multisystem inflammatory syndrome (17), Multisystem inflammatory syndrome in children (12), Systemic inflammatory response syndrome (9), Multisystem inflammatory syndrome in adults (7), Cytokine release syndrome, Distributive shock (3 each).
- Time to event onset[63]: n = 36, range: <24 hours to 205 days, median: 12 days.
  - <24 hours: 2 events (1 of which had a fatal outcome);
  - 1 day: 4 events (4 of which had a fatal outcome);
  - 2-7 days: 8 events (1 of which had a fatal outcome);
  - 8-14 days: 5 events (2 of which had a fatal outcome);
  - 15-30 days: 5 events (2 of which had a fatal outcome);
  - 31-180 days: 10 events (5 of which had a fatal outcome);
  - >180 days: 2 events (1 of which had a fatal outcome).
- Duration of relevant events[64]: n = 1 (7 days).
- Relevant event outcome: fatal (38), resolved/resolving (29), resolved with sequelae (1), not resolved (6), unknown (20).

Fatal cases (37)

In 37 fatal cases (reporting 38 relevant events with fatal outcome), the reported causes of death were coded to Multiple organ dysfunction syndrome (33), Distributive shock (3), Systemic inflammatory response syndrome (2). Of 37 cases, 19 involved elderly subjects. When the medical history was provided (28 cases), the most frequently (≥3) reported medical conditions included Hypertension (9), Atrial fibrillation (6), Diabetes mellitus (4), Asthma, Cardiac failure, Chronic obstructive pulmonary disease, COVID-19 (3 each).

Analysis by age group

- PM: Paediatric (19 [1 Infant, 6 Child, 12 Adolescent]), Adult (38), Elderly (28), Unknown (7).

  – Among the relevant multisystem inflammatory syndrome events, it was observed that:

    - PT Multiple organ dysfunction syndrome was reported at a higher frequency in the elderly population compared to the adult and paediatric populations (67.8% of the elderly population vs 42.1% of the adult population and 10.5% of the paediatric population).
    - PT Multisystem inflammatory syndrome was reported at a higher frequency in the paediatric population compared to the adult and elderly populations (26.3% of the paediatric population vs 21.0% of the adult population and 14.2% of the elderly population).
    - PT Multisystem inflammatory syndrome in children was reported, as expected, primarily in the paediatric population (63.1% were in the paediatric population).
    - PT Systemic inflammatory response syndrome was reported at similar frequency in the adults and the elderly population (10.5% of the adult population vs 10.7% of the elderly population; no cases in paediatric population).
    - PT Multisystem inflammatory syndrome in adults was reported, as expected, primarily in the adult population (18.4% of the adult population); no cases in paediatric or elderly population).
    - PT Cytokine release syndrome was observed only in the adult and elderly populations (5.2% in the adult population and 3.5% in the elderly population; no cases in paediatric population).
    - PT Distributive shock was observed only in the adult and elderly populations (2.6% in the adult population and 3.5% in the elderly population; no cases in paediatric population).

O/E Analysis

O/E analysis was performed for Multisystem inflammatory syndrome (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*). For the MIS analysis, the 21-24 years age group using the 21-day and 42-day risk windows has an O/E ratio greater than 1; however, the results are not statistically significant as the 95% confidence intervals include 1. For all other age groups and risk windows, the O/E ratio is less than 1.

Second Booster Analysis

Eight (8) cases reporting 9 events occurred after administration of a second booster vaccination. In 3 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. The remaining 5 cases involved homologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.5. Myocarditis and Pericarditis AESIs

Please refer to the Risk 'Myocarditis and Pericarditis' in Section 16.3.1.1 *Important Identified Risks – Myocarditis* and in Section 16.3.1.1.2. *Important Identified Risks – Pericarditis.*

16.3.3.1.6. Neurological AESIs (including demyelination)

Search Criteria[68] - SMQ Generalised convulsive seizures following immunisation (Narrow) OR SMQ Demyelination (Narrow and Broad) OR PTs Ataxia; Cataplexy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Meningitis viral; Miller Fisher syndrome; Narcolepsy; Neuropathy peripheral; Polyneuropathy.

Upon review, 4 PM cases were determined to be non-contributory and were not included in the discussion since these 4 cases involved exposures to the vaccine during the mother's pregnancy or through breastfeeding.

Clinical Trial Data

- Number of cases: 8 cases (BNT162b2 [4], blinded therapy [4]; 2.6% of 309 cases in the total CT dataset), compared to 15 cases (2.2%) retrieved in the PSUR #3.
- Country/region of incidence: US (5), [redacted] (1 each).
- Subjects' gender: female (6), male (2).
- Subjects' age in years: n = 8, range: 2 – 58 years, mean: 12.4, median: 5.50.
- Medical history (n = 7); the medical condition reported more than once was Febrile convulsion (3).
- COVID-19 medical history: None.
- Co-suspect medications: None.

[68] Three (3) new PTs have been included in the search strategy due to MedDRA upgrade v. 25.1 (Anti-sulfatide autoantibody positive, Ascending flaccid paralysis and Meningitis viral). Miller-Fisher syndrome, already included in the list of the AESI terms, has been reassigned to Neurological (previously in the Immune mediated).

- Reported relevant PTs: Seizure (4), Ataxia, Epilepsy, Febrile convulsion, Multiple sclerosis relapse, Narcolepsy (1 each). None of these SAEs were assessed as related to BNT162b2/blinded therapy.

- Relevant event outcome: resolved (5), resolved with sequelae (2), not resolved (2).

Post-Authorisation Data

- Number of relevant cases: 2597 (BNT162b2 [2474], BNT162b2 + BNT162b2 Omi BA.1 [49], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [81]) (0.9% of 282,992 cases in the total PM dataset), compared to 5111 cases (1.0%) retrieved in the PSUR #3.

- MC cases (1365), NMC cases (1232).

- Country/region of incidence (> 50): Germany (702), Poland (320), France (204), Japan (188), US (162), Czech Republic (106), UK (92), Finland (71), Italy (66), Australia, Sweden (63 each), Austria (62), Denmark (54), Norway (50); the remaining 394 cases were distributed among 40 countries.

- Subjects' gender: female (1440), male (869), unknown (288).

- Subjects' age in years: n = 2418, range: 6 months – 98 years, mean: 47, median: 47.0.

- Medical history (n = 1211); the most frequently (>61) reported medical conditions included Hypertension (171), Multiple sclerosis (117), Seasonal allergy (93), Asthma (79), Drug hypersensitivity (77), Epilepsy (76), Relapsing-remitting multiple sclerosis (73), Fibromyalgia (61).

- COVID-19 Medical history (n = 140): COVID-19 (114), Suspected COVID-19 (18), Post-acute COVID-19 syndrome (10), COVID-19 pneumonia (3), Coronavirus test positive (1).

- Co-suspect medications (n = 111 cases); the most frequently (≥3) reported co-suspect medications included elasomeran (23), influenza vaccine inact SPLIT 4V (14), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine (11 each), adalimumab (8), ocrelizumab (7), COVID-19 vaccine (4), influenza vaccine inact SAG 4V (3).

- Number of relevant events: 2819.

- Relevant event seriousness: serious (2541), non-serious (278).

- Most frequently (>53) reported relevant PTs: Seizure (663), Guillain-Barre syndrome (266), Neuropathy peripheral (263), Epilepsy (196), Polyneuropathy (170), Fibromyalgia (161), Multiple sclerosis (149), Multiple sclerosis relapse (140), Trigeminal neuralgia (128), Optic neuritis (78), Febrile convulsion (75), Ataxia (67), Meningitis (53).

- Time to event onset[63]: n = 1696, range: <24 hours to 497 days, median: 4 days.

  - <24 hours: 439 events (2 of which had a fatal outcome);
  - 1 day: 248 events (4 of which had a fatal outcome);
  - 2-7 days: 314 events (5 of which had a fatal outcome);
  - 8-14 days: 173 events (1 of which had a fatal outcome);
  - 15-30 days: 179 events (6 of which had a fatal outcome);
  - 31-180 days: 282 events (3 of which had a fatal outcome);
  - 181-497 days: 61 events (1 of which had a fatal outcome).

- Duration of relevant events[64]: n = 303, range: <24 hours to 578 days, median 21 day.

  - <24 hours: 77 events;
  - 1 day: 25 events;
  - 2-7 days: 32 events;
  - 8-14 days: 14 events;
  - 15-30 days: 71 events;
  - 31-180 days: 40 events;
  - 181-578 days: 44 events.

- Relevant event outcome[56]: fatal (29), resolved/resolving (782), resolved with sequelae (212), not resolved (854), unknown (953).

Fatal cases (26)

In 26 cases (reporting 29 relevant events with fatal outcome), the reported causes of death (≥3) included Seizure (14), Epilepsy, Guillain-Barre syndrome (3 each). Over half (16 of 26 cases) of the fatal cases involved elderly subjects. When the medical history was provided (26 cases), the most frequent (≥3) medical conditions included Hypertension (10), COVID-19, Type 2 diabetes mellitus (4 each), Chronic obstructive pulmonary disease (3).

Analysis by age group

- CT: Paediatric 7 [7 Child], Adult (1).

  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (187 [1 Infant, 67 Child, 119 Adolescent]), Adult (1768), Elderly (495), Unknown (147).

  - Among the most frequently (>53) reported relevant neurological events, it was observed that:

    - The PTs Febrile convulsion and Seizure were reported at higher frequencies in the paediatric population compared to the adult population and the elderly population

(10.7% and 54.6% in the paediatric population vs 2.9% and 25.1% in the adult population, and 0.8%, and 16.8% in the elderly population, respectively). This pattern is consistent with the known epidemiology of seizures.

- The PTs Neuropathy peripheral and Polyneuropathy were reported at higher frequencies in the elderly population compared to the paediatric population and the adult population (14.6% and 10.7% in the elderly population vs 2.1% and 0.5% in the paediatric population, and 9.3% and 6.1% in the adult population, respectively).
- The PTs Multiple sclerosis and Trigeminal neuralgia were reported at higher frequencies in the adult population compared to the paediatric population and the elderly population (7.2% and 5.7% in the adult population vs 1.6% and 1.1% in the paediatric population, and 0.8% and 3.6% in the elderly population, respectively).

O/E Analysis

O/E analysis was performed for Generalized convulsive, Fibromyalgia, Guillain-Barré syndrome, Meningitis, Narcolepsy, Multiple sclerosis (MS) and Polyneuropathy. The O/E ratio for polyneuropathy with BNT162b2 (monovalent presentation) using the 21-day risk window is 1.017 however the confidence interval includes 1 (95% CI [0.967, 1.068]). (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Second Booster Analysis

Ninety (90) cases reported 100 events occurred after administration of a second booster vaccination. In 19 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 71 cases, 51 involved homologous second booster and 39 heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.6.1. GBS/Miller Fisher Syndrome

Search criteria: SMQ Guillain-Barre syndrome (Narrow).

Clinical Trial Data

- During the current reporting period and previous PSUR #3 reporting period, there were no serious cases in the CT dataset.

Post-Authorisation Data

- Number of cases: 317 (BNT162b2 [298], BNT162b2 + BNT162b2 Omi BA.1 [6], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [15]) (0.1% of 282,992 cases, the total PM dataset), compared to 618 cases (0.1%) retrieved in the PSUR #3.

- MC cases (209), NMC cases (108).

- Country/region of incidence (≥10): Japan (64), Germany (58), France (30), US (28), Italy (18), Austria (15), Australia, Poland (13 each), UK (10); the remaining 68 cases were distributed among 26 countries.

- Subjects' gender: female (146), male (147) and unknown (24).

- Subjects' age in years: n = 285, range: 5 – 94 years, mean: 53.7, median: 57.0.

- Medical history (n = 142); the most frequently (≥6) reported medical conditions included Hypertension (37), Drug hypersensitivity, Type 2 diabetes mellitus (11 each), Diabetes mellitus (9), Guillain-Barre syndrome, Seasonal allergy (8 each), Gastrooesophageal reflux disease, Obesity (7 each), Chronic inflammatory demyelinating polyradiculoneuropathy, Paraesthesia (6 each).

- COVID-19 Medical history (n =18): COVID-19 (13), Suspected COVID-19 (3), COVID-19 pneumonia (2), Post-acute COVID-19 syndrome (1).

- Co-suspect medications (n = 17); the reported relevant co-suspect medications included influenza vaccine inact SPLIT 4V (8), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (3), diphtheria vaccine toxoid, pertussis vaccine acellular 5-component, polio vaccine inact 3V (vero), tetanus vaccine toxoid (2), COVID-19 vaccine, influenza vaccine inact SAG 4V, ipilimumab, nivolumab, rabies vaccine inact (chick embryo) (1 each).

- Number of relevant events: 338.

- Relevant event seriousness: serious (338).

- Relevant PTs: Guillain-Barre syndrome (266), Chronic inflammatory demyelinating polyradiculoneuropathy (36), Demyelinating polyneuropathy (16), Miller Fisher syndrome (12), Subacute inflammatory demyelinating polyneuropathy (3), Acute motor-sensory axonal neuropathy, Bickerstaff's encephalitis (2 each), Ascending flaccid paralysis (1).

- Time to event onset[63]: n = 166, range: <24 hours to 329 days, median: 13 day.

  - <24 hours: 10 events;
  - 1 day: 13 events;
  - 2-7 days: 33 events (1 of which had a fatal outcome);

- 8-14 days: 35 events;
- 15-30 days: 34 events (1 of which had a fatal outcome);
- 31-180 days: 34 events;
- 181-329 days: 7 events.

- Duration of relevant events[64]: n = 11, range: 5 - 405 days, median: 84 days.

  - 2 – 7 days: 1 event;
  - 8-14 days: 0 events;
  - 15-30 days: 3 events;
  - 31-180 days: 4 events;
  - 181-405 days: 3 events.

- Relevant event outcome[56]: fatal (3), resolved/resolving (96), resolved with sequelae (19), not resolved (111), unknown (111).

Fatal cases (3)

In 3 cases (reporting 3 relevant events with fatal outcome), the reported causes of death included Guillain-Barré syndrome (3), Hepatic failure, Hypokalaemia, Hyponatraemia, Multiple organ dysfunction syndrome, Myositis, Paraparesis, Pneumonia, Product use issue, Renal failure, Rhabdomyolysis (1 each). All 3 fatal cases involved elderly subjects with medical conditions that included Hypertension (2), Alcohol use, Chronic obstructive pulmonary disease, Emphysema, Ex-tobacco user, Rectosigmoid cancer, Sigmoidectomy, Thyroidectomy, Type 2 diabetes mellitus, and Walking aid user (1 each). In 1 of the 3 cases, based on a possible temporal association the causal association of suspect product BNT162b2 for the event of Guillain-Barre syndrome could not be excluded. The remaining 2 fatal cases provided limited information precluding a meaningful medical assessment.

Analysis by age group

PM: Paediatric (25), Adult (161), Elderly (104), and Unknown (27).

- Among the frequently (≥2%) reported relevant Guillain-Barré syndrome events, Miller Fisher syndrome was reported at a higher frequency in elderly population when compared to adult population (2.5% in adults vs 7.7% in elderly). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

O/E Analysis

O/E analysis was performed on Guillain-Barré syndrome (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No safety signals have emerged based on the review of these cases, and on analyses by age group and O/E. Safety surveillance will continue.

For completeness, the MAH informs that in June 2022, the Japan product information Important Precautions section was amended to state that cases of Guillain-Barré syndrome have been reported following inoculation with coronavirus modified uridine RNA vaccine, by request of the Japan Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency. No similar amendments were made to the MAH RSI.

16.3.3.1.7. Pregnancy related AESIs

Search criteria – PTs: Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal death; Maternal death affecting foetus; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Renal failure neonatal; Renal impairment neonatal; Stillbirth; Uterine rupture; Vasa praevia.

For relevant cases, please refer to Section 16.3.5.3 *Use in Pregnant/Lactating Women.*

16.3.3.1.8. Glomerulonephritis and Nephrotic Syndrome AESIs

Search criteria – HLT Glomerulonephritis and nephrotic syndrome (All Path).

Clinical Trial Data

- During the current reporting period and previous PSUR #3 reporting period, there were no serious cases in the CT dataset.

Post-Authorisation Data

- Number of cases: 198 (BNT162b2 [194], BNT162b2 + BNT162b2 Omi BA.1 [2], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [3]) (0.07% of 282,992 cases, the total PM dataset), compared to 276 (0.05%) retrieved in PSUR #3.
- MC cases (152), NMC cases (46).
- Country/region of incidence: Japan (80), Germany (36), Italy (15), France (12), US (11), Australia (8), UK (7); the remaining 29 cases were distributed among 17 countries.
- Subjects' gender: female (74), male (96) and unknown (28).
- Subjects' age in years: n = 160, range: 7 – 88 years, mean: 46.6, median: 47.0.

- Medical history (n = 105); the most frequently (≥5) reported relevant medical conditions included Hypertension (21), Haematuria (15), Proteinuria (6), IgA nephropathy, Nephrotic syndrome (5 each).
- COVID-19 Medical history (n = 5): COVID-19 (5).
- Co-suspect medications (n= 2); the reported relevant co-suspect medications included COVID 19 vaccine prot. Subunit (NVX COV 2373), and influenza vaccine (1 each).
- Number of relevant events: 230
- Relevant event seriousness: serious (229), non-serious (1).
- Most frequently reported relevant PTs (>7): IgA nephropathy (60), Nephrotic syndrome (55), Glomerulonephritis (19), Glomerulonephritis membranous, Granulomatosis with polyangiitis (15 each), Glomerulonephritis minimal lesion, Glomerulonephritis rapidly progressive (13 each), Focal segmental glomerulosclerosis (12), and Microscopic polyangiitis (7).
- Time to event onset[63]: n = 68, range: 1 day to 304 days, median: 28 days.
  - 1 day: 10 events;
  - 2-7 days: 11 events;
  - 8-14 days: 6 events;
  - 15-30 days: 10 events;
  - 31-180 days: 27 events;
  - 181-304 days: 4 events.
- Duration of relevant events[64]: n = 2, range: 8 - 362 days.
  - 8-14 days: 1 event;
  - 15-31 days: 0 event;
  - 32-180 days: 0 event;
  - 181-362 days: 1 event.
- Relevant event outcome: fatal (3), resolved/resolving (71), resolved with sequelae (5), not resolved (53), unknown (98).

Fatal cases (3)

In 3 cases (reporting 3 relevant events with fatal outcome), the reported causes of death were coded to Nephrotic syndrome (3 each). Medical history was provided in 2 cases and included Neuropathy and Renal disorder (1 each).

Analysis by age group

PM: Paediatric (20), Adult (96), Elderly (48) and Unknown (34).

- Among the frequently (≥2%) reported Glomerulonephritis and Nephrotic Syndrome AEs, the PT IgA nephropathy was higher in adult population when compared to

elderly population (28.1% in adults vs 6.3% in elderly). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

O/E Analysis

O/E analysis was performed for Glomerulonephritis/nephrotic syndrome (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Second Booster Analysis

Six (6) cases reported 8 events occurred after administration of a second booster vaccination. In 2 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 4 cases, 3 involved homologous second booster and 1 heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

Please refer to Section 15 *Overview of Signals: New, Ongoing, or Closed* for IgA nephropathy. No new significant safety information has emerged based on the review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.9. Stroke

Search criteria – HLT Central nervous system haemorrhages and cerebrovascular accidents (All path); Cerebrovascular venous and sinus thrombosis (Primary Path).

Clinical Trial Data

- Number of cases: 11 cases (BNT162b2 [10], blinded therapy [1]; 3.5% of 309 cases in the total CT dataset), compared to 19 cases (2.8%) retrieved in the PSUR #3.
- Country/region of incidence: US (10), Brazil (1).
- Subjects' gender: female (5), male (6).
- Subjects' age in years: n = 11, range: 17 months – 82, mean: 53.6, median: 59.0.
- Medical history (n = 8): medical conditions reported more than twice included Hypertension (6), Type 2 diabetes mellitus, Dyslipidaemia (2 each).
- COVID-19 Medical history: None.
- Co-suspect medications (n= 1): ethinylestradiol, gestodene (1).
- Reported relevant PTs: Cerebrovascular accident (4), Ischaemic stroke (3), Haemorrhage intracranial (2), Cerebral venous sinus thrombosis, Cerebral venous thrombosis (1 each). None of these SAEs were assessed as related to BNT162b2 or blinded therapy.
- Relevant event outcome: fatal (1), resolved/resolving (9), resolved with sequelae (1).

Post-Authorisation Data

- Number of cases: 1132 (0.4% of 282,992 cases in the total PM dataset), compared to 3091 cases (0.6%) retrieved in the PSUR #3. BNT162b2 (1030), BNT162b2 + BNT162b2 Omi BA.4/BA.5 (64), BNT162b2 + BNT162b2 Omi BA.1 (41).
- MC cases (534), NMC cases (598).
- Country/region of incidence (>50): Germany (361), France (114), Japan (78), US (71), Poland, UK (50 each); the remaining 408 cases were distributed among 39 countries.
- Subjects' gender: female (576), male (495), unknown (61).
- Subjects' age in years: n = 1033, range: 7 – 102, mean: 61.3, median: 63.0.
- Medical history (n = 612); the most frequently (>20) reported medical conditions included Hypertension (245), Diabetes mellitus (49), Type 2 diabetes mellitus (42), Tobacco user (36), Seasonal allergy (34), Dyslipidaemia (33), Atrial fibrillation, Obesity (29 each), Cerebrovascular accident (28), Asthma, Hypercholesterolaemia (27 each), Depression (24), Hypothyroidism (23), Drug hypersensitivity, Hyperlipidaemia (21 each).
- COVID-19 medical history (n = 48); COVID-19 (41), COVID-19 pneumonia, Suspected COVID-19 (3 each), SARS-CoV-2 test positive (2), Asymptomatic COVID-19 (1).
- Co-suspect medications (n = 59 cases); the most frequently (≥2) reported co-suspect medications included apixaban, elasomeran (7 each), influenza vaccine, influenza vaccine inact SPLIT 4V (6 each), adalimumab (5), ethinylestradiol, levonorgestrel (4), acetylsalicylate lysine, influenza vaccine inact SAG 4V, metformin (3 each), alprazolam, dapagliflozin, omeprazole, simvastatin (2 each).
- Number of relevant events: 1308.
- Relevant event seriousness: serious (1305).
- Most frequently (≥10) reported relevant PTs: Cerebrovascular accident (499), Cerebral infarction (166), Ischaemic stroke (123), Cerebral haemorrhage (113), Cerebral venous sinus thrombosis (60), Cerebral thrombosis (44), Subarachnoid haemorrhage (29), Cerebral ischaemia (25), Cerebellar infarction (22), Cerebral venous thrombosis, Haemorrhagic stroke (20 each), Haemorrhage intracranial (13), Ischaemic cerebral infarction, Transverse sinus thrombosis (12 each), Embolic stroke (11), Cerebral artery embolism, Thalamus haemorrhage (10 each).
- Time to event onset[63]: n = 863, range: <24 hours to 601 days, median: 14 days.
  - <24 hours: 63 events (4 of which had a fatal outcome);
  - 1 day: 99 events (8 of which had a fatal outcome);
  - 2-7 days: 188 events (16 of which had a fatal outcome);
  - 8-14 days: 92 events (7 of which had a fatal outcome);
  - 15-30 days: 117 events (13 of which had a fatal outcome);
  - 31-180 days: 227 events (12 of which had a fatal outcome);
  - >180 days: 77 events (11 of which had a fatal outcome).

- Duration of relevant events[64]: n = 84, range: <24 hours to 505 days, median 19 days.
  - <24 hours: 10 events;
  - 1 day: 7 events;
  - 2-7 days: 8 events;
  - 8-14 days: 14 events;
  - 15-30 days: 8 events;
  - 31-180 days: 18 events;
  - >180 days: 19 events.

- Relevant event outcome[56]: fatal (107), resolved/resolving (309), resolved with sequelae (189), not resolved (268), unknown (440).

Fatal cases (86)

In 86 cases (reporting 107 relevant events with fatal outcome), the reported causes of death (≥3) included Cerebrovascular accident (28), Cerebral haemorrhage (26), Cerebral infarction (10), Haemorrhagic stroke (9), Haemorrhage intracranial (5), Ischaemic stroke, Subarachnoid haemorrhage (4 each), Cerebral artery embolism, Cerebral thrombosis, Embolic stroke (3 each).

Analysis by age group

- CT: Adult (6), Elderly (4), Child (1).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (9 [2 Child, 7 Adolescent]), Adult (558), Elderly (485), Unknown (80).
  - Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible. Between the elderly and adult populations, there were no significant differences observed in the reporting proportion of the most frequently (≥10) reported relevant stroke-related events.

O/E Analysis

O/E analysis was performed for CVST, Ischaemic stroke and Haemorrhagic stroke respectively (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

The CVST analysis using the low background rate (Appendix 5.7, Table 12), males and females 18-24 and 25-49 years, as well as overall monovalent dose 1 and dose 2, had an O/E ratio greater than 1 in either the 21-day and/or 42-day risk windows. However, the 95% CIs

for some age groups included 1, indicating lack of statistical significance. For all other stratifications using the low background rate, the O/E ratio is less than 1.

Second Booster Analysis

Seventy-four (74) cases reporting 91 events occurred after administration of a second booster vaccination. In 9 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 65 cases, 43 involved homologous second booster and 22 heterologous second booster.

Conclusion

No significant new safety information was identified based on a review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.10. Sudden Death

Search criteria – PT Sudden Death.

Please refer to Section 16.3.4.1 *Death*.

16.3.3.1.11. Thromboembolic AESIs

Search criteria[69] - HLGT (All path) Embolism and thrombosis (excluding PTs reviewed as Stroke AESIs) OR PT Coagulopathy.

Clinical Trial Data

- Number of cases: 5 (BNT162b2 [5]; 1.6% of 309 cases in the total CT dataset), compared to 17 cases (2.5%) retrieved in the PSUR #3.
- Country/region of incidence: US (4), [redacted] (1).
- Subjects' gender: female (2), male (3).
- Subjects' age in years: n = 5, range: 31 – 76, mean: 56.6, median: 59.
- Medical history (n = 3); the medical condition reported more than once was Hypertension (2).
- COVID-19 medical history: None.
- Co-suspect medications (n=1): ethinylestradiol, ferrous fumarate, norethisterone acetate (1).

[69] Four (4) new PTs have been included in the search strategy due to MedDRA upgrade v. 25.1 (Aortic aneurysm thrombosis, Mesenteric vein embolism, Ophthalmic vascular thrombosis and Spermatic vein thrombosis).

- Reported relevant PTs: Pulmonary embolism (4), Deep vein thrombosis (1). None of these SAEs were assessed as related to BNT162b2.

- Relevant event outcome: fatal (1), resolved/resolving (2), resolved with sequelae (1), not resolved (1).

Post-Authorisation Data

- Number of cases: 2064 (0.7 % of 282,992 cases in the total PM dataset), compared to 6102 cases (1.2%) retrieved in the PSUR #3. BNT162b2 (1916), BNT162b2 + BNT162b2 Omi BA.4/BA.5 (90), BNT162b2 + BNT162b2 Omi BA.1 (78).

- MC cases (1035), NMC cases (1029).
- Country/region of incidence (>50): Germany (608), France (254), Poland (117), UK (106), Denmark (104), US (100), Australia (81), Austria (77), Sweden (74), Japan (71), Italy (69), Slovakia (60); the remaining 343 cases were distributed among 35 countries.
- Subjects' gender: female (1072), male (858), unknown (134).
- Subjects' age in years: n = 1885, range: 11 – 99, mean: 57.2, median: 58.0.
- Medical history (n = 1045); the most frequently (>50) reported medical conditions included Hypertension (260), Obesity (69), Non-tobacco user, Type 2 diabetes mellitus (58 each), Seasonal allergy (55), Asthma, and Drug hypersensitivity (54 each).
- COVID-19 Medical history (n = 113): COVID-19 (102), Suspected COVID-19 (8), Post-acute COVID-19 syndrome (3), Asymptomatic COVID-19, COVID-19 pneumonia (2 each), Coronavirus infection (1).
- Co-suspect medications (n = 98 cases); the most frequently (≥3) reported co-suspect medications included elasomeran (23), influenza vaccine inact SPLIT 4V (10), influenza vaccine inact SAG 4V (8), adalimumab, ethinylestradiol, levonorgestrel, influenza vaccine (5 each), apixaban (4), COVID-19 vaccine, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), pneumococcal vaccine polysacch 23V (3 each).
- Number of relevant events: 2451.
- Relevant event seriousness: serious (2263), non-serious (188).
- Most frequently (≥50) reported relevant PTs: Pulmonary embolism (635), Thrombosis (523), Deep vein thrombosis (371), Thrombophlebitis (94), Superficial vein thrombosis (81), Coagulopathy (79), Venous thrombosis limb (70), Retinal vein occlusion (65), Venous thrombosis (64), Embolism (51).
- Time to event onset[63]: n = 1533, range: < 24 hours to 529 days, median: 14 days.
  - <24 hours: 89 events (3 of which had a fatal outcome);
  - 1 day: 100 events (5 of which had a fatal outcome);
  - 2-7 days: 370 events (22 of which had a fatal outcome);
  - 8-14 days: 235 events (11 of which had a fatal outcome);

  - 15-30 days: 217 events (5 of which had a fatal outcome);
  - 31-180 days: 409 events (3 of which had a fatal outcome);
  - >180 days: 113 events (3 of which had a fatal outcome).

- Duration of relevant events[64]: n = 123, range: <24 hours to 528 days, median 22 days.

  - <24 hours: 14 events;
  - 1 day: 2 events;
  - 2-7 days: 26 events;
  - 8-14 days: 15 events;
  - 15-30 days: 10 events;
  - 31-180 days: 36 events;
  - >180 days: 20 events.

- Relevant event outcome[56]: fatal (106), resolved/resolving (730), resolved with sequelae (211), not resolved (592), unknown (821).

Fatal cases (82)

In 82 cases (reporting 106 relevant events with fatal outcome), the reported causes of death (>3) included Pulmonary embolism (42), Thrombosis (19), Deep vein thrombosis (8), Coagulopathy (6), Coronary artery thrombosis, Thrombosis with thrombocytopenia syndrome (5 each), Embolism (4). Most (48 of 82 cases) of the fatal cases involved elderly subjects. When the medical history was provided (73 cases), the most frequently (>5) medical conditions included the PTs Hypertension (22), COVID-19, Obesity (8 each), Diabetes mellitus (7), Dementia (6).

Analysis by age group

- CT: Adults (4), Elderly (1).

  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (22 [2 Child, 20 Adolescent]), Adults (1178), Elderly (714), Unknown (150).

  - No significant difference was observed in the reporting proportion of the most frequently (≥50) reported thromboembolic AESIs, between the paediatric, adult and elderly populations.

O/E Analysis

O/E analysis was performed for Arterial thromboembolism, Deep vein thrombosis, Disseminated intravascular coagulation, Thrombotic thrombocytopenia syndrome and Venous thromboembolism respectively (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Second Booster Analysis

One hundred and forty-nine (149) cases reporting 194 events occurred after administration of a second booster vaccination. In of 35 these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 114 cases, 80 involved homologous second booster and 34 heterologous second booster. No new significant safety information was identified based on the review of the second booster vaccination cases.

Conclusion

No safety signals have emerged based on the review of these cases and on the analyses by age group, O/E and second booster. Safety surveillance will continue.

16.3.3.1.12. AESIs in subjects with Malnutrition, HIV infection, Tuberculosis

Search criteria – PT Decode (History): Acute HIV infection; Asymptomatic HIV infection; Congenital HIV infection; HIV infection; HIV infection CDC Group I; HIV infection CDC Group II; HIV infection CDC Group III; HIV infection CDC Group IV subgroup A; HIV infection CDC Group IV subgroup B; HIV infection CDC Group IV subgroup C1; HIV infection CDC Group IV subgroup C2; HIV infection CDC Group IV subgroup D; HIV infection CDC Group IV subgroup E; HIV infection CDC category A; HIV infection CDC category B; HIV infection CDC category C; HIV infection CDC group IV; HIV infection WHO clinical stage I; HIV infection WHO clinical stage II; HIV infection WHO clinical stage III; HIV infection WHO clinical stage IV; Malnutrition; Perinatal HIV infection; Prophylaxis against HIV infection; Tuberculosis.

Clinical Trial Data

- Number of cases: 2 (BNT162b2, BNT162b2s01 [1 each]) (0.6% of 309 cases, the total CT dataset, compared to 11 cases (1.6%) retrieved in the PSUR #3.
- Country/region of incidence: [redacted] (1 each).
- Subjects' gender: [redacted] (2)
- Subjects' age in years: n = 2, range: [redacted], mean: 36.0, median: 36.0.
- Medical history (n = 2): Malnutrition, Tuberculosis (1 each).
- COVID-19 Medical history: None.
- Co-suspect medications: None.
- Reported PTs (2): Atrial fibrillation, Urinary tract infection (1 each). None of the events were related to BNT162b2.
- Relevant event outcome: resolved (2).

Post-Authorisation Data

- Number of cases: 145 (0.05% of 282,992 cases, the total PM dataset), compared to 197 cases (0.04%) retrieved in the PSUR #3. BNT162b2 (138), BNT162b2 + BNT162b2 Omi BA.1 (4), BNT162b2 + BNT162b2 Omi BA.4/BA.5 (3).

Subjects with pre-existing HIV Infection: 80 (0.02% of 282,992 cases, the total PM dataset)

- MC cases (32), NMC cases (48).
- Country/region of incidence[70]: France (22), US (13), Germany (12), Denmark, Sweden (5 each), Italy (4), Portugal, Puerto Rico, UK (3 each), Norway (2); the remaining 8 cases were distributed among 8 countries.
- Subjects' gender: female (19), male (58) and unknown (3).
- Subjects' age in years: n = 74, range: 21 – 74, mean: 50.7, median: 52.5.
- COVID-19 Medical history: COVID-19 (4).
- Co-suspect medications (n = 6): COVID-19 vaccine, elasomeran (4 each), emtricitabine, tenofovir disoproxil fumarate, influenza vaccine inact SAG 4V, ruxolitinib, tamsulosin (1 each).
- Of the 80 cases reporting a pre-existing HIV condition, 11 subjects reported cardiac disorders. The events (15) in these cases were coded to the PTs Myocardial infarction, Palpitations (3 each), Tachycardia (2), Angina pectoris, arrhythmia, Cardiovascular disorder, Coronary artery disease, Myocarditis, Supraventricular extrasystoles, Ventricular extrasystoles (1 each). Of the 15 events, 12 were assessed as serious and 3 events were non-serious. Outcome of the events was reported as resolved (1), not resolved (5), fatal (1), and unknown (8).
- Of the 80 cases, 28 subjects reported nervous system disorders. The events (59) reported more than once in these cases were coded to the PTs Headache (15), Dizziness (7), Hypoaesthesia, Paraesthesia, Peripheral sensory neuropathy (3 each), Somnolence (2). Of the 59 events, 21 were assessed as serious and 38 events as non-serious. Outcome was reported as resolved/resolving (13), not resolved (13), fatal (3), and unknown (31).
- Of the 80 cases, 27 subjects reported infectious events. The events (34) in these cases were coded to PTs COVID-19 (17), HIV infection (3), Acne pustular, Chronic hepatitis B, Coronavirus infection, COVID-19 pneumonia, Cryptococcosis, Encephalitis, Encephalitis viral, Gastrointestinal infection, Human herpesvirus 8 infection, Influenza, Klebsiella infection, Meningitis aseptic, Progressive multifocal leukoencephalopathy, Sepsis (1 each). Of the 34 events, 31 were assessed as serious and 3 events were non-serious. Outcome of the events was reported as resolved/resolving (6), not resolved (6), fatal (3), and unknown (19).

[70] There were 2 cases reported from low- and middle-income countries (Serbia, South Africa [1 each]).

- Time to event onset[63]: n = 168, range: <24 hours to 340 days, median: 4.5 days.
  - <24 hours: 34 events; (3 of which had a fatal outcome);
  - 1 day: 19 events; (3 of which had a fatal outcome);
  - 2-7 days: 25 events;
  - 8-14 days: 25 events;
  - 15-30 days: 12 events; (4 of which had a fatal outcome);
  - 31-180 days: 41 events;
  - 181-340 days: 12 events; (2 of which had a fatal outcome).

- Duration of relevant events[64]: n = 22, range: 2 - 55 days, median: 4 days.
  - 2 – 7 days: 17 events;
  - 8-14 days: 1 event;
  - 15-30 days: 2 events;
  - 31-55 days: 2 events.

- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing HIV infection when compared to the subjects without the disease.

- Of the 80 cases, 68 cases involved adults, 6 cases involved elderly and in 6 cases age group was not reported. Due to the low volume of cases reported in elderly, it was not possible to make a meaningful comparison between the adults and elderly subject population.

Subjects with pre-existing tuberculosis: 56 (0.01% of 282,992 cases, the total PM dataset)

- MC cases (28), NMC cases (28).
- Country/region of incidence[71]: France (20), Germany (10), Sweden (6), Brazil, South Africa (4 each), US (3), [redacted] (1 each).
- Subjects' gender: female (39), male (17).
- Subjects' age in years: n = 51, range: 15 – 87, mean: 59.3, median: 65.
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications (7): elasomeran (3), adalimumab, atorvastatin calcium, ezetimibe, COVID-19 vaccine, influenza vaccine inact SPLIT 4V, mycophenolate, tacrolimus, ursodeoxycholic acid (1 each).

[71] There were 10 cases reported from low- and middle-income countries (Brazil, South Africa [4 each], Philippines and Serbia [1 each]).

- Of the 56 cases reporting pre-existing tuberculosis, 11 subjects reported cardiac disorders. The events (13) in these cases were coded to the PTs Cardiac failure, Left ventricular failure, Palpitations (2 each), Arrhythmia, Cardiac arrest, Cardiac disorder, Cardiomegaly, Myocarditis, Myopericarditis, Tachycardia (1 each). Of the 13 events, 11 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (1), resolved with sequelae (3), not resolved (1), resolved (2), and unknown (6).
- Of the 56 cases, 18 subjects reported nervous system disorders. The events (40) in these cases were coded to PTs Headache (9), Dizziness (6), Balance disorder, Disturbance in attention, Hypoaesthesia (2 each), Ataxia, Central nervous system lesion, Dysstasia, Epilepsy, Focal dyscognitive seizures, Formication, Hemiparesis, Hypersomnia, Motor dysfunction, Muscle spasticity, Myasthenic syndrome, Neuralgia, Neurosarcoidosis, Nystagmus, Paraesthesia, Peripheral sensory neuropathy, Taste disorder, VIth nerve paralysis, White matter lesion (1 each). Of the 40 events, 18 were assessed as serious and 22 events were non-serious. Outcome of the events was reported as resolved/resolving (14), not resolved (12), resolved with sequelae (2), and unknown (13).
- Of the 56 cases, 15 subjects reported infectious events. The events (20) in these cases were coded to the PTs COVID-19 (6), Pneumonia (3), Bronchitis (2), Chorioretinitis, COVID-19 pneumonia, HIV infection, Human herpesvirus 8 infection, Infection, Ophthalmic herpes zoster, Post-acute COVID-19 syndrome, Sepsis, Tuberculosis of eye (1 each). Of the 20 events, 18 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as resolved/resolving (5), not resolved (3), and unknown (12).
- Time to event onset[63]: n = 136, range: <24 hours to 223 days, median: 2 days.
  - <24 hours: 30 events (2 of which had a fatal outcome);
  - 1 day: 31 events (none of which had a fatal outcome);
  - 2-7 days: 32 events (none of which had a fatal outcome);
  - 8-14 days: 4 events (none of which had a fatal outcome);
  - 15-30 days: 1 event (none of which had a fatal outcome);
  - 31-180 days: 31 events (none of which had a fatal outcome);
  - 181-223 days: 7 events (none of which had a fatal outcome).
- Duration of relevant events[64]: n = 28, range: less than 24 hours – 380 days, median 9 days.
  - <24 hours: 1 event;
  - 1 day: 5 events;
  - 2 – 7 days: 5 events;
  - 8-14 days: 6 events;
  - 15-30 days: 4 events;
  - 31-180 days: 5 events;
  - >180 days: 2 events.

- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing tuberculosis when compared to the subjects without the disease.

- Of the 56 cases, 24 cases involved adults, and 26 cases involved elderly, and the age group was not reported in 5 cases. The reporting proportion of cases involving infectious events was higher in elderly population (53.3%) when compared to the adult population (40.1%); and more elderly subjects reported cases involving nervous system disorders as compared to the adults (50% in elderly vs 44.4% in adults); and more elderly subjects reported cases involving cardiac events as compared to adults (63.7% in elderly vs 18.2% in adults).

Subjects with pre-existing malnutrition: 12 (<0.01% of 282,992 cases, the total PM dataset)

- MC cases (10), NMC cases (2).
- Country/region of incidence: France (5), Japan (2), [redacted] (1 each).
- Subjects' gender: female (6), male (6).
- Subjects' age in years: n = 12, range: 25 – 92, mean: 61.8, median: 64.5
- COVID-19 Medical history (n = 4): COVID-19 (4), COVID-19 pneumonia (1 each).
- Co-suspect medications (1): influenza vaccine inact SAG 4V (1).
- In these 12 cases, the most frequently reported events (54, ≥2 occurrences) were coded to the PTs COVID-19, General physical health deterioration, Off label use, Sudden death, Vaccination failure (2 each).
- Of the 12 cases reporting pre-existing malnutrition, 2 subjects reported PTs General physical health deterioration (2), and Anaemia D (1). Of the total 3 events, 1 event was assessed as serious, and 2 events were non-serious. Outcome of the events was reported as fatal (1) and unknown (2).
- Time to event onset[63]: n = 32, range: <24 hours to 181 days, median: 5 days.
  - <24 hours: 3 events (3 of which had a fatal outcome);
  - 1 day: 1 event (1 of which had a fatal outcome);
  - 2-7 days: 23 events (11 of which had a fatal outcome);
  - 31-180 days: 3 events (none of which had a fatal outcome);
  - 181 days: 2 events (2 of which had a fatal outcome).

- Duration of relevant events: n = 0; 5 occurrences with outcome of resolving.

Of the 12 cases, 6 were reported in elderly and 6 cases involved adults. Cases of nervous system disorders all occurred in elderly subjects. The reporting proportion of cases involving infectious events was equal when compared to adults and elderly subjects. The reporting proportion of cases involving cardiac events was higher in the elderly population (16.6%)

when compared to adults (8.3%). Generally, there was a low volume of cases reporting malnutrition in the current dataset.

Second Booster Analysis

Twelve (12) cases reporting 132 AEs occurred after administration of a second booster vaccination. In 8 of these cases, no or partial vaccination dates are available and/or onset dates of the AEs were not provided. In the remaining 4 cases, 4 involved homologous second booster and no cases reported heterologous second booster. No new significant safety information was identified based on the review of the remaining cases involving second booster vaccination.

Conclusion

No safety signals have emerged based on the review of these cases and on the second booster analysis. Safety surveillance will continue.

16.3.3.2. Clinical Reactogenicity Data on Baseline SARS-CoV-2 Positive and Baseline SARS-CoV-2 Negative Participants

New data originated from 2 analyses on adults 18-55 years and adults >55 years enrolled in C4591031 Substudy E.

Adults 18 through 55 Years of Age (C4591031 Substudy E)

There were no clinically meaningful differences in the overall patterns of reactogenicity (local reactions and systemic events) when evaluated by baseline SARS-CoV-2 status between the vaccine groups.

Across the bivalent BNT162b2 + BNT162b2 Omi BA.1 30 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 60 µg, and monovalent BNT162b2 Omi BA.1 60 µg vaccine groups, the frequencies of the most commonly reported local reaction of pain at the injection site were ≤84.3% for baseline positive and ≤87.3% for baseline negative participants, respectively. The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the local reactions by SARS-CoV-2 baseline status were not considered clinically meaningful.

Across the bivalent BNT162b2 + BNT162b2 Omi BA.1 30 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 60 µg, and monovalent BNT162b2 Omi BA.1 60 µg vaccine groups, fatigue and headache were ≤69.7% and ≤49.4%, respectively, for baseline positive participants and ≤80.4% and ≤60.4%, respectively, for baseline negative participants. The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the systemic events by SARS-CoV-2 baseline status were not considered clinically meaningful.

Adults >55 Years of Age (C4591031 Substudy E)

There were no clinically meaningful differences in the overall patterns of reactogenicity (local reactions and systemic events) when evaluated by baseline SARS-CoV-2 status between the vaccine groups.

Across the BNT162b2 30 µg, BNT162b2 60 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 30 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 60 µg, and monovalent BNT162b2 Omi BA.1 60 µg vaccine groups, the frequencies of the most commonly reported local reaction of pain at the injection site were ≤58.5% for baseline positive and ≤73.0% for baseline negative participants, respectively. The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the local reactions by SARS-CoV-2 baseline status were not considered clinically meaningful.

Across the BNT162b2 30 µg, BNT162b2 60 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 30 µg, bivalent BNT162b2 + BNT162b2 Omi BA.1 60 µg, and monovalent BNT162b2 Omi BA.1 60 µg vaccine groups, fatigue and headache were ≤51.2% and ≤32.1%, respectively, for baseline positive participants and ≤62.4% and ≤39.1%, respectively, for baseline negative participants. The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the systemic events by SARS-CoV-2 baseline status were not considered clinically meaningful.

Individuals ≥12 Years of Age (C4591044 Cohort 2)

There were no clinically meaningful differences in the overall pattern of reactogenicity when evaluated by baseline SARS-CoV-2 status across different age groups.

Across the age groups of 12 to 17 years, 18 to 55 years and >55 years of age, for participants who received a booster (dose 4) of BNT162b2 bivalent (WT/Omi BA.4/BA.5) 30 µg, the frequencies of the most commonly reported local reaction of pain at the injection site were ≤75.4% for baseline positive and ≤86.5% for baseline negative participants, respectively. For participants 18 to 55 years and >55 years of age who received a booster (dose 4) of BNT162b2 bivalent (WT/Omi BA.4/BA.5) 60 µg, the frequencies of the most commonly reported local reaction of pain at the injection site were ≤95.1% for baseline positive and ≤89.3% for baseline negative participants, respectively.

Across the age groups of 12 to 17 years, 18 to 55 years and >55 years of age, for participants who received a booster (dose 4) of BNT162b2 bivalent (WT/Omi BA.4/BA.5) 30 µg, fatigue and headache were ≤61.7% and ≤44.4%, respectively, for baseline positive participants and ≤84.6% and ≤69.2%, respectively, for baseline negative participants. For participants 18 to 55 years and >55 years of age who received a booster (dose 4) of BNT162b2 bivalent (WT/Omi BA.4/BA.5) 60 µg, fatigue and headache were ≤70.7% and ≤46.3%, respectively, for baseline positive participants and ≤64.3% and ≤42.9%, respectively, for baseline negative participants.

The baseline negative subgroup included a limited number of participants, and the results should be interpreted with caution. Overall, numerical differences in any of the local reactions by SARS-CoV-2 baseline status were not considered clinically meaningful.

16.3.3.3. Systemic Adverse Reactions

Search criteria – PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia.

Of the 79,327 cases, 14 cases were determined to be non-contributory and were not included in the discussion due to involving neonate, or infants exposed to the vaccine through breastfeeding.

Clinical Trial Data

- Number of cases: 1 (BNT162b2) (0.3% of 309 cases, the total CT dataset), compared to 11 cases (1.6%) retrieved in the PSUR #3.
- Country/region of incidence: [redacted].
- Subjects' gender: [redacted].
- Subjects' age in years[redacted].
- Medical history: None.
- COVID-19 Medical history: None.
- Co-suspect medications: None.
- Number of relevant events: 1.
- Relevant PT: Pyrexia (1), not assessed as related to BNT162b2 by the investigator and Sponsor.
- Time to event onset of relevant event: 71 days.
- Duration of relevant event: 10 days.
- Relevant event outcome: resolved.

Post-Authorisation Data

- Number of cases: 79,312 (BNT162b2 [75,216], BNT162b2 + BNT162b2 Omi BA.1 [2438], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [1784]) (28.0% of 282,992 cases in the total PM dataset), compared to 167,760 (33.0% retrieved in the PSUR #3).
- MC cases (26,682), NMC cases (52,630).
- Country/region of incidence (>1000): Sweden (19,349), Germany (11,263), Portugal (5549), Denmark (4619), Belgium (4160), Poland (4110) Norway (3284), France (2722), Spain (2428), Japan (2304), Romania (2068), Netherlands (1958), Finland (1906), Philippines (1796), Slovenia (1564), US (1536), Slovakia (1097), UK (1091); the remaining 6508 cases were distributed among 52 countries.

- Subjects' gender: female (54,363), male (20,794) and unknown (4155).
- Subjects' age in years: n = 75,038, range: 0.08 – 102, mean: 44.5; median: 44.0.
- Medical history (n = 21,115); the most frequently (>500) reported medical conditions included Hypertension (3479), Asthma (2190), Seasonal allergy (1632), Drug hypersensitivity (1381), Hypersensitivity (1134), Hypothyroidism (983), Pain (946), Depression (740), Migraine (727), Food allergy (588), Diabetes mellitus (550), Type 2 diabetes mellitus (523).
- COVID-19 Medical history (n = 3993): COVID-19 (3683), Suspected COVID-19 (192), post-acute COVID-19 syndrome (127), Coronavirus infection (34), SARS-CoV-2 test positive (14), COVID-19 pneumonia (13), Exposure to SARS-CoV-2 (7), SARS-CoV-2 antibody test positive (6), asymptomatic COVID-19 (2), coronavirus test positive (1).
- Co-suspects medications (n = 1375); the most frequently (≥10) reported co-suspect medications included elasomeran (542), Influenza vaccine (154), Influenza vaccine inact SAG 4V (101), COVID-19 vaccine NRVV AD (78), Influenza vaccine inact SPLIT 4V (77), COVID-19 vaccine (65), Adalimumab (55), Ocrelizumab (33), COVID-19 vaccine NRVV AD26 (16), Pneumococcal vaccine (11), and Paracetamol (10).
- Number of relevant events: 152,454.
- Relevant event seriousness: serious (12,028), non-serious (140,426).
- Relevant PTs: Headache (35,637), Fatigue (31,585), Pyrexia (29,952), Myalgia (23,460), Arthralgia (17,222), Chills (14,598).
- Time to event onset[63]: n = 107,824, range: from <24 hours to 1096 days, median: 1 day.
  - <24 hours: 42,344 events (27 of which had a fatal outcome);
  - 1 day: 41,597 events (21 of which had a fatal outcome);
  - 2-7 days: 13,513 events (11 of which had a fatal outcome);
  - 8-14 days: 2933 events (4 of which had a fatal outcome);
  - 15-30 days: 2663 events (5 of which had a fatal outcome);
  - 31-181 days: 3606 events (15 of which had a fatal outcome);
  - ≥182 days: 1168 events (12 of which had a fatal outcome).
- Duration of relevant events[64]: n = 38,982, range: <24 hours to 930 days, median 2 days.
  - <24 hours: 3288 events;
  - 1 day: 13,301 events;
  - 2-7 days: 18,783 events;
  - 8-14 days: 1112 events;
  - 15-30 days: 592 events;
  - 31-181 days: 1037 events;
  - ≥182 days: 869 events.
- Relevant event outcome: fatal (130), resolved/resolving (76,253), resolved with sequelae (2559), not resolved (37,467), unknown (36,045).

Fatal cases

In 109 cases, the following relevant events (130) were reported as fatal: PTs Pyrexia (61), Fatigue (27), Headache (20), Chills (9), Myalgia (8), and Arthralgia (5). More than half (64 of 109 cases, 58.7%) of the cases with a fatal outcome involved elderly subjects. Review of these cases did not identify any new significant safety information.

Analysis by age group

CT: Paediatric (1, PTs Pyrexia [1]).

- A meaningful comparison between the different age groups is not possible due to the low number of cases.

PM

- An analysis of relevant PM events by age group, event seriousness and event outcome are provided in Table 73. In the current reporting interval, the most frequent systemic adverse reactions in adult subjects (in order from highest to lowest frequencies) were PTs Headache (31,001), Fatigue (27,068), Pyrexia (24,061), Myalgia (20,285), Arthralgia (14,416), and Chills (12,745); the most frequent systemic adverse reactions in elderly subjects were PTs Fatigue (3213), Pyrexia (3116), Headache (2779), Myalgia (2371), Arthralgia (2206), and Chills (1298); and the most frequent systemic adverse reactions in paediatric subjects were PTs Pyrexia (1834), Headache (1175), Fatigue (613), Myalgia (357), Chills (263), and Arthralgia (208). Across the age groups in the table below, the greatest number of events were reported in the adult population, followed by the elderly. The majority of systemic adverse reactions (92.1%) were non-serious events with 51.7% of the events resolved, resolved with sequelae or resolving at the time of reporting.

Table 73. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 4450 n (%)	**Adults N = 129,576 n (%)**	**Elderly N = 14,983 n (%)**	**Unknown N = 3445 n (%)**
Arthralgia				
Total Events	208 (4.7%)	14416 (11.1%)	2206 (14.7%)	392 (11.4%)
Serious Events	36 (0.8%)	1239 (1.0%)	354 (2.4%)	37 (1.1%)
Event Outcome: Fatal	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)	0 (0.0%)
Not Resolved	47 (1.1%)	4292 (3.3%)	900 (6.0%)	101 (2.9%)
Resolved with sequelae	3 (0.1%)	236 (0.2%)	53 (0.4%)	1 (<0.1%)
Resolved/Resolving	98 (2.2%)	5811 (4.5%)	772 (5.2%)	87 (2.5%)
Unknown	59 (1.3%)	4076 (3.1%)	478 (3.2%)	203 (5.9%)
Chills				
Total Events	263 (5.9%)	12745 (9.8%)	1298 (8.7%)	292 (8.5%)

Table 73. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 4450 n (%)	Adults N = 129,576 n (%)	Elderly N = 14,983 n (%)	Unknown N = 3445 n (%)
Serious Events	31 (0.7%)	585 (0.5%)	129 (0.9%)	22 (0.6%)
Event Outcome: Fatal	1 (<0.1%)	3 (<0.1%)	5 (<0.1%)	0 (0.0%)
Not Resolved	36 (0.8%)	1746 (1.3%)	187 (1.2%)	25 (0.7%)
Resolved with sequelae	2 (<0.1%)	101 (0.1%)	22 (0.1%)	0 (0.0%)
Resolved/Resolving	164 (3.7%)	8045 (6.2%)	816 (5.4%)	107 (3.1%)
Unknown	60 (1.3%)	2850 (2.2%)	268 (1.8%)	160 (4.6%)
Fatigue				
Total Events	613 (13.8%)	27068 (20.9%)	3213 (21.4%)	691 (20.1%)
Serious Events	114 (2.6%)	2284 (1.8%)	488 (3.3%)	73 (2.1%)
Event Outcome: Fatal	1 (<0.1%)	4 (<0.1%)	20 (0.1%)	2 (0.1%)
Not Resolved	183 (4.1%)	8763 (6.8%)	1054 (7.0%)	147 (4.3%)
Resolved with sequelae	5 (0.1%)	676 (0.5%)	111 (0.7%)	2 (0.1%)
Resolved/Resolving	261 (5.9%)	11432 (8.8%)	1225 (8.2%)	185 (5.4%)
Unknown	163 (3.7%)	6193 (4.8%)	803 (5.4%)	355 (10.3%)
Headache				
Total Events	1175 (26.4%)	31001 (23.9%)	2779 (18.5%)	682 (19.8%)
Serious Events	211 (4.7%)	2115 (1.6%)	340 (2.3%)	60 (1.7%)
Event Outcome: Fatal	3 (0.1%)	7 (<0.1%)	8 (0.1%)	2 (0.1%)
Not Resolved	215 (4.8%)	8144 (6.3%)	747 (5.0%)	105 (3.0%)
Resolved with sequelae	6 (0.1%)	503 (0.4%)	70 (0.5%)	3 (0.1%)
Resolved/Resolving	646 (14.5%)	15376 (11.9%)	1401 (9.4%)	199 (5.8%)
Unknown	305 (6.9%)	6971 (5.4%)	553 (3.7%)	373 (10.8%)
Myalgia				
Total Events	357 (8.0%)	20285 (15.7%)	2371 (15.8%)	447 (13.0%)
Serious Events	56 (1.3%)	1428 (1.1%)	296 (2.0%)	34 (1.0%)
Event Outcome[56]: Fatal	3 (0.1%)	2 (<0.1%)	3 (<0.1%)	0 (0.0%)
Not Resolved	75 (1.7%)	5553 (4.3%)	901 (6.0%)	73 (2.1%)
Resolved with sequelae	1 (<0.1%)	469 (0.4%)	77 (0.5%)	0 (0.0%)
Resolved/Resolving	192 (4.3%)	9179 (7.1%)	987 (6.6%)	150 (4.4%)
Unknown	86 (1.9%)	5082 (3.9%)	403 (2.7%)	224 (6.5%)
Pyrexia				
Total Events	1834 (41.2%)	24061 (18.6%)	3116 (20.8%)	941 (27.3%)
Serious Events	302 (6.8%)	1328 (1.0%)	402 (2.7%)	64 (1.9%)
Event Outcome: Fatal	11 (0.2%)	13 (<0.1%)	36 (0.2%)	1 (<0.1%)
Not Resolved	169 (3.8%)	3600 (2.8%)	331 (2.2%)	73 (2.1%)
Resolved with sequelae	6 (0.1%)	186 (0.1%)	25 (0.2%)	1 (<0.1%)
Resolved/Resolving	1284 (28.9%)	15666 (12.1%)	1852 (12.4%)	318 (9.2%)
Unknown	364 (8.2%)	4596 (3.5%)	872 (5.8%)	548 (15.9%)

N: Total number of events in the population subset; n: number of events; percentage (%) calculated as n/N.

Analysis by dose

Number of vaccine doses administered: 1 dose in 43,445 cases, 2 doses in 57,532 cases; 3 doses in 21,232 cases, 4 doses in 8542 cases, and in 21,704 cases the dose was either not specified or reported as greater than 4 doses.

CT:

- Vaccination dose number: 3 doses (1).
- A meaningful comparison by dose is not possible due to the low number of CT cases.

PM:

- An analysis of relevant PM events by dose, event seriousness and event outcome are provided in Table 74. In general, the proportion of serious events were highest in those subjects who had received four doses of the vaccine; following this, the highest proportion of serious events were reported in those who had received three and two doses of the vaccine, respectively.

Table 74. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 43,445 n (%)	2 Doses N = 57,532 n (%)	3 Doses N = 21,231 n (%)	4 Doses N = 8542 n (%)	Dose Not Specified/ Other N = 21,704 n (%)
Arthralgia					
Total Events	4940 (11.4%)	6701 (11.6%)	2410 (11.4%)	929 (10.9%)	2242 (10.3%)
Serious Events	390 (0.9%)	571 (1.0%)	345 (1.6%)	150 (1.8%)	210 (1.0%)
Event Outcome: Fatal	0 (0.0%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Not Resolved	1467 (3.4%)	1803 (3.1%)	1022 (4.8%)	319 (3.7%)	729 (3.4%)
Resolved with sequelae	80 (0.2%)	106 (0.2%)	65 (0.3%)	10 (0.1%)	32 (0.1%)
Resolved/Resolving	2000 (4.6%)	2470 (4.3%)	878 (4.1%)	474 (5.5%)	946 (4.4%)
Unknown	1393 (3.2%)	2321 (4.0%)	444 (2.1%)	125 (1.5%)	533 (2.5%)
Chills					
Total Events	3734 (8.6%)	5835 (10.1%)	2069 (9.7%)	1035 (12.1%)	1925 (8.9%)
Serious Events	169 (0.4%)	245 (0.4%)	144 (0.7%)	128 (1.5%)	81 (0.4%)
Event Outcome: Fatal	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Not Resolved	511 (1.2%)	676 (1.2%)	404 (1.9%)	183 (2.1%)	220 (1.0%)
Resolved with sequelae	37 (0.1%)	36 (0.1%)	25 (0.1%)	5 (0.1%)	22 (0.1%)
Resolved/Resolving	2317 (5.3%)	3649 (6.3%)	1301 (6.1%)	722 (8.5%)	1143 (5.3%)
Unknown	868 (2.0%)	1473 (2.6%)	336 (1.6%)	123 (1.4%)	538 (2.5%)
Fatigue					
Total Events	9738 (22.4%)	11722 (20.4%)	4524 (21.3%)	1560 (18.3%)	4041 (18.6%)
Serious Events	731 (1.7%)	1040 (1.8%)	642 (3.0%)	210 (2.5%)	336 (1.5%)
Event Outcome: Fatal	6 (<0.1%)	9 (<0.1%)	6 (<0.1%)	3 (<0.1%)	3 (<0.1%)
Not Resolved	2988 (6.9%)	3558 (6.2%)	1932 (9.1%)	580 (6.8%)	1089 (5.0%)

Table 74. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 43,445 n (%)	2 Doses N = 57,532 n (%)	3 Doses N = 21,231 n (%)	4 Doses N = 8542 n (%)	Dose Not Specified/ Other N = 21,704 n (%)
Resolved with sequelae	219 (0.5%)	305 (0.5%)	174 (0.8%)	16 (0.2%)	80 (0.4%)
Resolved/Resolving	4437 (10.2%)	4733 (8.2%)	1499 (7.1%)	701 (8.2%)	1733 (8.0%)
Unknown	2088 (4.8%)	3117 (5.4%)	913 (4.3%)	260 (3.0%)	1136 (5.2%)
Headache					
Total Events	10859 (25.0%)	13098 (22.8%)	4689 (22.1%)	1813 (21.2%)	5178 (23.9%)
Serious Events	696 (1.6%)	931 (1.6%)	547 (2.6%)	228 (2.7%)	324 (1.5%)
Event Outcome[56]: Fatal	2 (<0.1%)	3 (<0.1%)	5 (<0.1%)	4 (<0.1%)	6 (<0.1%)
Not Resolved	2743 (6.3%)	3171 (5.5%)	1642 (7.7%)	534 (6.3%)	1121 (5.2%)
Resolved with sequelae	154 (0.4%)	244 (0.4%)	111 (0.5%)	11 (0.1%)	62 (0.3%)
Resolved/Resolving	5657 (13.0%)	6271 (10.9%)	2107 (9.9%)	1035 (12.1%)	2552 (11.8%)
Unknown	2303 (5.3%)	3409 (5.9%)	824 (3.9%)	229 (2.7%)	1437 (6.6%)
Myalgia					
Total Events	6700 (15.4%)	8976 (15.6%)	3326 (15.7%)	1316 (15.4%)	3142 (14.5%)
Serious Events	468 (1.1%)	634 (1.1%)	373 (1.8%)	167 (2.0%)	172 (0.8%)
Event Outcome: Fatal	0 (0.0%)	0 (0.0%)	2 (<0.1%)	3 (<0.1%)	3 (<0.1%)
Not Resolved	1837 (4.2%)	2207 (3.8%)	1361 (6.4%)	459 (5.4%)	738 (3.4%)
Resolved with sequelae	141 (0.3%)	202 (0.4%)	133 (0.6%)	15 (0.2%)	56 (0.3%)
Resolved/Resolving	3110 (7.2%)	3855 (6.7%)	1380 (6.5%)	720 (8.4%)	1443 (6.6%)
Unknown	1612 (3.7%)	2712 (4.7%)	450 (2.1%)	119 (1.4%)	902 (4.2%)
Pyrexia					
Total Events	7474 (17.2%)	11200 (19.5%)	4213 (19.8%)	1889 (22.1%)	5176 (23.8%)
Serious Events	419 (1.0%)	692 (1.2%)	448 (2.1%)	252 (3.0%)	285 (1.3%)
Event Outcome: Fatal	2 (<0.1%)	16 (<0.1%)	9 (<0.1%)	14 (0.2%)	20 (0.1%)
Not Resolved	1176 (2.7%)	1468 (2.6%)	695 (3.3%)	280 (3.3%)	554 (2.6%)
Resolved with sequelae	55 (0.1%)	82 (0.1%)	39 (0.2%)	4 (<0.1%)	38 (0.2%)
Resolved/Resolving	4779 (11.0%)	7179 (12.5%)	2455 (11.6%)	1170 (13.7%)	3537 (16.3%)
Unknown	1462 (3.4%)	2455 (4.3%)	1015 (4.8%)	421 (4.9%)	1027 (4.7%)

N: Total number of events in the population subset; n: number of events; percentage (%) calculated as n/N.

Conclusion

Systemic adverse reactions were reported in 79,313 (1 CT and 79,312 PM) cases representing 28.0 % of the cases in the total dataset for the reporting period. The majority of events (92.1%) were non-serious events with 51.7% of the events resolved, resolved with sequelae or resolving at the time of reporting. Evaluation of systemic adverse reaction cases did not reveal any significant new safety information based on analysis by age group or by dose. Systemic adverse reactions are appropriately described in the RSI. Surveillance of systemic adverse reactions will continue.

16.3.3.4. Age-Related Adverse Reactions

All adverse events reported during the reporting period were reviewed in the context of age categories. For the overall demographic information for all CT and PM cases refer to Section 6.3.1.1. *General Overview – All Cases*.

Clinical Trial Data

- Number of cases: 309 (cross-referenced to Section 6.3.1.2).
- Time to event onset[63]: n = 306, range: <24 hours to 708 days, median: 132.5 days.
  - <24 hours: 4 events (none of which had a fatal outcome);
  - 1 day: 1 event;
  - 2-7 days: 3 events;
  - 8-14 days: 7 events;
  - 15-30 days: 18 events;
  - 31-180 days: 181 events;
  - >181 days: 92 events.
- Relevant event outcome: fatal (34), resolved/resolving (278), resolved with sequelae (22), not resolved (46), unknown (1).

Post-Authorisation Data

- Number of cases: 282,992 (cross-referenced to Section 6.3.1.3 *General Overview – Post-Authorisation Data*).
- Time to event onset[63] (n = 554,973), range: <24 hours to 1096 days, median: 1 day.
  - <24 hours: 199,063 events (518 of which had a fatal outcome);
  - 1 day: 111,103 events;
  - 2-7 days: 70,240 events;
  - 8-14 days: 22,206 events;
  - 15-30 days: 24,063 events;
  - 31-180 days: 113,305 events;
  - >181 days: 14,993 events.
- Relevant event outcome[56]: fatal (3387), resolved/resolving (240,539), resolved with sequelae (16,321), not resolved (182,629), unknown (397,698).

Analysis by age group

- CT: Paediatric (107), Adults (118), Elderly (82).

The 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 75, Table 76 and Table 77. The top 5 SOCs were generally comparable for all age groups except the Cardiac disorders SOC and the

Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age groups; the Pregnancy, puerperium and perinatal conditions SOC for the adult age group, and the Respiratory, thoracic and mediastinal disorders SOC for the paediatric age group. Of note, 82 cases reported 89 events in the Infections and infestations SOC, which was a SOCs of the most frequently reported AEs in all 3 age groups.

- There were 33 cases reporting 37 events in the Cardiac disorders SOC for the adult and elderly age groups. Twenty-nine (29) cases reported relevant medical history (e.g., Acute myocardial infarction, Angina pectoris, Arrhythmia, Atrial fibrillation, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Cardiac murmur, Cardiac pacemaker insertion, Cardiomyopathy, Congestive cardiomyopathy, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery disease, Coronary artery stenosis, Diabetes mellitus, Ejection fraction decreased, Heart rate irregular, Hyperlipidaemia, Hypertension, Mitral valve incompetence, Myocardial infarction, Obesity, Sleep apnoea syndrome, Tobacco user), which may have contributed to the relevant events. The most frequently reported events (≥2) in this SOC for the adult and elderly age group were Atrial fibrillation (6), Cardiac failure congestive (5), Cardiac arrest, Myocardial infarction (4 each), Acute myocardial infarction (3), and Coronary artery disease (2).

- There were 29 cases reporting 29 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Four (4) cases reported pre-existing medical history of cancer (e.g., colon cancer, leukemia, lung neoplasm malignant, prostate cancer, skin cancer). The most frequently reported events (≥2) in this SOC for the adult and elderly age group were Prostate cancer (3), Adenocarcinoma pancreas, Leukemia, and Squamous cell carcinoma (2 each). When reported, latency from vaccination ranged from 14 days to 695 days with a median of 169 days. Of the 22 events reporting latency, the majority of the neoplasm latencies (15 events) were reported between 14 days to 9 months.

- There were 9 cases reporting 12 events in the Pregnancy, puerperium and perinatal conditions SOC for the adult age group. The 12 events reported were Abortion spontaneous, Premature labour (2 each), Abortion missed, Ectopic pregnancy, Hyperemesis gravidarum, Oligohydramnios, Placenta praevia, Premature separation of placenta, Premature rupture of membranes, and Pre-eclampsia (1 each). The events were assessed as unrelated to BNT162b2/blinded therapy by the investigator and the Sponsor.

- There were 12 cases reporting 12 events in the Respiratory, thoracic and mediastinal disorders SOC for the paediatric age group. The 12 events reported were Asthma (3), Sleep apnoea syndrome (2), Asthmatic crisis, Bronchial hyperreactivity, Bronchospasm, Hypoxia, Pneumonitis, Respiratory arrest, Wheezing (1 each). The events were assessed as unrelated to BNT162b2/blinded therapy by the investigator and the Sponsor. All events resolved.

Table 75. Clinical Trial Data: Number of AEs in the Top 6 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups

SOC	Adult	Paediatric	Elderly	Unknown
Infections and infestations	21	57	11	0
Injury, poisoning and procedural complications	18	13	6	0
General disorders and administration site conditions	13	7	5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13	1	16	0
Cardiac disorders[a]	12	0	25	0
Pregnancy, puerperium and perinatal conditions	12	0	0	0

a. There were 6 SOCs reported for the Adult group since the number of AEs in the Cardiac disorders and the Pregnancy, puerperium and perinatal conditions were the same (n=12).

Table 76. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

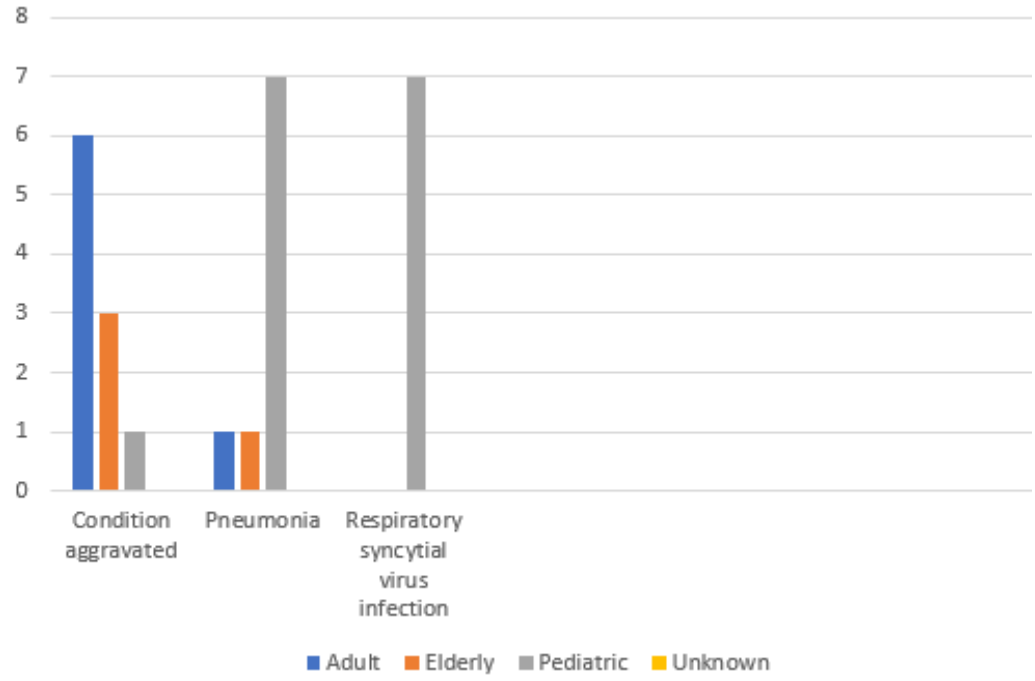
SOC	Paediatric	Adult	Elderly	Unknown
Infections and infestations	57	21	11	0
Injury, poisoning and procedural complications	13	18	6	0
Nervous system disorders	12	10	8	0
Respiratory, thoracic and mediastinal disorders	12	10	3	0
General disorders and administration site conditions	7	13	5	0

Table 77. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups

SOC	Elderly	Adult	Paediatric	Unknown
Cardiac disorders	25	12	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16	13	1	0
Infections and infestations	11	21	57	0
Nervous system disorders	8	10	12	0
Musculoskeletal and connective tissue disorders	8	4	0	0

The distribution of the most frequently reported serious PTs (≥ 2%) by age group in the 307 CT cases where the participants were directly exposed to BNT162b2, is shown in Figure 7 below.

Figure 7. Events Reported in ≥2% of All Clinical Trial Cases by Age Group



- PM: Paediatric (12,822), Adults (208,210), Elderly (37,066) and Unknown (24,838).

- The majority of the PM AE reports are for individuals in the adult age group, followed by elderly and paediatric reports. This is not unexpected based on available exposure data (e.g. from US and EU) which indicates that while a higher percentage of individuals >65 years of age have received at least one dose of vaccine, the absolute number of vaccinated individuals aged 18-64 is greater than those who are >65 years.

The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group are presented in Table 78, Table 79, and Table 80.

The top 5 SOCs were generally comparable for all age groups except the Musculoskeletal and connective tissue disorders SOC (higher proportion of reports in the adult and elderly groups), and the Gastrointestinal disorders SOC (higher proportion of reports in the paediatric age group).

- Most events in the Musculoskeletal and connective tissue disorders SOC in the adult and elderly groups were assessed as non-serious (62,338); whereas 9659 events were serious. Event outcome was reported as resolved/resolving (27,468), not resolved (23,982), resolved with sequelae (2235), unknown (23,703), and fatal (53). The fatal cases are reviewed in Section 16.3.4.1, *Death*. The most commonly reported PTs (>1000) for the adult and elderly groups in the Musculoskeletal and connective tissue disorders SOC were Myalgia (21,888), Arthralgia (16,086), Pain in extremity (11,824), Limb discomfort (2863), Back pain (2278), Muscular weakness (1666), Neck pain (1625), Musculoskeletal stiffness (1467), Muscle spasms (1329), and

Mobility decreased (1304). It is not unexpected for these events to be reported more frequently in adult and elderly subjects compared to paediatric subjects.

- In the Gastrointestinal disorders SOC for the paediatric age group, 511 events were assessed as serious and 1403 as non-serious. Event outcome was reported as resolved/resolving (1059), not resolved (265), resolved with sequelae (20), unknown (556), and fatal (16). The fatal cases are reviewed in Section 16.3.4.1, *Death*. The most commonly reported PTs (≥10) in the Gastrointestinal disorders SOC for the paediatric age group were Vomiting (573), Nausea (500), Abdominal pain (272), Diarrhoea (188), Abdominal pain upper (89), Lip swelling (32), Dysphagia (18), Odynophagia (13), Abdominal discomfort, Gastritis (12 each), Abdominal pain lower, Gastrointestinal disorder (11 each), and Constipation (10). Vomiting, Diarrhoea, and Nausea are listed or consistent with listed events as per the current RSI.

Table 78. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups

SOC	Adult	Elderly	Paediatric	Unknown
General disorders and administration site conditions	211,602	29,175	8256	12,886
Nervous system disorders	75,758	11,500	3207	4402
Infections and Infestations	51,063	10,752	2450	3165
Musculoskeletal and connective tissue disorders	61,658	10,287	1153	4050
Injury, poisoning and procedural complications	39,173	10,758	7148	27,398

Table 79. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

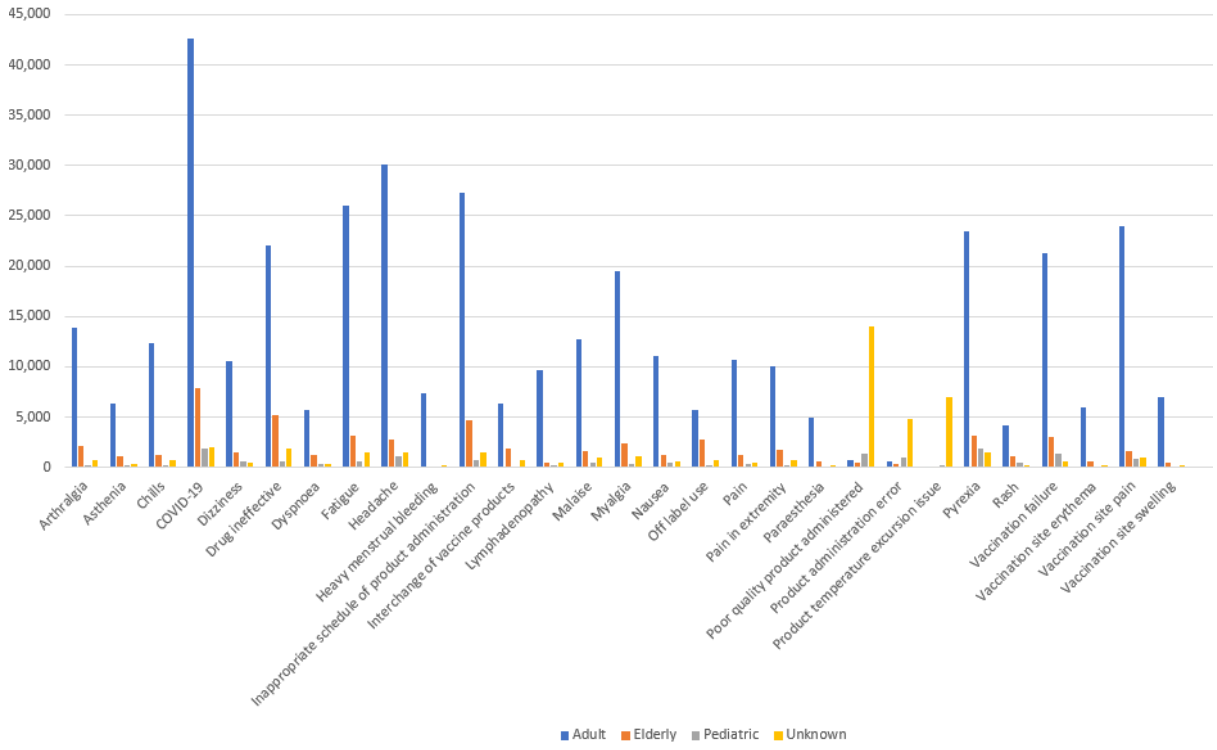
SOC	Paediatric	Adult	Elderly	Unknown
General disorders and administration site conditions	8256	211,602	29,175	12,886
Injury, poisoning and procedural complications	7148	39,173	10,758	27,398
Nervous system disorders	3207	75,758	11,500	4402
Infections and Infestations	2450	51,063	10,752	3165
Gastrointestinal disorders	1913	28,993	4698	1626

Table 80. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups

SOC	Elderly	Adult	Paediatric	Unknown
General disorders and administration site conditions	29,175	211,602	8256	12,886
Nervous system disorders	11,500	75,758	3207	4402
Injury, poisoning and procedural complications	10,758	39,173	7148	27,398
Infections and Infestations	10,752	51,063	2450	3165
Musculoskeletal and connective tissue disorders	10,287	61,658	1153	4050

The distribution of the most frequently reported overall PTs (≥ 2%) by age group is shown in Figure 8. Most of these events are listed or consistent with listed events as per the current RSI.

Figure 8. Events Reported in ≥ 2% of All Post-Marketing Cases by Age Group



Conclusion

Most of the frequently reported SOCs and overall PTs with the COVID-19 vaccine across the age groups were listed or consistent with listed events as per the current RSI. The analysis of age-related AEs did not identify new significant safety information.

16.3.4. Evaluation of Special Situations

In the PRAC AR of the PSUR #3 (EMEA/H/C/PSUSA/00010898/202206), the following request was made: *For future PSURs in the section 'Evaluation of special situations', the overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Upon review of the incremental data of cases evaluated for all the above mentioned topics, no new safety issues/signals or reporting pattern changes were detected. These topics have

been removed from the evaluation of special situations discussed in Section 16.3.4. *Evaluation of Special Situations* of the PSUR.

New data identified during the reporting interval for use of BNT162b2 by special subject situations is described below.

16.3.4.1. Death

Search criteria - Death cases are identified based on the following criteria:

- If the case or event outcome is "Fatal".
- If the date of death field has a value.
- If any of the history type values is "Death" or "Autopsy".
- If the death field is set to "Yes".
- If the case contains one of the following terms: High Level Group Term: Fatal outcomes; Preferred Terms: Assisted suicide, Completed suicide.

Clinical Trial Data

- Number of cases: 28 (blinded therapy [2], BNT162b2 [25], placebo [1]) (9.1 % of 309 cases, the total CT dataset), compared to 34 cases (5.1%) retrieved in the PSUR #3.
- Country/region of incidence: the US (17), Argentina, South Africa (5 each) and Lithuania (1).
- Subjects' gender: female (9) and male (19).
- Subjects' age in years: n = 28, range: 14.0 – 87.0, mean: 60.3, median: 61.5.
- Medical history (n = 21); the most frequently (>3) reported medical conditions included Hypertension (14), Type 2 diabetes mellitus, Obesity (7 each), Depression and Hyperlipidaemia (5 each).
- COVID-19 Medical history: None.
- Causes of death most frequently reported (>2): Disease progression (7), Death (6), and Cardiac arrest (3).
- Autopsy results: None
- Events with a fatal outcome (n = 34): The most frequently reported PTs (>2): Death (6) and Cardiac arrest (3). None of the fatal events were assessed as related to blinded therapy/BNT162b2.
- Co-suspect medications: None.
- Time to fatal event onset[63]: n = 28, range: 47 – 357 days, median: 169 days.
  - 31-181 days: 16 events;
  - 182-240 days: 4 events;
  - 241-365 days: 8 events.

Post-Authorisation Data

- Number of cases: 1234[72] (0.4% of 282,992 cases, the total PM dataset), (BNT162b2 [1106], BNT162b2 + BNT162b2 Omi BA.1 [39] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [97]) compared to 3163 (0.6%) retrieved in the PSUR #3.

- MC cases (753), NMC cases (481).
- Country/region of incidence (>50): Germany (185), the US (166), Japan (154), Philippines (130), France (97).
- Subjects' gender: female (617), male (464), unknown (153).
- Subjects' age in years: n = 1010, range: 7.0 months – 103.0 years, mean: 65.9, median: 72.0.
- Medical history (n = 602);[73] the most frequently reported (>40) medical conditions included cardiac and vascular disorders [e.g., Hypertension (200), Atrial fibrillation (56)]. Other most frequently reported (>40) medical conditions included Diabetes mellitus (59), Type 2 diabetes mellitus (52), Chronic obstructive pulmonary disease (49).
- COVID-19 Medical history (n = 51): COVID-19 (42), Suspected COVID-19 (4), Exposure to SARS-CoV-2 (3), Asymptomatic COVID-19, Coronavirus test positive, SARS-CoV-2 test positive (1 each).
- Causes of death most frequently reported (>40): Death (308), Cardiac arrest (77), COVID-19 (67), Dyspnoea, Myocardial infarction (57 each), Cardio-respiratory arrest, Pyrexia (52 each), Myocardial injury (51) and Drug ineffective (41).
- Autopsy results were provided in a minority of cases (58 cases) and the most commonly (≥5) reported results included Myocarditis (9), Arteriosclerosis (7), Pneumonia, Pulmonary congestion, Pulmonary embolism, Pulmonary oedema (5 each).
- Co-suspect medications (n = 91); the most frequently reported (>3) included influenza vaccine inact SPLIT 4V (15), COVID-19 vaccine (13), elasomeran (12), influenza vaccine inact SAG 4V (10), apixaban (7), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine (4 each).
- Cases with confounders and risk factors: 638 fatal cases included one or more contributing factors, which precluded a meaningful causality assessment: co-suspect (91 cases), concomitant drugs (246 cases) and/or underlying medical history/risk factors (653 cases).

[72] During the current reporting interval, there were 67 additional cases reporting subjects' death that were excluded from further analysis in this subsection as: death was mentioned as incidental information only with none of the reported events having a fatal outcome (36) and cases which reported foetal death/still birth/ abortion induced/involved transplacental/transmammary exposure are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women* (31).

[73] This list excluded the medical history terms indicative of COVID-19. Of note, more than 1 medical history was reported in some cases.

- Events with a fatal outcome (n = 3313): The most frequently reported (>50) fatal events included Death (283), Off label use (112), Dyspnoea (79), Cardiac arrest (76), Immunisation (74), COVID-19 (70), Drug ineffective (66), Pyrexia (60), Interchange of vaccine products, Myocardial infarction (58 each), Myocardial injury (51).
- Time from vaccination to fatal event (n = 3072), range: <24 hours to 365 days, median: 151.5.
  - <24 hours: 715 events;
  - 1 day: 433 events;
  - 2-7 days: 615 events;
  - 8-14 days: 214 events;
  - 15-30 days: 271 events;
  - 31-181 days: 527 events;
  - 182-240 days: 131 events
  - 241-365 days: 166 events.

Analysis by age group

- CT: Adults (18-64) (14) and Elderly (65 years and older) (13).
  - A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.
- PM: Paediatric (17 years and under) (49), Adults (18-64 years) (332), Elderly (65 years and older) (644), and Unknown (209).
  - There is a higher reporting proportion of fatal events in the elderly population compared to the adult population (52.2% vs 26.9%, respectively). As would be expected, the reporting proportion of fatal events in the paediatric population is low (4.0%.

Most of the cases reporting a fatal outcome (36.1%) were in subjects over 75 years of age. The elderly population is generally considered a priority group targeted for vaccination by many regions and countries, including Europe and the US (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2.[74,75,76]

[74] Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA. ECDC, February 2021.

[75] https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/COVID-19/evidence-table-phase-1b-1c.html.

[76] WHO Roadmap for Prioritizing Population Groups for Vaccines against COVID-19; ACIP COVID-19 Vaccines Working Group, Phased Allocation of COVID-19 Vaccines (Dec 01, 2020); JCVI updated interim advice on priority groups for COVID-19 vaccination (Sept 25, 2020).

Analysis by dose

- Number of vaccine doses administered:
  - First dose (125 cases). Of the 125 cases, 35 cases (28.0%) reported a latency of same day to 3 days after vaccination. Majority of these cases (>10) originated from Australia (32), Germany (16), France (12), Philippines (12), Japan (11). The most frequently reported (>5) fatal events included Death (23), Adverse event following immunisation (12), Cardiac arrest (11), Myocarditis (9), Cardiac failure, Concomitant disease aggravated, Fatigue, Myocardial infarction, Pneumonia (6 each).
  - Second dose (244 cases). Of the 244 cases, 49 cases (20.1 %) reported a latency of same day to 3 days after vaccination. Majority of these cases (>10) originated from Germany (53), Philippines (36), Japan (26), France (17), the US (16), Spain (12). The most frequently reported (>20) fatal events included Death (35), Drug ineffective (33), Dyspnoea (24), COVID-19 (21).
  - Third dose (264 cases). Of the 264 cases, 79 cases (29.9%) reported a latency of same day to 3 days after vaccination. Majority of these cases (>20) originated from Germany (58), Japan (29), Spain (25), Philippines (23), France (22). The most frequently reported (>20) fatal events included Death (33), COVID-19 (30), Vaccination failure (27).
  - Fourth dose (194 cases). Of the 194 cases, 185 cases (95.3%) reported a latency of same day to 3 days after vaccination. Majority of these cases (>10) originated from Japan (47), France (25), Germany (20), Italy (16), the US (13). The most frequently reported (>20) fatal events included Off label use (75), Immunisation (69), Death (34), Sudden death (21).
  - Fifth dose (36 cases). Of the 36 cases, 30 cases (85.7%) reported a latency of same day to 3 days after vaccination. Majority of these cases (>20) originated from Japan (21). The most frequently reported (>5) fatal events included Cardio-respiratory arrest (8), Death (8), Interchange of vaccine products (7), Off label use (6).
  - In the remaining cases (371), dose number was not specified. Of the 371 cases, 34 cases (9.1%) reported a latency of same day to 3 days after vaccination. Majority of these cases (>10) originated from the US (126), Philippines (49), Malaysia (41), Germany (36), Japan (20), France (18), United Kingdom (16). The most frequently reported (>5) fatal events included Death (150), Myocardial injury (50), Dyspnoea (20), Myocardial infarction (19), Pyrexia (16), Drug ineffective (12), COVID-19 (11).

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

Conclusion

No new risks were identified following review of fatal cases.

16.3.4.1.1. Death Review by Age Group

This is a high-level overview of the 1262 cases in the interval reporting period (see Section 16.3.4.1 for further details). According to the corePSUR19[53] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 5.8.1.[77]

Interval Reporting Period

- CT (28 cases): Adults (18-64) (14) and Elderly (65 years and older) (13)
  - The top 4 MedDRA SOCs with the most frequently reported (>2) fatal events in the interval period by age group is presented in the table below.

Table 81. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval

SOC	Total number of events	18-24 years	25-49 years	50-59 years	60-69 years	70+ years
Cardiac disorders	10	0	0	2	2	6
General disorders and administration site conditions	7	0	2	2	1	2
Respiratory, thoracic and mediastinal disorders	5	0	1	3	0	1
Infections and infestations	3	0	0	1	2	0

Of note, multiple AEs may be reported in a single case.

- PM (1234 cases): Paediatric (17 years and under) (49), Adults (18-64 years) (332), Elderly (65 years and older) (644), and Unknown (209).
  - The top 5 MedDRA SOCs with the most frequently reported (>300) events with a fatal outcome by age group in the post-authorisation data are presented in the table below.

Table 82. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval

SOC	Total number of events	≤ 17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years	Unknown
General disorders and administration site conditions	1066	48	21	111	83	136	546	121
Cardiac disorders	641	17	15	73	71	92	299	74

[77] Please note that the numbers of AEs reported in the appendix may not match with the numbers of AEs reported in Table 81 and Table 82, since in the appendix all the events included in the fatal cases are reported, while in the above mentioned tables, only AEs with fatal outcome are reported.

Table 82. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval

SOC	Total number of events	≤ 17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years	Unknown
Nervous system disorders	606	26	5	62	58	97	335	23
Respiratory, thoracic and mediastinal disorders	569	16	8	49	49	84	348	15
Infections and infestations	387	11	3	23	33	50	253	14

Of note, multiple AEs may be reported in a single case.

Cumulative Reporting Period

Cumulative through 18 December 2022

This is a high-level overview of the 14,945 cumulative cases with a fatal outcome. According to the corePSUR19 guidance,[53] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 5.8.2.[78]

Clinical Trial Data

- Number of cases: 181[79] (6.6% of 2724 cases, the total CT dataset; 173 cases involved blinded therapy [68]/BNT162b2 [105]). In the remaining 8 cases subjects received placebo.
- Causes of death most frequently reported (≥7): Disease progression (39), Death (19), Cardiac arrest (18), Completed suicide (11), Myocardial infarction (10), Cardio-respiratory arrest, Neoplasm progression (8 each), Acute myocardial infarction, Acute respiratory failure, Pulmonary embolism (7 each).
- Autopsy results were provided in 10 cases and the most commonly (≥2) reported included Arteriosclerosis, Hypertensive heart disease, Pulmonary embolism (2 each).
- Events with a fatal outcome (n = 242); the most frequently reported PTs (≥5) included Death (19), Cardiac arrest, Completed suicide (11 each), Cardio-respiratory arrest,

[78] Please note that the numbers of AEs reported in the appendix may not match with the numbers of AEs reported in Table 83 and Table 84, since in the appendix all the events included in the fatal cases are reported, while in the above mentioned tables, only AEs with fatal outcome are reported.

[79] There were 17 additional cases reporting subject deaths that were excluded from further analysis in this subsection because: death was mentioned as incidental information only with none of the reported events presenting a fatal outcome (12), one case of overdose not associated with vaccine administration, and cases which involved transplacental exposure/baby cases (4) are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.

Myocardial infarction (9 each), Pulmonary embolism, Septic shock (7 each), Acute myocardial infarction, Acute respiratory failure, Condition aggravated, COVID-19 pneumonia, Pneumonia, Road traffic accident (5 each).

Post-Authorisation Data

- Number of cases: 14,764[80] (0.9 % of 1,689,088 cases, the total cumulative PM dataset).
- MC cases (10,357), NMC cases (4407).
- Causes of death most frequently reported (>500): Death (3446), COVID-19 (1361), Cardiac arrest (971), Dyspnoea (787), Myocardial infarction (672), Sudden death (655), Cardio-respiratory arrest (612), Vaccination failure (603), Pyrexia (596), Drug ineffective, Pulmonary embolism (555 each), and Cardiac failure (536).
- Autopsy results were provided in 795 cases and the most commonly (> 30) results described: Pulmonary embolism (87), Pulmonary oedema (68), Arteriosclerosis (62), Myocardial infarction (54), Arteriosclerosis coronary artery (51), Myocarditis (50), Acute myocardial infarction (48), Cardiac hypertrophy (34), Cardiomegaly (33), Pulmonary congestion (31).
- Events with a fatal outcome (n = 36,586): The most frequently reported (>500) events included Death (3300), COVID-19 (1457), Cardiac arrest (990), Dyspnoea (895), Drug ineffective (777), Vaccination failure (773), Sudden death (749), Pyrexia (685), Myocardial infarction (681), Cardio-respiratory arrest (625), Pulmonary embolism (583), Cardiac failure (538), Immunisation (537).

Analysis by age group:

- CT**:** Paediatric (1), Adults (93), and Elderly (87).

The top 6 MedDRA SOCs with the most frequently reported (≥19) events with a fatal outcome cumulative by age group is presented in Table 83.

[80] During the current reporting interval, there were 548 additional cases reporting subject deaths that were excluded from further analysis in this subsection because: death was mentioned as incidental information only with none of the reported events presenting a fatal outcome (219), cases involving exposure to a vaccinated person (4), and 325 cases which reported foetal death/still birth/spontaneous abortion/involved transplacental or trans-mammary exposure, of which 36 are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women* for the reporting interval.

Table 83. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	≤17 years	18 - 30 years	31 - 50 years	51 - 64 years	65 - 74 years	≥ 75 years	Total Number of Events
Cardiac disorders	-	-	3	17	16	9	45
Infections and infestations	-	-	6	12	15	8	41
General disorders and administration site conditions	-	-	9	12	7	5	33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	-	2	4	13	11	30
Respiratory, thoracic and mediastinal disorders	-	1	2	10	8	2	23
Injury, poisoning and procedural complications	1	4	6	6	1	1	19

Of note, multiple AEs may be reported in a single case.

  - A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome in the paediatric and young adult age groups.

- PM: Paediatric: [≤ 17 years] (207), Adult: [18-64 years] (3003), Elderly: [65 years and older] (10,236), Unknown (1318).

  - The top 5 MedDRA SOCs with the most frequently reported (>3000) events with a fatal outcome cumulative by age group in the PM data are presented in the table below.

Table 84. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	≤17 years	18 - 30 years	31 - 50 years	51 - 64 years	65 - 74 years	≥ 75 years	Unknown	Total Number of Events
General disorders and administration site conditions	144	176	630	931	1634	5129	872	9516
Cardiac disorders	87	179	533	757	1077	2733	213	5579
Nervous system disorders	71	129	346	533	809	2186	121	4195

Table 84. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	≤17 years	18 - 30 years	31 - 50 years	51 - 64 years	65 - 74 years	≥ 75 years	Unknown	Total Number of Events
Respiratory, thoracic and mediastinal disorders	71	72	298	462	742	2198	87	3930
Infections and infestations	38	41	107	258	667	2391	262	3764

Of note, multiple AEs may be reported in a single case

There is a higher reporting proportion of most frequently reported fatal events (listed above) in the elderly population when compared to the adult population (73.0% vs 20.4%, respectively). A meaningful comparison between the elderly vs paediatric population is not possible due to the low number of paediatric fatal cases reported (1.6%). Most of the cases reporting a fatal outcome (52.3%) were in subjects over 75 years of age. The elderly population were generally considered a priority group targeted for vaccination by many regions and countries, including Europe and the US (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2.[74,75,76]

O/E Analysis

O/E analysis was performed for events with a fatal outcome (see Appendix 5.7 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

16.3.4.2. Lack of Therapeutic Efficacy

Company conventions for MedDRA coding of cases indicative of lack of efficacy:

The coding conventions for COVID-19 vaccine cases indicative of lack of efficacy was revised on 20 Sep 2022, as shown below:

Coding lack of efficacy for monovalent vaccine (BNT162b2):

- PT "Vaccination failure" is coded when ALL of the following criteria are met:
    - The subject received the appropriate series of 2 doses (or 3 doses for age 6 months to < 5 years) based on the CDS.
    - At least 7 days have elapsed since administration of the second dose (or the third dose for age 6 months to < 5 years).

- The subject experiences COVID-19 infection (confirmed by laboratory tests or reported by HCP).

- PT "Drug ineffective" is coded when any of the following applies:
  - The COVID-19 infection is not reported by HCP or not confirmed through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied by consumers, e.g., "the vaccine did not work", "I got COVID-19".
  - It is unknown:
    - Whether the subject has received the 2 doses (or 3 doses for age 6 months to < 5 years) within the correct intervals based on the CDS;
    - How many days have passed since the first dose (including unspecified number of days like "a few days", "some days", etc.);
    - If 7 days have passed since the second dose of vaccine (or the third dose for age 6 months to < 5 years).
  - The subject experiences COVID-19 infection 14 days after receiving the first dose up to and through 6 days after receipt of the second dose (or the third dose for age 6 months to < 5 years).

- Note: A case is considered a potential LOE case after the immune system has had sufficient time (14 days) to respond to the vaccine, even if the vaccination course is not complete.

This is the summary of the coding conventions based on the timing of vaccination:

From 1st dose to day 13 post 1st dose	**From day 14 post 1st dose to day 6 post 2nd dose (or 3rd dose for age 6 months to < 5 years)**	**From day 7 post 2nd dose (or 3rd dose for age 6 months to < 5 years)**
Code only the events describing the COVID-19 infection	Code "Drug ineffective"	Code "Vaccination failure"
Scenario not considered LOE	Scenario considered LOE as "Drug ineffective"	Scenario considered LOE as "Vaccination failure"

Coding lack of efficacy for bivalent booster dose (BNT162b2 + BNT162b2 Omi BA; BNT162b2 + BNT162b2 Omi BA.4/BA.5):

During the reporting interval, BNT162b2 bivalent vaccine was approved for administration as a booster dose in individuals > 5 years of age.

For only cases involving BNT162b2 bivalent vaccine, PT Vaccination failure is coded when ALL of the following criteria are met, otherwise PT Drug ineffective is coded.

- The subject received the appropriate primary series of 2 monovalent doses and the bivalent booster dose based on the CDS.

- At least 7 days have elapsed since administration of the bivalent booster dose.
- The subject experiences COVID-19 infection (confirmed by laboratory tests or reported by HCP).

Lack of efficacy cases[81]

Search criteria - PTs Drug ineffective; Vaccination failure.

- Of the 56,122 cases, 27 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - 1 case is not considered as true LOE case because the subject developed COVID-19 infection between days 1-13 from the first dose.
  - 2 cases were invalidated in the safety database after the PSUR DLP.
  - 1 case was not a LOE report (subject did not develop COVID-19 infection).
  - In 23 cases, the LOE PT did not refer to BNT162b2 vaccine.

Clinical Trial Data

There were no lack of efficacy cases in the clinical trial dataset for this reporting period or for the reporting period of PSUR #3.

Post-Authorisation Data

- Number of cases: 56,095 (BNT162b2 [55,240], BNT162b2 + BNT162b2 Omi BA.1 [116] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [739]) (19.8% of 282,992 cases, the total PM dataset), compared to 51,028 cases (10.1%) in PSUR #3. The increase in the reporting proportion of LOE cases was multifactorial:
  - A high number of cases were reported from Austria (40,496 cases in the current PSUR), as compared to the previous PSURs (31,629 cases in PSUR #3, 9009 cases in PSUR #2 and 204 cases in PSUR #1) due to the active solicitation of LOE cases, including retrospective cases, by the Austrian Board of Health starting from August 2021. Additionally, reviewing Austria cases, it is notable that these case reports, although received during the current reporting period, were reflective of events that had occurred during earlier vaccination campaigns with BNT162b2 Original.
  - In addition, the epidemiology of the virus has changed since December 2021 in that the Omicron variant has become predominant in most regions. The majority of the LOE cases received during the current reporting interval involved the monovalent vaccine, the efficacy of which against Omicron variants is less than against the previous dominant variants of concern. The first approval of BNT162b2 bivalent vaccine was received in US on 02 Sep 2022.

[81] LOE cases are assessed according to the definition provided in the EMA corePSUR19 guidance (EMA/362988/2021) and classified into confirmed vaccination failure, suspected vaccination failure, and not a vaccination failure.

  - Of note, there are BNT162b2 LOE reports created from AE reports received for Nirmatrelvir/Ritonavir (Paxlovid®) based on the BNT162b2 vaccine history reported in the cases (AEs reported for Paxlovid in individuals with COVID-19 following vaccination with BNT162b2 will be appropriately databased as LOE cases for BNT162b2 as well).

- MC cases (44,659), NMC cases (11,436).
- Country/region of incidence (≥2%): Austria (40,496), US (5803), France (2393), UK (1433), Netherlands (1329); the remaining 4641 cases were distributed among 61 countries.
- Subjects' gender: female (31,282), male (23,820) and unknown (993).
- Subjects' age in years: n = 53,357, range: 1.1 – 103.0, mean: 45.8, median: 45.0.
- Relevant lack of efficacy events[82]: 56,095 (Vaccination failure [26,359] and Drug ineffective [29,736]).
- Relevant event seriousness[83]: all serious.

Confirmed vaccination failure (25,883 cases)

There were 25,883 confirmed vaccination failure cases, including 149 cases involving bivalent booster dose administration. Due to the small bivalent dataset, except for the dose and latency, the other information (demographics and COVID-19 event related details) was presented together for all confirmed vaccination failure cases.

- Age groups: Child (43), Adolescent (1368), Adult (21,320), Elderly (2948) and Unknown (204).
- Reported COVID-19 infection related events[84]: COVID-19 (25,792[85]), COVID-19 pneumonia (82), Breakthrough COVID-19 (30), SARS-CoV-2 test positive (12), and Post-acute COVID-19 syndrome (6).
- Outcome of COVID-19 infection related events: resolved/resolving (1025), resolved with sequelae (19), not resolved (712), unknown (24,131), and fatal (35).
- Of the 25,883 subjects with confirmed vaccination failure, in 213 cases, the COVID-19 events were severe, resulting in:
  - Hospitalisation (non-fatal/non-life threatening): 163

[82] LOE PTs recorded in the 56,095 cases were Vaccination failure (26,296) and Drug ineffective (29,799). Upon review after DLP, some cases were re-assessed: in 95 cases the PT Drug ineffective was reassessed to Vaccination failure; and in 32 cases the PT Vaccination failure was reassessed to Drug ineffective.

[83] Includes 1 case where LOE was captured as non-serious and upgraded to serious after the PSUR DLP.

[84] Some cases reported more than 1 PT referring to COVID-19 infection.

[85] Including 1 case where PT Suspected COVID-19 was revised to COVID-19 after DLP.

- Disability: 12
- Life threatening: 5
- Death: 33.

Cases involving BNT162b2: 25,734 cases

Vaccination failure was reported in 25,734 cases, indicative of appropriately and fully vaccinated subjects (appropriate series of 2 doses at the appropriate interval [or 3 doses for age 6 months to <5 years]), who developed clinical, and laboratory confirmed (e.g., COVID-19 PCR test, antigen test) COVID-19 infection, on or after day 7 post second dose (or third dose for age 6 months to < 5 years). In 4350 of these 25,734 cases, a booster dose was also administered (including 3644 cases with administration of the third dose, 692 cases with administration of the fourth dose, and 14 cases with administration of the fifth dose).

- Time to event onset was known for 24,407 cases; in the remaining 1327 cases, it was implied that vaccination failure was reported on or after day 7 post second dose (or third dose for age 6 months to < 5 years), however, detailed information was not provided.
  - Time to onset reported after the second dose.
    - day 7 to ≤ 150 days: 15,089 subjects
    - ≥ 151 days to ≤ 617 days: 6046 subjects
  - Time to onset reported after the third dose.
    - day 1 to ≤ 150 days: 2226 subjects
    - ≥ 151 days to ≤ 501 days: 749 subjects
  - Time to onset reported after the fourth dose.
    - day 1 to ≤ 150 days: 259 subjects
    - ≥ 151 days to ≤ 351 days: 36 subjects
  - Time to onset reported after the fifth dose.
    - 111 days and 197 days: 2 subjects, respectively

Cases involving BNT162b2 + BNT162b2 Omi BA.1: 6 cases

Vaccination failure was reported in 6 cases, indicative of appropriately and fully vaccinated subjects (appropriate series of 2 monovalent doses and the bivalent booster dose [BNT162b2 + BNT162b2 Omi BA.1], at the appropriate interval), who developed clinical, and laboratory confirmed (e.g., COVID-19 PCR test, antigen test) COVID-19 infection, on or after day 7 post administration of the bivalent booster dose.

- Time to onset after the bivalent booster dose.
  - Day 7 to ≤ 18 days: 6 subjects

Cases involving BNT162b2 + BNT162b2 Omi BA.4/BA.5: 143 cases

Vaccination failure was reported in 143 cases, indicative of appropriately and fully vaccinated subjects (appropriate series of 2 monovalent doses and the bivalent booster dose [BNT162b2 + BNT162b2 Omi BA.4/BA.5], at the appropriate interval), who developed

clinical, and laboratory confirmed (e.g., COVID-19 PCR test, antigen test) COVID-19 infection, on or after day 7 post administration of the bivalent booster dose.

- Time to event onset was known for 63 cases; in the remaining 80 cases, it was implied that vaccination failure was reported on or after day 7 post bivalent booster dose administration, however, detailed information was not provided.
  - Time to onset after the bivalent booster dose.
    - Day 7 to ≤ 96 days: 63 subjects

Suspected vaccination failure (763 cases)

There were 763 suspected vaccination failure cases, including 3 cases involving bivalent booster dose administration. Due to the small bivalent dataset, except for the dose and latency, the other information (demographics and COVID-19 event related details) was presented together for all suspected vaccination failure cases.

- Age groups: Child (7), Adolescent (17), Adult (468), Elderly (221) and Unknown (50).
- Reported COVID-19 infection related events[84]: COVID-19 (486), Suspected COVID-19 (250), Asymptomatic COVID-19 (19), COVID-19 pneumonia (7), Post-acute COVID-19 syndrome (7), Breakthrough COVID-19 (3), and Coronavirus infection (1).
- Outcome of COVID-19 infection related events: resolved/resolving (170), resolved with sequelae (7), not resolved (82), unknown (504), and fatal (10).

Cases involving BNT162b2: 760 cases

Lack of efficacy (PTs Drug ineffective or Vaccination failure) was reported in 760 cases, wherein the subjects received 2 doses of vaccine (or 3 doses for age 6 months to <5 years) at appropriate interval and reported to develop COVID-19 infection on or after day 7 post second dose (or 3 doses for age 6 months to <5 years), but laboratory confirmation of the infection (e.g., COVID-19 PCR test, antigen test) was not reported or clinical disease was unconfirmed (i.e., asymptomatic COVID-19). In 468 of these 760 cases, a booster dose was also administered (including 316 cases with administration of the third dose, 150 cases with administration of the fourth dose, and 2 cases with administration of the fifth dose).

- Time to event onset was known for 241 cases; in the remaining 519 cases, it was implied that lack of efficacy was reported on or after day 7 post second dose (or third dose for age 6 months to < 5 years), however, detailed information was not provided.
  - Time to onset reported after the second dose.
    - day 7 to ≤ 150 days: 46 subjects
    - ≥ 151 days to ≤ 589 days: 77 subjects
  - Time to onset reported after the third dose.
    - day 1 to ≤ 150 days: 48 subjects
    - ≥ 151 days to ≤ 357 days: 50 subjects

- Time to onset reported after the fourth dose.
  - day 1 to ≤ 150 days: 17 subjects
  - ≥ 151 days to ≤ 182 days: 3 subjects

Cases involving BNT162b2 + BNT162b2 Omi BA.1: None

Cases involving BNT162b2 + BNT162b2 Omi BA.4/BA.5: 3 cases

Lack of efficacy (PTs Drug ineffective or Vaccination failure) was reported in 3 cases, wherein the subjects received appropriate series of 2 monovalent doses and the bivalent booster dose [BNT162b2 + BNT162b2 Omi BA.4/BA.5] at the appropriate interval, and reported to develop COVID-19 infection on or after day 7 post administration of the bivalent booster dose, but laboratory confirmation of the infection (e.g., COVID-19 PCR test, antigen test) was not reported or clinical disease was unconfirmed (i.e., asymptomatic COVID-19).

- Time to onset after the bivalent booster dose.
  - Day 7 to ≤ 20 days: 3 subjects

Not a vaccination failure cases (29,449 cases)

There were 29,449 cases assessed as not a vaccination failure, including 703 cases involving bivalent booster dose administration (BNT162b2 + BNT162b2 Omi BA.1 [110] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [593]).

For cases involving the monovalent vaccine, these cases were indicative of occurrence of COVID-19 infections:

- in subjects who experienced COVID-19 infection from day 14 after receipt of the first dose to day 6 after receipt of the second dose (or the third dose for age 6 months to <5 years);

- in subjects who have not received the appropriate series of 2 doses (or 3 doses for age 6 months to <5 years) or for whom it was not possible to determine whether they received the appropriate series of 2 doses (or 3 doses for age 6 months to <5 years) at the appropriate interval;

- in subjects for whom it was not possible to determine how many days have passed since the first or second dose administration (or the third dose administration for age 6 months to <5 years).

For cases involving the bivalent vaccine, these cases were indicative of occurrence of COVID-19 infections:

- in subjects who experienced COVID-19 infection before day 7 after receipt of the bivalent booster dose;

- in subjects who have not received the appropriate primary series of 2 monovalent doses and/or the bivalent booster dose, or for whom it was not possible to determine whether they received the appropriate series at the appropriate interval;

– in subjects for whom it was not possible to determine how many days have passed since the bivalent booster dose administration.

Due to the small bivalent dataset, the information on demographics and COVID-19 event related details was presented together for all cases assessed as not a vaccination failure.

- Age groups: Infant (3), Child (105), Adolescent (442), Adult (22,440), Elderly (5143) and Unknown (1316).

- Reported COVID-19 infection related events[84]: COVID-19 (27,905[86]), Suspected COVID-19 (1400), COVID-19 pneumonia (84), Asymptomatic COVID-19 (42), Breakthrough COVID-19 (40), Post-acute COVID-19 syndrome (24), SARS-CoV-2 test positive (12), Multisystem inflammatory syndrome in children (3), SARS-CoV-2 sepsis (2), and Coronavirus infection (1)

- Outcome of COVID-19 infection related events: resolved/resolving (1746), resolved with sequelae (67), not resolved (1235), unknown (26,402), and fatal (63).

According to the RSI, subjects receiving the monovalent vaccine may not be protected until at least 7 days after their second dose of the vaccine (or the third dose for age 6 months to <5 years). Similarly, subjects receiving the bivalent booster dose may not be protected until at least 7 days after the bivalent booster dose administration. Therefore, for the above 29,449 cases where lack of efficacy was reported, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness.

SARS-CoV-2 Variants (6529 cases)

In 6529 of the 56,095 cases, information on SARS-CoV-2 variants was provided.

- *Delta (India) variant[87] (4668 cases[88])*

  – Product: BNT162b2 (4668)
  – Country/region of incidence (>2): Austria (4643), France (7), and Israel (5).
  – Lack of efficacy events: Vaccination failure (3214) and Drug ineffective (1454).
  – Outcome of COVID-19 infection related events: resolved/resolving (9), not resolved (1), unknown (4657), and fatal (1).

[86] Including 1 case where PT COVID-19 treatment was revised to COVID-19 after DLP.

[87] As per WHO Nomenclature (Countries in which earliest samples were documented were additionally listed, when applicable).

[88] Includes 15 cases wherein lineage was specified as B.1.617.

- *Omicron variant*[87] *(1857 cases*[89]*)*

  - Product: BNT162b2 (1852), BNT162b2 + BNT162b2 Omi BA.1 [1] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [4]
  - Country/region of incidence (>2): Austria (1654), Canada (116), Germany (29), France, US (13 each), Israel (9), Romania (8), and Italy (3)
  - Lack of efficacy events: Vaccination failure (1403) and Drug ineffective (454).
  - Outcome of COVID-19 infection related events[84]: resolved/resolving (26), resolved with sequelae (1), not resolved (2), unknown (1828), and fatal (1).

- *Alpha (UK) variant*[87] *(4 cases)*

  - Product: BNT162b2 (4)
  - Country/region of incidence: Belgium (2), [redacted] (1 each)
  - Lack of efficacy events: Vaccination failure (1) and Drug ineffective (3).
  - Outcome of COVID-19 infection related events: not resolved (1), unknown (3).

Literature

Review of the literature identified significant new information with regards to the use of BNT162b2 and lack of therapeutic efficacy.

Conclusion

No new safety signals have emerged based on a review of these cases.

16.3.5. Update on Special Patient Populations

In the PRAC AR of the PSUR #3, the following request was made: *For future PSURs in the section 'Update on special patient populations', the use in frail patients with co-morbidities, and/or interactions with other vaccines should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal*.

Response

Upon review of the incremental data of cases reported in frail patients with comorbidities and/or interactions with other vaccines, no new safety issues/signals or reporting pattern changes were detected. These populations have been removed from the populations discussed in Section 16.3.5. *Update on Special Patient Populations* of the PSUR.

The following commitment was included in the Medsafe AR of the PSUR#3: *In future safety reports, the sponsor should commit to presenting data on number and type of adverse events reported in <5 year olds after dose 1, 2 and 3. We note the majority of the current safety*

[89] Includes 3 cases where both Delta and Omicron variants were reported.

data presented in this PSUR in children <5 years of age are likely to be situations where the child has been administered an off-label product (ie, not the marron cap). Future reports should make a distinction between ADRs reported in <5 year olds following the 3 mcg maroon cap formulation vs given another product not approved for this age group. Safety Reports should continue to be submitted."

Response

Please refer to Section 16.3.5.2.1 for a general overview of paediatric subjects aged 6 months through less than 5 years and to Section 9.2.2 for medication errors reported in this population.

The following commitment was included in the PRAC updated AR for var1014: *The MAH will submit the following safety data the next PSUR: The MAH has committed to continue to closely monitor emerging trends or findings, while further data on the age group 5-11 years of age and booster are being collected within the EU context. The MAH is expected to continue monitor and better quantify the risk of myocarditis and pericarditis in the 5-11 years of age group and following the booster dose(s) and discuss any relevant findings in the upcoming PSUR. The Rapporteur should be notified immediately in case of unexpected findings or trends*."

Response

Please refer to Section 16.3.5.2.2 for a general overview of paediatric subjects aged 5 through less than 12 years and to Section 16.3.1.1.1 and to Section 16.3.1.1.2 for myocarditis and pericarditis reported in this population.

As part of the approval letter for the emergency use of Tozinameran - COVID-19 mRNA vaccine (nucleoside modified) - COMIRNATY®, the WHO requested the MAH to present the outcome of the cases of pregnancy observed in the clinical studies.

Response

Please refer to Section 16.3.5.3 *Use in Pregnant/Lactating Women* for a general overview of the use of BNT162b2 in this population.

Any new data identified during the reporting interval for use of BNT162b2 by special patient populations is analysed below.

16.3.5.1. Use in Elderly Patients

Clinical Trial Data

- Number of cases: 82 (BNT162b2 [66], blinded therapy [15], BNT162b2s01 [1]) (26.5% of 309 cases in the total CT dataset), compared to 211 cases (31.6%) retrieved in the PSUR #3.
- Country/region of incidence: US (77), Argentina (2), [redacted] (1 each).
- Subjects' gender: female (28), male (54).
- Subjects' age in years: n = 82, range: 65 – 87, mean: 73.8, median: 74.0.
- Medical history (n = 74): the most frequently (≥10) reported medical conditions included the following HLGTs: Vascular hypertensive disorders (42), Lipid metabolism disorders (32), Joint disorders (24), Glucose metabolism disorders (incl diabetes mellitus) (23), Bronchial disorders (excl neoplasms), Prostatic disorders (excl infections and inflammations) (16 each), Appetite and general nutritional disorders (15), Gastrointestinal motility and defaecation conditions (14), Allergic conditions (13), Bone and joint therapeutic procedures (12), Cardiac arrhythmias, Coronary artery disorders, Musculoskeletal and connective tissue disorders NEC (11 each), Depressed mood disorders and disturbances, Vascular therapeutic procedures (10 each).
- COVID-19 Medical history: None.
- Co-suspect medications (n = 1): dabigatran (1).
- Number of events: 95.
- Most frequently (≥3) reported PTs: Cardiac failure congestive (5), Atrial fibrillation (4), Cardiac arrest, Condition aggravated, Prostate cancer (3 each).
- None of the 95 events were assessed as related to BNT162b2, blinded therapy, or BNT162b2s01 by the investigator and Sponsor.
- Time to event onset[63]: n = 85, range: from <24 hours to 708 days, median: 175 days.
  - <24 hours: 1 event;
  - 8-14 days: 3 events;
  - 15-30 days: 1 event;
  - 31-181 days: 38 events (6 of which had a fatal outcome);
  - ≥182 days: 42 events. (7 of which had a fatal outcome).
- Event outcome: fatal (14), resolved/resolving (55), resolved with sequelae (7), not resolved (19).

Post-Authorisation Data

- Number of cases: 37,070 (BNT162b2 [34,504], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [2064], BNT162b2 + BNT162b2 Omi BA.1 [950]) (13.1% of 282,992 cases in the total PM dataset), compared to 56,584 cases (11.1%) retrieved in the PSUR #3.

- MC cases (20,336), NMC cases (16,734).
- Country/region of incidence (>300): Austria (7772), Germany (4730), US (3905), Sweden (3416), France (2966), Denmark (2240), Japan (2018), UK (1359), Belgium (1075), Poland (965), Spain (770), Netherlands (684), Australia (606), Italy (491), Norway (459), Philippines (410), Canada (395), Portugal (355), Finland (350), Slovenia (336), Slovakia (325); the remaining 1443 cases were distributed among 48 countries.
- Subjects' gender: female (21,599), male (14,119), unknown (1352).
- Subjects' age in years: n = 35,556, range: 65 – 111, mean: 73.3, median: 72.0.
- Medical history (n = 12,718); the most frequently (≥500) reported medical conditions included the following HLGTs: Vascular hypertensive disorders (4384), Allergic conditions (1910), Glucose metabolism disorders (incl diabetes mellitus) (1688), Bronchial disorders (excl neoplasms) (1270), Lipid metabolism disorders (1184), Joint disorders (1080), Thyroid gland disorders (976), Cardiac arrhythmias (966), General system disorders NEC (944), Therapeutic procedures and supportive care NEC (876), Epidermal and dermal conditions (730), Lifestyle issues (724), Coronary artery disorders (704), Gastrointestinal motility and defaecation conditions (668), Central nervous system vascular disorders (561).
- COVID-19 Medical history (n = 986): COVID-19 (854), Suspected COVID-19 (98), Post-acute COVID-19 syndrome (15), COVID-19 pneumonia (12), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (9 each), Coronavirus infection (4), SARS-CoV-2 test positive (3), COVID-19 treatment, SARS-CoV-2 antibody test positive (1 each).
- Co-suspect medications (n = 2660); the most frequently (≥10) reported co-suspect medications included COVID-19 vaccine (784), elasomeran (647), COVID-19 vaccine NRVV AD (516), influenza vaccine inact SAG 4V (152), influenza vaccine (149), influenza vaccine inact SPLIT 4V (101), adalimumab (73), COVID-19 vaccine NRVV AD26 (23), apixaban (19), influenza vaccine inact SPLIT 3V, mepolizumab, pneumococcal vaccine (17 each), pneumococcal polysaccharide vaccine 23-valent (15), upadacitinib (13), varicella zoster vaccine RGE (10).
- Number of events: 106,670; the most frequently (≥1000) reported events included COVID-19 (7941), Drug ineffective (5247), Inappropriate schedule of product administration (4691), Fatigue (3186), Pyrexia (3108), Vaccination failure (3069), Headache (2768), Off label use (2758), Myalgia (2354), Arthralgia (2163), Immunisation (1886), Interchange of vaccine products (1867), Pain in extremity (1761), Vaccination site pain (1685), Malaise (1679), Dizziness (1495), Nausea (1302), Chills (1293), Dyspnoea (1229), Pain (1179), Asthenia, (1163), Rash (1088).
- Event seriousness: serious (43,338), non-serious (63,380).

- Time to event onset[63]: n = 71,452, range: from <24 hours to 617 days, median: 2 days.
  - <24 hours: 23,948 events (376 of which had a fatal outcome);
  - 1 day: 10,489 events (229 of which had a fatal outcome);
  - 2-7 days: 11,248 events (273 of which had a fatal outcome);
  - 8-14 days: 3763 events (89 of which had a fatal outcome);
  - 15-30 days: 3602 events (94 of which had a fatal outcome);
  - 31-181 days: 15,309 events (195 of which had a fatal outcome);
  - ≥182 days: 3093 events (195 of which had a fatal outcome).

- Event outcome: fatal (2111), resolved/resolving (28,289), resolved with sequelae (2570), not resolved (22,812), unknown (51,084).

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 in elderly subjects.

Conclusion

No significant differences in the reporting proportion of the most frequently reported AEs were noted between the elderly dataset and the non-elderly dataset, apart from the following PTs for which the reporting proportion was notably higher in the elderly population compared to the non-elderly population: Off label use (7.4% versus 2.8%) and Immunisation (5.1% versus 0.7%).

The interval data reviewed did not identify any new safety information regarding the use of BNT162b2 in elderly subjects.

16.3.5.2. Use in Paediatric Patients

Search criteria - Paediatric cases are identified as cases where the Age Range derived field value for the patient is “Less than or equal to 17 years”. Cases indicative of exposure to the vaccine during the mother’s pregnancy or through breastfeeding were excluded.

- Of the 12,762 cases, 2 cases were determined to be non-contributory and were not included in the discussion because the subjects were older than 17 years.

16.3.5.2.1. Paediatric Subjects <5 Years of Age

Clinical Trial Data

- Number of cases: 62 (blinded therapy [30], and BNT162b2 [32]), originated from clinical studies C4591007, C4591007-OPENLABEL and C4591024 (20.1% of 309 cases, the total CT dataset), compared to 62 cases (9.3%) retrieved in the PSUR #3.
- Country/region of incidence: US (35), Poland (15), Brazil, Spain (5 each), and Finland (2).
- Subjects’ gender: female (30), male (32).

- Subjects' age in years: n = 62, range: 0.58 – 4, mean: 2.3, median: 2.0.
- Medical history (n = 33); the most frequently (≥2) reported included Asthma (6), Bronchiolitis (5), Eczema (4), Diarrhoea, Food allergy (3 each), Bronchial hyperreactivity, Clostridium difficile infection, Cough, Dermatitis atopic, Seasonal allergy, Ventricular septal defect, Vomiting, and Wheezing (2 each).
- COVID-19 Medical history (n = 3): COVID-19 (3).
- Co-suspect medications: None.
- PTs (n = 76); PTs reported in more than 1 case: Pneumonia, Respiratory syncytial virus infection (6 each), Bronchiolitis (4), Adenovirus infection, Respiratory syncytial virus bronchiolitis (3 each), Asthma, COVID-19, Fall, Gastroenteritis viral, Immune thrombocytopenia, Kawasaki's disease, Lower respiratory tract infection viral, and Rhinovirus infection (2 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset[63]: n = 74, range: from <24 hours to 236 days, median: 90 days.
  - <24 hours: 2 events;
  - 2-7 days: 1 event;
  - 8-14 days: 3 events;
  - 15-30 days: 5 events;
  - 31-298 days: 63 events.
- Duration of relevant events[64]: n = 63, range: <24 hours to 43 days, median: 7 days.
  - <24 hours: 2 events;
  - 1 day: 5 events;
  - 2-7 days: 29 events;
  - 8-14 days: 9 events;
  - 15-43 days: 18 events.
- Event outcome: resolved/resolving (68), not resolved (7), resolved with sequelae (1).

Post-Authorisation Data

- Number of cases: 606 (BNT162b2 [592], BNT162b2 + BNT162b2 Omi BA.1 [1] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [24])[67] (0.2% of 282,992 cases, the total PM dataset), compared to 275 cases (0.5%) retrieved in the PSUR #3.
- MC cases (456), NMC cases (150).
- Country/region of incidence: US (497), Germany (22), Australia (16), Japan (14), Brazil (11), Iraq, Taiwan, Province of China (10 each), Belgium, Canada, Costa Rica, Poland (3 each); the remaining 14 cases were distributed among 10 countries.
- Subjects' gender: female (228), male (298) and unknown (80).
- Subjects' age in years: n = 595, range: 0.04 - 4.92, mean: 2.7, median: 3.0.

- Medical history (n = 58); the most frequently (≥2) reported medical conditions included Autism spectrum disorder (6), Asthma, Food allergy, Hypersensitivity, Seasonal allergy (4 each), Ear infection, Eczema, Nasal congestion, Otitis media (3 each), Atrioventricular septal defect, Bronchitis, Cardiac disorder, Dermatitis atopic, Febrile convulsion, Hyperacusis, Influenza, Lung disorder, Milk allergy, Obesity, Trisomy 21 (2 each).
- COVID-19 Medical history (n = 15): COVID-19 (15).
- Co-suspect medications (n = 50); the most frequently (≥3) reported included influenza vaccine (23), elasomeran (9), diphtheria/pertussis/polio/tetanus vaccine, measles/mumps/rubella vaccine, measles/mumps/rubella/varicella vaccine (8 each), hepatitis A vaccine (7), varicella zoster vaccine (5), and polio vaccine (3).
- Number of events: 1455.
    - Most frequently reported PTs (≥2) in subjects <6 months (n = 49): Product administered to patient of inappropriate age (13), Pyrexia (5), Off label use, Vaccination site swelling (3 each), Arthralgia, Overdose, Pain in extremity, Product use issue, Vaccination site erythema (2 each)
    - Most frequently reported PTs (≥3) in subjects 6 months through 4 years (n = 1406):
        - Following dose 1
            - Formulation 3 mcg (Maroon cap) (n = 213): Overdose (36), Product preparation error (18), Product preparation issue (17), Poor quality product administered (15), Product administration error (13), Product use issue (11), Off label use (10), Product administered at inappropriate site (8), COVID-19 (5), Drug ineffective, Underdose (4 each), Cough, Expired product administered, Nasal congestion, Pyrexia, Vomiting (3 each)
            - Formulation other/unknown (n = 418): Product administered to patient of inappropriate age (98), Overdose (67), Pyrexia (21), Product administered at inappropriate site (16), Product use issue (11), Vomiting, Wrong product administered (8 each), Diarrhoea, Fatigue, Rash, Vaccination error (6 each), Headache, Rhinorrhoea (5 each), Cough, Decreased appetite (4 each), Abdominal pain, Dyspnoea, Urticaria (3 each)
        - Following dose 2
            - Formulation 3 mcg (Maroon cap) (n = 176): Poor quality product administered (28), Overdose (22), Product administration error (20), Inappropriate schedule of product administration, Product preparation error (13 each), Product preparation issue (10), Product administered at inappropriate site (8), Pyrexia (7), Expired product administered, Interchange of vaccine products, Off label use, Product temperature excursion issue (6 each), Wrong product administered (4)
            - Formulation other/unknown (n = 124): Product administered to patient of inappropriate age (26), Overdose (25), Off label use, Pyrexia (7 each), Inappropriate schedule of product administration, Interchange

of vaccine products (5 each), Poor quality product administered, Wrong product administered (3 each)

- Following dose 3
  - Formulation 3 mcg (Maroon cap) (n = 63): Inappropriate schedule of product administration (21), Poor quality product administered, Product administration error (10 each), Product preparation error (5), Overdose (4), Off label use (3)
  - Formulation other/unknown (n = 67): Product administered to patient of inappropriate age (16), Overdose (14), Off label use (5), Inappropriate schedule of product administration, Product administered at inappropriate site, Product use issue (3 each)
- Following dose other/unknown
  - Formulation 3 mcg (Maroon cap) (n = 159): Poor quality product administered (44), Product administration error (31), Overdose (21), Product temperature excursion issue (12), Product preparation error, Product preparation issue (11 each), Expired product administered (4), Pyrexia (3)
  - Formulation other/unknown (n = 186): Product administered to patient of inappropriate age (58), Overdose (47), Off label use, Poor quality product administered (7 each), Product use issue, Pyrexia, Wrong product administered (6 each), Product administration error (4), Incorrect route of product administration (3)

- Event seriousness: serious (121), non-serious (1334).
- Time to event onset[63]: n = 992, range: from <24 hours to 196 days, median: <1 day.
  - <24 hours: 820 events;
  - 1 day: 83 events;
  - 2-7 days: 59 events;
  - 8-14 days: 8 events;
  - 15-196 days: 22 events.
- Duration of relevant events[64]: n = 66, range: from <24 hours to 24 days, median: 3 days.
  - <24 hours: 11 events;
  - 1 day: 14 events;
  - 2-7 days: 27 events;
  - 8-14 days: 9 events;
  - 15-24 days: 5 events.
- Event outcome: fatal (7), resolved/resolving (232), not resolved (78), resolved with sequelae (7), unknown (1131).

Fatal cases (3)

- Age: [redacted]

- MC case (1), NMC cases (2).
- Gender: [redacted]
- Country: [redacted].
- Fatal PTs (7): Death, Ear haemorrhage, Epistaxis, Eye haemorrhage, Mouth haemorrhage, Pneumonia, Pulmonary oedema (1 each).
- Medical history (n = 1): Nasopharyngitis (1).

The 3 fatal cases are summarised below:

- In 1 case[90] (NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The limited information provided prevented any meaningful assessment.

- In the remaining 2 cases (1 MC and 1 NMC[90]) reporting the following fatal PTs Ear haemorrhage, Epistaxis, Eye haemorrhage, Mouth haemorrhage, Pneumonia, Pulmonary oedema (1 each), no confounding factors have been identified; therefore, a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results provided evidence of a causal relationship.

16.3.5.2.2. Paediatric Subjects ≥5 Years and ≤ 11 Years of Age

Clinical Trial Data

- Number of cases: 34 (blinded therapy [9] and BNT162b2 [25]), originated from clinical studies C4591007, C4591007-OPENLABEL and C4591024 (11.0% of 309 cases, the total CT dataset), compared to 25 cases (3.7%) retrieved in the PSUR #3.
- Country/region of incidence: US (19), Brazil (7), Finland (4), Poland (3), and [redacted] (1).
- Subjects' gender: female (16), male (18).
- Subjects' age in years: n = 34, range: 5 – 11, mean: 8.1, median: 9.0.
- Medical history (n = 27); the most frequently (≥2) reported medical conditions included Asthma, Renal transplant (4 each), Gastrostomy, Seasonal allergy (3 each), Conductive deafness, Cystostomy, Eustachian tube dysfunction, Febrile convulsion, Gastrooesophageal reflux disease, Generalised anxiety disorder, Heart transplant, Medical device implantation, Myringotomy, Obstructive nephropathy, Rhinitis allergic, and Seizure (2 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.

[90] After DLP, the case reporting Death and the case reporting the fatal PTs Ear haemorrhage, Epistaxis, Eye haemorrhage, Mouth haemorrhage have been made invalid since the reporter had no first-hand knowledge of the reported events.

- PTs (42): Seizure, Urinary tract infection (3 each), Appendicitis (2), Abdominal abscess, Abdominal pain, Acute kidney injury, Anaemia, Anaphylactic reaction, Asthma, Asthmatic crisis, Balanoposthitis, Clostridium difficile colitis, Disruptive mood dysregulation disorder, Epilepsy, Escherichia infection, Facial bones fracture, Femur fracture, Gastroenteritis, Hydrocele, Hypertension, Hypoglycaemia, Influenza like illness, Kidney transplant rejection, Lower limb fracture, Narcolepsy, Phimosis, Pneumonia, Procedural failure, Respiratory arrest, Respiratory syncytial virus infection, Respiratory tract infection, Sickle cell anaemia with crisis, Sinusitis, Sleep apnoea syndrome, Suicidal ideation, Tethered cord syndrome, and Urinary retention (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset[63]: n = 41, range: 15 days to 345 days, median: 117.5 days.
  - <1 24 hours: 0 events;
  - 1 day: 0 events;
  - 2-14 days: 0 events;
  - 15-30 days: 3 events;
  - 31-90 days: 7 events;
  - 91-345 days: 31 events.
- Duration of relevant events[64]: n = 30, range: <24 hours to 201 days, median 3 days.
  - <24 hours: 2 events;
  - 1 day: 4 events;
  - 2-7 days: 18 events;
  - 8-201 days: 6 events.
- Event outcome: resolved/resolving (32), resolved with sequelae (4), not resolved (6).

Post-Authorisation Data

- Number of cases: 4983 (BNT162b2 [4798], BNT162b2 + BNT162b2 Omi BA.1 [12] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [295])[67](1.8% of 282,992 cases, the total PM dataset), compared to 9605 cases (1.9%) retrieved in the PSUR #3.
- MC cases (4104), NMC cases (879).
- Country/region of incidence (≥2%): US (2064), Philippines (799), Malaysia (513), Japan (496), Spain (147), Australia (124), Taiwan, Province of China (123), and Canada (109).
- Subjects' gender: female (1961), male (1933) and unknown (1089).
- Subjects' age in years: n = 4273, range: 5 – 11.42, mean: 8.1, median: 8.0.
- Medical history (n = 284); the most frequently (≥5) reported medical conditions included Asthma (49), Hypersensitivity (25), Food allergy (24), Attention deficit hyperactivity disorder (15), Rhinitis allergic (14), Obesity, Seasonal allergy (11 each), Autism spectrum disorder (10), Dermatitis atopic, Epilepsy (9 each), Cystic fibrosis (8), Abdominal pain, Constipation, Eczema, Non-tobacco user (7 each), Allergy to animal,

Type 1 diabetes mellitus (6 each), Drug hypersensitivity, Hypertension, Mite allergy, Premature baby, Rash, and Urticaria (5 each).

- COVID-19 Medical history (n = 61): COVID-19 (52), Suspected COVID-19 (6), Coronavirus infection, Coronavirus test positive, and Exposure to SARS-CoV-2 (1 each).
- Co-suspect medications (n = 124); the most frequently (≥5) reported included influenza vaccine (93), diphtheria/pertussis/tetanus vaccine (19), HPV vaccine (17), hepatitis A vaccine, hepatitis B vaccine (6 each), and meningococcal vaccine A/C/Y/W conj (tet tox) (5).
- Number of events: 10,602.
- Event seriousness: serious (1666), non-serious (8938).
- Most frequently reported PTs (>3% of cases): Poor quality product administered (955), Expired product administered (809), Pyrexia (717), Product administration error (690), Overdose (435), Vaccination site pain (351), Product preparation error (306), Product administered to patient of inappropriate age (279), Headache (275), Vomiting (267), Rash (245), Product temperature excursion issue (214), Inappropriate schedule of product administration (165), and Cough (149).
- Time to event onset[63]: n = 6949, range: from <24 hours to 368 days, median: <24 hours.
  - <24 hours: 4534 events;
  - 1 day: 871 events;
  - 2-7 days: 650 events;
  - 8-14 days: 196 events;
  - 15-30 days: 180 events;
  - 31-60 days: 150 events;
  - 61-385 days: 368 events.
- Duration of relevant events[64]: n = 1070, range: from <24 hours to 203 days, median 1 day.
  - <24 hours: 217 events;
  - 1 day: 323 events;
  - 2-7 days: 381 events;
  - 8-14 days: 67 events;
  - 15-203 days: 82 events.
- Relevant event outcome: resolved/resolving (3803), resolved with sequelae (21), not resolved (554), fatal (39), unknown (6192).

Fatal cases (18)

[redacted] Age: [redacted]

- MC cases (12), NMC cases (6).
- Gender: females (11), males (5), unknown (2).

- Country: Philippines (11), Japan, US (2 each), [redacted] (1 each).
- Fatal PTs (58); the most frequently (≥ 2) reported AEs included Death, Pyrexia (5 each), Cardiac arrest, Headache, Seizure, and Vomiting (2 each).
- Medical history (n = 2): Asthma, Colitis ulcerative, Coronavirus test negative, Coronavirus test positive, Cough, Exanthema subitem, Febrile convulsion, Influenza, Nasopharyngitis, Pyrexia, Rash, Rhinitis allergic, Seizure, Status epilepticus, Thyroid cancer, and Thyroid operation (1 each).

  The 18 fatal cases are summarised below:

- In 5 cases (1 MC and 4 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The limited information provided prevented any meaningful assessment.

- In the remaining 13 cases (11 MC and 2 NMC) reporting the following fatal PTs Pyrexia (5), Cardiac arrest, Headache, Seizure, Vomiting (2 each), Abdominal pain, Altered state of consciousness, Brain death, Brain herniation, Brain oedema, Cardio-respiratory arrest, COVID-19, Depressed level of consciousness, Diarrhoea, Dyspnoea, Encephalopathy, Hepatorenal syndrome, Immune thrombocytopenia, Malaise, Multiple organ dysfunction syndrome, Myocarditis, Nasopharyngitis, Pulseless electrical activity, Rash, Sepsis, and Septic shock (1 each), no confounding factors have been identified. In most cases (10) the limited information available does not allow a medically meaningful assessment; in the remaining cases (3) a causality between the vaccination and the occurrence of the fatalities cannot be ruled out.

16.3.5.2.3. Paediatric Subjects ≥12 Years of Age

Clinical Trial Data

- Number of cases: 11 (BNT162b2 [5] and blinded therapy [6]) originated from Protocol C4591001-OPEN LABEL (4), C4591007 (4), C4591007-OPEN LABEL (1), and C4591031 (2) (3.6% of 309 cases, the total CT dataset), compared to 15 cases (2.2%) retrieved in the PSUR #3.
- Country/region of incidence: US (10) and [redacted] (1).
- Subjects' gender: female (6) and male (5).
- Subjects' age in years: n = 11, range: 12 – 15, mean: 13.5, median: 14.0.
- Medical history (n = 5); the most frequently (≥2) reported medical conditions included Depression and Seasonal allergy (2 each).
- COVID-19 Medical history: None.
- Co-suspect medications: None.
- PTs (14): Suicidal ideation (2), Abdominal migraine, Asthenia, Concussion, Condition aggravated, Epiphyseal fracture, Migraine, Ovarian cyst, Pharyngitis, Rhabdomyosarcoma, Road traffic accident, Sleep apnoea syndrome, and Suicide attempt (1 each).

  All events were assessed as unrelated to BNT162b2 or blinded therapy.

- Time to event onset[63]: n = 9, range: from 21 days to 422 days, median: 86 days.
  - <24 hours to 14 days: 0 events;
  - 15-30 days: 2 events;
  - 31-60 days: 1 event;
  - 61-90 days: 2 events;
  - 91-422 days: 4 events.
- Duration of relevant events[64]: n = 7, range: from 4 days to 63 days, median 14 days.
  - 4 days: 2 events;
  - 5-14 days: 2 events;
  - 15-63 days: 3 events.
- Event outcome: fatal (1), resolved/resolving (9), resolved with sequelae (4).

Post-Authorisation Data

- Number of cases: 7064 (BNT162b2 [6885], BNT162b2 + BNT162b2 Omi BA.1 [78] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [196])[67] (2.5% of 282,992 cases, the total PM dataset), compared to 21,945 cases (4.3%) retrieved in the PSUR #3.
- MC cases (4818), NMC cases (2246).
- Country/region of incidence (>2%): Austria (1904), France (672), Philippines (576), US (565), Sweden (542), Germany (344), Japan (286), Mexico (229), Poland (176), Spain (175), Iraq (163), Taiwan, Province of China (160), and UK (156).
- Subjects' gender: female (3719), male (3028) and unknown (317).
- Subjects' age in years: n = 6857, range: 12 - 17, mean: 14.8, median: 15.0.
- Medical history (n = 827); the most frequently (≥15) reported medical conditions included Asthma (115), Hypersensitivity, Seasonal allergy (68 each), Food allergy (47), Attention deficit hyperactivity disorder (29), Autism spectrum disorder (26), Drug hypersensitivity, Mite allergy (25 each), Headache, Obesity (23 each), Epilepsy (22), Allergy to animal (21), Illness, Migraine (16 each), Dermatitis atopic, Non-tobacco user, and Rhinitis allergic (15 each).
- COVID-19 Medical history (n = 247): COVID-19 (221), Suspected COVID-19 (22), Post-acute COVID-19 syndrome (3), Exposure to SARS-CoV-2 (2), and Coronavirus infection (1).
- Co-suspect medications (n = 127); the most frequently (≥5) reported co-suspect medications included COVID-19 vaccine (65), influenza vaccine (28), HPV vaccine (11), and elasomeran (5).
- Number of events: 19,068.
- Relevant event seriousness: serious (7806), non-serious (11,271).

- Most frequently reported PTs (≥2%): COVID-19 (1783), Vaccination failure (1375), Pyrexia (1060), Headache (887), Fatigue (502), Vaccination site pain (497), Inappropriate schedule of product administration (491), Drug ineffective (452), Dizziness (433), and Nausea (384).
- Time to event onset[63]: (n = 15,003), range: from <24 hours to 700 days, median: 1 day.
  - <24 hours: 5432 events;
  - 1 day: 2663 events;
  - 2-7 days: 1482 events;
  - 8-14 days: 357 events;
  - 15-30 days: 571 events;
  - 31-90 days: 1444 events;
  - 91-181 days: 2540 days;
  - 182-700 days: 514 events.
- Duration of relevant events[64]: n = 2318, range: <24 hours to 512 days, median 2 days.
  - <24 hours: 441 events;
  - 1 day: 610 events;
  - 2-7 days: 893 events;
  - 8-14 days: 149 events;
  - 15-30 days: 83 events;
  - 31-512 days: 142 events.
- Relevant event outcome: fatal (73), resolved/resolving (6266), not resolved (2979), resolved with sequelae (176), unknown (9599).

Fatal cases (28)

- Age: [redacted].
- MC cases (21), NMC cases (7).
- Gender: females (11), males (16), unknown (1).
- Country (≥ 2): Philippines (9), Australia, Germany, Ireland, Taiwan, Province of China, and UK (2 each).
- Fatal PTs (73); the most frequently (≥ 3) reported AEs included Pyrexia (6), Abdominal pain, Death (4 each), Dyspnoea, and Myalgia (3 each).
- Medical history (n = 6): Obesity (2), Acute stress disorder, Addison's disease, Asthma, Disturbance in attention, Epilepsy, Flashback, Neonatal asphyxia, Nightmare, Oral contraception, Patient isolation, and Psychological abuse (1 each).

  The 28 fatal cases are summarised below:

- In 3 cases (1 MC and 2 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The time to fatal event onset is

available in 2 cases: 6 days and 190 days (1 each). The limited information provided prevented any meaningful assessment.

- In 4 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

  - MC case; age: [redacted]; fatal PTs: Pulmonary embolism, Dizziness, Disease recurrence, Deep vein thrombosis, occurred 2 days after the dose 3 (booster) of BNT162b2; medical history: obesity, oral contraception; autopsy revealed pulmonary embolism. Forensic pathology examination revealed fresh clot material tamping out in the left central pulmonary artery and loosely lying clots in places in the peripheral pulmonary artery on the right, a wall-adherent blood clot that had started to be cleared was found in the lobe artery of the left upper lobe. In this respect, in the case of the subject's clots in the pulmonary arteries may have spread before the booster vaccination.

  - MC case; age: [redacted]; fatal PTs: Cardiac arrest, Circulatory collapse, Dyspnoea, occurred 10 days after the 1st dose of BNT162b2; medical history: asthma; autopsy: unknown if performed.

  - MC case; age: [redacted]; fatal PTs: Pulmonary embolism (onset 2 days after the 3rd dose of BNT162b2); medical history: obesity; concomitant medication: oral contraception; autopsy results: due to wall adherent blood clots found in one lower lobe artery it can be concluded that the clots must have been existing before the booster vaccination. With obesity in context with intake of oral contraceptive drug, 2 risk factors were present regarding the occurrence of thromboembolic events. A relation between death and booster vaccination is not assumed.

  - MC case; age: [redacted]; fatal PTs Encephalitis viral, Brain oedema, Encephalopathy (onset date not provided; dose number of BNT162b2 unknown); medical history: Addison's disease. Autopsy results: provisional anatomical diagnosis of profound adrenal pathology consistent with Addison's disease, cause of death was massive brain oedema due to viral encephalitis.

- In the remaining 21 cases (16 MC and 5 NMC) reporting the following fatal PTs Pyrexia (6), Abdominal pain (4), Myalgia (3), Dyspnoea, Haematemesis, Vomiting (2 each), Adverse event following immunisation, Arthralgia, Asthenia, Asthma, Bradycardia, Calculus bladder, Cardiac arrest, Cardio-respiratory arrest, Chest pain, Chills, Cold sweat, COVID-19, Death, Dengue fever, Diarrhoea, Encephalitis post immunisation, Epistaxis, Fatigue, General physical health deterioration, Headache, Immunisation, Infection, Malaise, Muscular weakness, Myocardial infarction, Myocarditis, Oedema, Off label use, Pain, Platelet count decreased, Pneumatosis intestinalis, Pneumoperitoneum, Pulmonary oedema, Respiratory distress, Seizure, Sensory disturbance, Septic shock, Sudden cardiac death, Syncope, and Vaccination error (1 each), no confounding factors have been identified. In 14 cases the limited information available does not allow a medically meaningful assessment, in the

remaining 7 cases a causality between the vaccination and the occurrence of the fatalities cannot be ruled out.

Analysis of confounders and risk factors

- Among the 12,760 cases involving paediatric subjects, 1845 included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (700 cases), underlying medical history and/or comorbidities (1531 cases) or predisposing factors (e.g., asthma, depression, diabetes, menstrual disorders, migraine, obesity, seizures/epilepsy) (181 cases).

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

Conclusion

No relevant differences in the occurrence of the most frequently reported events, case seriousness and case outcomes were identified among the 3 paediatric age groups presented above. Of the frequently reported AEs in the paediatric dataset, the following AEs had a higher reporting proportion compared to the non-paediatric dataset: Pyrexia (14.5% versus 11.1%), Vaccination failure (11.2% versus 10.2%), Rash (3.5% versus 2.2%), Poor quality product administered (10.9% versus 0.5%), Product administration error (8.3% versus 0.4%), Product temperature excursion issue (2.2% versus 0.1%), Expired product administered (6.9% versus 0.1%), Overdose (5.5% versus 0.1%), Product administered to patient of inappropriate age (4.7% versus 0.0%), Vomiting (4.5% versus 1.8%), Product preparation error (3.0% versus 0.0%), Chest pain (2.6% versus 1.6%), Vaccination error (2.3% versus 0.2%), Cough (2.2% versus 1.3%), Abdominal pain (2.1% versus 1.1%), Wrong product administered (2.0% versus 0.3%), and Pruritus (2.0% versus 1.5%).

No new significant safety information was identified based on the review of the cases reported in the overall paediatric population. The most frequently reported AEs[91] were consistent with the known reactogenicity of the vaccine and listed in Section 4.4 Special warnings and precautions for use and/or in Section 4.8 Undesirable effects of the CDS.

16.3.5.3. Use in Pregnant/Lactating Women[92,93]

These requests are addressed within the section, providing a cumulative review of pregnancy and lactation cases originating from clinical trials along with incremental pregnancy and

[91] For the CT cases, the analysis was focused on AEs assessed as related to BNT162b2 or blinded therapy.

[92] Exposure *in utero* cases are included.

[93] Search criteria - "Selects Pregnancy cases from the data set. Pregnancy cases are identified as cases where:
– Patient Pregnant Flag is “Yes”;

incremental lactation cases from CTs, and incremental pregnancy and lactation cases from PM and presenting the data according to annex 3 of the "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

Clinical Trial Data

Cumulative review (Pregnancy Cases)

- Number of pregnancy cases: 746 (27.4% of the total 2724 cases from the CT dataset). These 746 cases represent 706 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 40 pregnancies). Cases originated from clinical studies C4591006 (354), C4591001 (155), C4591015 (120)[94], C4591001-OPENLABEL (98), C4591031-OPENLABEL (14), C4591031 (9), C4591020 (2), C4591017 (1), BNT162-17 (6) and BNT162-01-OPENLABEL (1) and study treatment was reported as BNT162b2 (513), blinded therapy (189), placebo (43) and BNT162C2 (1).
- Country/region of incidence: Japan (350), US (206), South Africa (54), Brazil (52), Argentina (48), Spain (19), UK (12), Germany (3) and Turkey (2).
- Of the 641 mother cases, 470 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The frequently reported pregnancy related events (>1) were coded to the PTs Maternal exposure before pregnancy (294), Maternal exposure during pregnancy (152), Maternal exposure timing unspecified (11), Exposure during pregnancy (9), Maternal exposure via partner during pregnancy (2).
- One hundred seventy (171) mother cases, 147 serious and 22 non-serious, reported additional clinical events, which occurred in the vaccinated mothers.
    - The frequently reported pregnancy related events (>1) reported in these cases were coded to the PTs Maternal exposure during pregnancy (59), Abortion spontaneous (47), Maternal exposure before pregnancy (33), Premature labour (9), Pre-eclampsia (8), Cephalo-pelvic disproportion (6), Premature separation of placenta, Abortion missed (5 each), Ectopic pregnancy, Foetal death, Postpartum haemorrhage (4 each), Abortion threatened, Gestational hypertension, Hyperemesis gravidarum, Premature delivery (3 each), Abortion incomplete, Exposure during pregnancy, Uterine disorder, Placenta previa (2 each).
    - Other reported clinical events included COVID-19 (8), Anaemia, Miscarriage of partner (2 each), Abdominal wall haematoma, Cholelithiasis, Dehydration, Diabetes

– If there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly;
– If Delivery Notes are available;
– If any of the valid events on the case contains one of the following:"
SOC Pregnancy, puerperium and perinatal conditions, or
HLT Exposures associated with pregnancy, delivery and lactation; Lactation disorders, or PT Exposure via body fluid.

[94] C4591015 is the maternal immunisation study, the cases represent SAEs identified while pregnant, not reporting the pregnancy.

mellitus inadequate control, Drug eruption, Endometritis, Lower respiratory tract infection, Osteoarthritis, Pneumonia, Pruritis, Pyelonephritis, Sepsis, Urinary tract infection, Urinary tract procedural complication, Vascular pseudoaneurysm, Venous thrombosis limb (1 each).

- Of the 65 cases reporting spontaneous abortion or abortion related events, in 29 cases mother had a medical history of spontaneous abortion, alcohol/ tobacco use during pregnancy, ectopic pregnancy, obesity, diabetes mellitus, uterine disorder, depression or anembryonic gestation which might have contributed to the event and in 36 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
- Of the 21 cases reporting elective termination, in 11 cases, mother had a medical history of spontaneous abortion, induced abortion, alcohol/ tobacco use and in remaining 10 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
- In 4 cases reporting ectopic pregnancy, in 2 cases, mother had a medical history of tobacco use and ectopic pregnancy which might have contributed to the event and in the remaining 2 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
- In 3 cases reporting foetal death/stillbirth mother had a medical history of amniotic cavity infection, HIV infection and/or spontaneous abortion which might have contributed to the event.

- 105 baby/foetal cases, 102 serious and 3 non-serious. Cases are classified according to pregnancy outcome.
  - Pregnancy outcome: Live birth with congenital anomaly: 36 of these cases reported 42 congenital anomalies that coded to the PTs Atrial septal defect (5), Ankyloglossia congenital, Hypoxic-ischaemic encephalopathy, Neonatal hypotension, Trisomy 21 (2 each), Cleft lip, Coma neonatal, Congenital rubella syndrome, Congenital skin dimples, Congenital skin disorder, Craniosynostosis, DiGeorge's syndrome, Gnathoschisis, Microcephaly, Neonatal pneumothorax, Neonatal intestinal perforation, Neonatal seizure, Nervous system disorder, Newborn persistent pulmonary hypertension, Osteochondrodysplasia, Patent ductus arteriosus, Polydactyly, Pulmonary valve stenosis congenital, Pyelonephritis acute, Renal failure neonatal, Renal tubular necrosis, Sepsis neonatal, Sex chromosome abnormality, Syndactyly, Talipes, Thanatophoric dwarfism, Thrombocytopenia neonatal, Ventricular septal defect, Vesicoureteric reflux (1 each). Of these 36 cases, information regarding trimester of exposure was available in 17 cases. Of these 17 cases, in 12 cases foetus was exposed during 3rd trimester, in 4 cases foetus was exposed during 2nd trimester and in 1 case exposure occurred during 1st trimester. Of these 36 cases, in 8 cases the mother of the baby was on multiple concomitant medications, or alcohol/tobacco use during pregnancy, suffered gestational diabetes, was of advanced age (i.e., [redacted] years) and/or had a medical history of in vitro fertilization. In the remaining 28 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Still birth without foetal defect: During the reporting period there was 1 case reporting stillbirth without foetal defect. The event reported in this case was coded to PT Neonatal respiratory distress syndrome. The information regarding trimester of exposure was unknown. In this case mother of the baby had underlying medical history of amniotic cavity infection which might have led to the development of the reported event.
- Pregnancy outcome: Live birth without congenital anomaly: 68 cases reported live birth babies without congenital anomaly. Of these 68 cases, information regarding trimester of exposure was available in 40 cases. Of these 40 cases, in 21 cases, foetus was exposed during 3rd trimester, in 15 cases foetus was exposed during 2nd trimester and in 4 cases exposure occurred during 1st trimester. The frequently reported events (>1) in these 68 cases were coded to PTs Jaundice neonatal (11), Foetal distress syndrome (8), Premature baby (7), Neonatal pneumonia, Neonatal respiratory distress, Bronchiolitis, Neonatal respiratory distress syndrome, Hyperbilirubinaemia neonatal (3 each), Foetal hypokinesia, Neonatal tachypnoea, Dehydration, Gastroenteritis, Patent ductus arteriosus, Anaemia neonatal, Sepsis neonatal, Hypoglycaemia neonatal, Meconium aspiration syndrome (2 each). In all these 68 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 746 cases, 712 cases provided pregnancy outcomes which are provided in Table 85 below. Pregnancy outcome was pending or not provided in the remaining 34 cases.

Table 85. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval[a]

Pregnancy outcome	Prospective cases 589 (79.0% of pregnancy cases)				Retrospective cases 123 (16.5% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1st trimester	After 1st trimester	During all pregnancy	Unknown	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	3	1	0	0	0
Spontaneous abortion	23	0	0	25	5	1	0	8
Elective termination (foetal defects)	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	15	0	0	3	2	0	0	1
Stillbirth with foetal defects	0	1	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	2	0	0	0	1
Live birth with congenital anomaly	1	24	0	18	3	0	0	7
Live birth without congenital anomaly	104	99	0	271	16	21	0	57
Total	***143***	***124***	***0***	***322***	***27***	***22***	***0***	***74***

a. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception

Cumulative review (Lactation cases)

- Number of lactation cases: 162 (5.9% of the total 2724 cases from the CT dataset). All these 162 cases were non-serious. Of these 162 cases, 161 cases reported only exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events. In the remaining case, the clinical event was coded to PT Respiratory syncytial virus infection. In this case, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Incremental review (CT cases)

- Number of pregnancy cases: 11 (3.6% of the total 309 cases from the CT dataset). These 11 cases represent 10 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 1 pregnancy). Cases originated from clinical studies C4591001-OPENLABEL (9) and C4591031 (2) and study treatment was reported as BNT162b2 (9) and blinded therapy (2).
- Country/region of incidence: Brazil (5), US (4), Argentina (2).
- Nine (9) serious maternal cases reported additional clinical events, which occurred in the vaccinated pregnant females.
    - The frequently reported pregnancy related events (>1) reported in these cases were coded to the PTs Abortion spontaneous, Maternal exposure before pregnancy, Premature labour (2 each).
    - Other reported clinical events coded to the PTs Diabetes mellitus inadequate control and Sepsis (1 each).
    - All the 3 cases reporting spontaneous abortion or abortion related events, mother had a medical history of uterine leiomyoma, spontaneous abortion and/or had underlying condition of obesity which might have contributed to the event.
- Two (2) serious baby/foetal cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: 2 of these cases reported 2 congenital anomalies that coded to the PTs Adnexa uteri cyst and Foetal growth restriction (1 each). In these 2 cases, information regarding trimester of exposure was unknown. Of these 2 cases, in 1 case reporting Foetal growth restriction, the mother of the baby had a medical history of tobacco use. In the remaining 1 case, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

All the 11 cases provided pregnancy outcomes which are provided in Table 86 below.

Table 86. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval[a]

Pregnancy outcome	Prospective cases 11 (100% of pregnancy cases)				Retrospective cases 0 (0% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1st trimester	After 1st trimester	During all pregnancy	Unknown	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	1	0	0	0	0
Spontaneous abortion	1	0	0	2	0	0	0	0
Elective termination (foetal defects)	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	0	0	0	0	0
Live birth with congenital anomaly	0	0	0	3	0	0	0	0
Live birth without congenital anomaly	1	1	0	2	0	0	0	0
Total	***2***	***1***	***0***	***8***	***0***	***0***	***0***	***0***

a. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception

Post-Authorisation Data

Incremental review (Pregnancy cases)

- Number of pregnancy cases: 988 (0.3% of 282,992 cases, the total PM dataset), compared to 3642 cases (0.7%) retrieved in the PSUR #3. These 988 cases represent 896 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 92 pregnancies).
- Country/region of incidence (>50): France (162), Germany (161), US (75), Philippines (70), Japan (57).
- Of the 863 mother cases, 161 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (75), Maternal exposure timing unspecified (52), Paternal exposure before pregnancy (19), Maternal exposure before pregnancy (11), Exposure during pregnancy (4).
- There were 702 mother cases of which 473 were serious and 229 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. Additional pregnancy related events reported in these cases (>15) were coded to the PTs Abortion spontaneous (134), Labour pain (26), Menstrual disorder, Menstruation irregular (22 each)[95]. Other frequently reported (>40) clinical events coded to the PTs COVID-19 (110), Headache (78), Fatigue (59), Vaccination site pain (48), Malaise (44).
- One hundred twenty-five (125) baby/foetal cases, 113 serious and 12 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: 47 of these cases reported 86 congenital anomalies that coded to the PTs Atrial septal defect (6), Foetal growth restriction (4), Congenital anomaly, Foetal cardiac disorder, Heterotaxia, Ventricular septal defect (3 each), Congenital tricuspid valve atresia, Patent ductus arteriosus, Ankyloglossia congenital, Syndactyly, Hypospadias (2 each), Acrochordon, Adactyly, Anomalous pulmonary venous connection, Astigmatism, Body dysmorphic disorder Foetal malformation, Bronchial atresia, Bronchial dysplasia, Cardiac malposition, Cardiac septal hypertrophy, Cataract congenital, Cleft lip and palate, Congenital aortic valve incompetence, Congenital cystic kidney disease, Congenital hydronephrosis, Congenital mitral valve incompetence, Congenital pulmonary airway malformation, Congenital tongue anomaly, Congenital ureteropelvic junction obstruction, Craniosynostosis, Developmental delay, Dysmorphism, Fallot's tetralogy, Foetal growth abnormality, Food protein-induced enterocolitis syndrome, Haemangioma congenital, Hypertelorism, Hypertrophic cardiomyopathy, Hypoplastic right heart syndrome, Infantile haemangioma, Inguinal hernia, Labial tie, Limb reduction defect, Mediastinal shift, Microcephaly, Microtia, Neonatal deafness, Neonatal intestinal perforation, Oculoauriculovertebral dysplasia, Penis disorder, Penoscrotal fusion, Periventricular leukomalacia, Polydactyly, Proximal focal femoral

[95] Few additional events reported were coded to PTs Pre-eclampsia (8), Amniotic cavity infection (2).

deficiency, Pulmonary malformation, Renal aplasia, Renal disorder, Spinal disorder, Splenic infarction, Talipes, Tongue disorder, Trismus, Trisomy 21, Wolf-Hirschhorn syndrome (1 each). Of these 47 cases, information regarding trimester of exposure was available in 16 cases. Of these 16 cases, in 11 cases foetus was exposed during 1st trimester, in 4 cases foetus was exposed during 2nd trimester and in 1 case foetus was exposed during 3rd trimester. Of these 47 cases, in 3 cases mother had underlying medical history (i.e., tobacco use, use of concomitant medication misoprostol or unspecified contraceptive medication) which might have contributed to the reported event. In the remaining 44 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: 10 cases reported spontaneous abortion. Of these 10 cases, information regarding trimester of exposure was provided in 6 cases. Of these 6 cases, in 5 cases, foetus was exposed during 1st trimester, in 1 case foetus was exposed during 2nd trimester. The events in these 10 cases other than exposure related events were coded to PTs Foetal growth restriction (7), Congenital anomaly, Foetal death, Small for dates baby, Abortion spontaneous, Foetal vascular malperfusion (1 each). Of these 10 cases, in 1 case mother had underlying medical history (i.e., gestational diabetes) which might have contributed to the reported events. In the remaining 9 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Elective termination: 4 cases reported elective termination of pregnancy. All these, 4 cases reported elective termination due to foetal defects. Of these 4 cases, information regarding trimester of exposure was provided in 2 cases. Of these 2 cases, in 1 cases foetus was exposed during 1st trimester, in 1 case, foetus was exposed during 2nd trimester. The events reported in these 4 cases other than exposure related events were coded to PTs Anophthalmos, Cerebellar hypoplasia, Congenital central nervous system anomaly, Congenital hydrocephalus, Congenital midline defect, Lissencephaly, Thanatophoric dwarfism, Trisomy 18, Twin reversed arterial perfusion sequence malformation (1 each). In these 4 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Stillbirth: 9 cases reported foetal death/ neonatal death. Of these 9 cases, 8 cases reported stillbirth with foetal defects and remaining 1 case reported stillbirth without foetal defect. Of these 9 cases, information regarding trimester of exposure was provided in 4 cases. Of these 4 cases, in 2 cases foetus was exposed during 1st trimester, in the remaining 2 cases, foetus was exposed during 2nd trimester. The events reported in these 9 cases other than exposure related events were coded to PTs Foetal death (3), Premature baby, Foetal heart rate abnormal, Congenital anomaly (2 each), Death neonatal, Foetal growth restriction, Growth disorder, Haemorrhagic vasculitis, Heart disease congenital, Hydrocephalus, Low birth weight baby, Placental insufficiency, Premature baby death, Pulmonary congestion, Pulmonary haemorrhage, Umbilical cord abnormality (1 each). Of these 9 cases, in 2 cases mother had underlying medical history (i.e., gestational diabetes or threatened

labour) which might have contributed to the reported event. In the remaining 7 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Live birth without congenital anomaly: 55 cases reported live birth babies without congenital anomaly. Of these 55 cases, information regarding trimester of exposure was available in 20 cases. Of these 20 cases, in 9 cases, foetus was exposed during 2nd trimester, in 6 cases, foetus was exposed during 1st trimester, and in 5 cases exposure occurred during 3rd trimester. The frequently reported events (>2) in these 55 cases other than exposure related events were coded to PTs Premature baby (21), Foetal growth restriction (7), Foetal hypokinesia (5), Tachycardia foetal (3). Of these 55 cases, in 7 case reporting Premature baby (5), Foetal hypokinesia, Foetal growth restriction, Foetal arrhythmia, Meconium in amniotic fluid, Tachycardia foetal (1 each), the mother of the baby had underlying medical history (i.e., gestational diabetes or obesity) which might have led to development of reported event. In the remaining 48 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 988 cases, 659 cases provided pregnancy outcomes which are provided in Table 87 below. Pregnancy outcome was pending or not provided in the remaining 329 cases.

Table 87. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a,b]

Pregnancy outcome	Prospective cases 271 (27.4% of pregnancy cases)				Retrospective cases 388 (39.3% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1st trimester	After 1st trimester	During all pregnancy	Unknown	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	1	0	0	1	0	0	0	3
Spontaneous abortion	1	0	0	8	31	4	0	91
Elective termination (foetal defects)	0	0	0	0	1	2	0	3
Elective termination (no foetal defects or unknown)	0	0	0	0	0	1	0	3
Stillbirth with foetal defects	0	0	0	0	4	7	0	5
Stillbirth without foetal defects	0	0	0	0	2	1	0	7
Live birth with congenital anomaly	3	1	0	7	19	9	0	24
Live birth without congenital anomaly	20	49	0	180	10	39	0	122
Total	***25***	***50***	***0***	***196***	***67***	***63***	***0***	***258***

a. 19 June 2022 through 18 December 2022.
b. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception

Incremental review (Lactation cases)

- Number of lactation cases: 302 (0.1% of 282,992 cases, the total PM dataset), compared to 3771 cases (0. 7%) retrieved in the PSUR #3.
  - Breast feeding baby cases: 224, of which:
  - One hundred fifty-seven (157) cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events.
  - Sixty-seven (67) cases, 14 serious and 53 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk); the frequently reported clinical events (≥5) were coded to the PTs Pyrexia (11), Restlessness (9), Diarrhoea (8), Poor feeding infant (7), Abdominal pain (6), Crying, Fatigue, Infantile vomiting (5 each).
- Breast feeding mother cases: 78, of which:
  - Twenty-six (26) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
  - Fifty-two (52) cases, 10 serious and 42 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (≥5) were coded to the PTs Pyrexia (11), Headache (8), Chills, Myalgia (7 each), Breast pain, Heavy menstrual bleeding, Fatigue, Menstruation irregular (5 each).

Literature

Review of the literature did not identify any new information regarding the use of BNT162b2 in pregnant/lactating women was identified.

Conclusion

There were no safety signals regarding use in pregnant/lactating women that emerged from the review of these cases or the medical literature.

16.3.5.4. Use in Immunocompromised Patients

Search criteria - Patients with Medical history of PTs included in Malignancy related conditions (SMQ Narrow); Malignancy related therapeutic and diagnostic procedures (SMQ Narrow); Malignant or unspecified tumours (SMQ Narrow); HLGT: Immunodeficiency syndromes (Primary Path); HLT: Retroviral infections (Primary Path); PTs: Allogenic bone marrow transplantation therapy; Allogenic stem cell transplantation; Autologous bone marrow transplantation therapy; Autologous haematopoietic stem cell transplant; Bone marrow transplant; Cord blood transplant therapy; Heart transplant; Liver transplant; Lung transplant; Pancreas islet cell transplant; Renal transplant; Small intestine transplant; Stem cell transplant.

Clinical Trial Data

- Number of cases: 32 (BNT162b2 [27], blinded therapy [4], and Placebo [1]) (10.4% of 309 cases, the total CT dataset), compared to 110 cases (16.5%) retrieved in the PSUR #3.
- Country/region of incidence: US (24), Brazil, Germany (3 each), New Zealand (2).
- Subjects' gender: female (18), and male (14).
- Subjects' age in years (n = 32), range: 2–79 years, mean: 41.9 years, median: 48.5 years.
- Medical history (n = 32); the most frequently (≥5) reported relevant medical conditions included Hysterectomy (10), Cholecystectomy, Renal transplant (5 each).
- COVID-19 Medical history: COVID-19 (1).
- Co-suspect medications (n = 5): blinded therapy (4), placebo (1).
- Number of events: 37.
- Most frequently reported clinical PTs (>1): Condition aggravated (3), Bipolar I disorder, Cardiac arrest, Leukaemia, Respiratory syncytial virus infection, Urinary tract infection (2 each).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.
- Time to event onset[63]: (n = 34 events), range: 14 days to 353 days, median: 127 days.
    - 8-14 days: 3 events;
    - 15-30 days: 2 events;
    - 31-100 days: 6 events;
    - 101-200 days: 17 events;
    - 201-353 days: 6 events.
- Duration of event: n = 25, range: 1 day to 222 days, median: 5 days
    - 1 day: 3 events;
    - 2-7 days: 14 events;
    - 8-14 days: 4 events;
    - 15-30 days: 2 events;
    - 31-222 days: 2 events.
- Reported event outcome: fatal (1), resolved/resolving (27), resolved with sequelae (3), not resolved (6).

Post-Authorisation Data

- Number of cases: 4879 (1.7% of 282,992 cases, the total PM dataset), compared to 8815 cases (1.7%) retrieved in the PSUR #3.
- MC cases (1928), NMC cases (2951).
- Country/region of incidence: France (919), Sweden (916), US (629), Germany (605), UK (345), Denmark (201), Italy (189), Japan (176), Belgium, Spain (101 each), the remaining 697 cases were distributed among 43 countries.
- Subjects' gender: female (3283), male (1365) and unknown/no data (231).
- Subjects' age in years (n = 4486), range: 1 – 102 years, mean: 60.0, median: 61.0.
- Medical history (n = 4879); the most frequently (≥200) reported relevant medical conditions included Breast cancer (718), Thyroidectomy (312), Neoplasm malignant (309), Immunodeficiency (301), Hysterectomy (269), Prostate cancer (261).
- COVID-19 Medical history (n = 358): COVID-19 (297), Suspected COVID-19 (39), Post-acute COVID-19 syndrome (8), Asymptomatic COVID-19 (6), COVID-19 pneumonia (3), SARS-CoV-2 test positive (2), Coronavirus infection, Coronavirus test positive, SARS-CoV-2 antibody test positive (1 each).
- Co-suspect medications (n = 542); the most frequently (≥10) reported co-suspect medications included COVID-19 vaccine (170), elasomeran (141), COVID-19 vaccine NRVV AD (79), influenza vaccine (18), influenza vaccine inact SPLIT 4V (13), influenza vaccine inact SAG 4V (12), COVID-19 vaccine NRVV AD26 (11).
- Number of events: 19,204.
- Event seriousness[33]: serious (8,602), non-serious (10,619).
- Most frequently reported clinical PTs (≥3%): COVID-19 (783), Fatigue (656), Headache (569), Pyrexia (503), Myalgia (363), Arthralgia (361), Vaccination site pain (351), Malaise (320), Interchange of vaccine products (307), Pain (305), Pain in extremity (302), Dizziness (282), Nausea (256), Immunisation[96] (244), Chills (237), Asthenia (222), Dyspnoea (218), Lymphadenopathy (171), Diarrhoea and Rash (134 each).
- Time to event onset[63]: n = 11,315, range: <24 hours to ≤580 days, median: 1 day.
  - <24 hours: 3539 events;
  - 1 day: 2227 events;
  - 2-7 days: 2021 events;
  - 8-14 days: 688 events;
  - 15-30 days: 716 events;
  - 31-181 days: 1504 events.

[96] PT selected per case processing conventions to indicate cases reporting third/booster doses.

  - ≥182 days: 620 events.

- Duration of event: n = 1986, range: <24 hours to 195 days, median: 2 days.
  - <24 hours: 207 events;
  - 1 day: 419 events;
  - 2-7 days: 829 events;
  - 8-14 days: 219 events;
  - 15-30 days: 138 events;
  - 31-181 days: 169 events;
  - ≥182 days: 5 events.
- Event outcome[56]: fatal (533), resolved/resolving (5398), resolved with sequelae (511), not resolved (4656), unknown (8168).

Analysis by age group

- CT Data: Paediatric (11), Adults (11), and Elderly (10).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (36), Adults (2528), Elderly (1977) and Unknown (338).
  - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to PTs Headache, Myalgia, Vaccination site pain, Pain, Chills, Lymphadenopathy, and Paraesthesia.
  - A higher reporting proportion of following events was noted when comparison was done between adult and elderly population and is included in the table below.

Events	Reporting proportion in adults N= 2528	Reporting proportion in elderly N= 1997
Headache	16.7% (421 cases)	6.6% (131 cases)
Myalgia	10.0% (253 cases)	5.3% (104 cases)
Vaccination site pain	9.8% (247 cases)	5.0% (98 cases)
Pain	8.6% (217 cases)	4.0% (79 cases)
Chills	6.8% (173 cases)	2.9% (57 cases)
Lymphadenopathy	5.3% (134 cases)	1.7% (34 cases)
Paraesthesia	3.6% (92 cases)	1.8% (36 cases)

  - No comparison was made to the paediatric population considering limited number of cases.

Conclusion

No new significant safety information was identified based on a review of these cases.

16.3.5.5. Use in Patients with Autoimmune or Inflammatory Disorders

Search criteria - Patients with Medical history PTs included in: SMQ Immune-mediated/autoimmune disorders (Narrow and Broad scope); HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction.

Clinical Trial Data

- Number of cases: 46 (BNT162b2 [34], blinded therapy [12]) (14.9% of 309 cases, the total CT dataset), compared to 102 cases (15.3%) retrieved in the PSUR #3.
- Number of events: 57.
- PTs recorded more than once: Cardiac arrest, Cardiac failure congestive, Chronic obstructive pulmonary disease, Diverticulitis, Hypotension, Myocardial infarction (2 each).
- None of the 57 events were assessed as related to BNT162b2 or blinded therapy by the investigator and Sponsor.
- Event outcome: fatal (3), resolved/resolving (44), resolved with sequelae (3), not resolved (6), unknown (1).

Post-Authorisation Data

- Number of cases: 12,868 (BNT162b2 [12,195], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [504], BNT162b2 + BNT162b2 Omi BA.1 [266]) (4.5% of 282,992 cases, the total PM dataset), compared to 21,000 cases (4.1%) retrieved in the PSUR #3.
- MC cases (3671), NMC cases (9197).
- Number of events: 52,064.
- Of the 12,868 cases, the most frequently (>500) clinical PTs included Fatigue (2188), Headache (1968), COVID-19 (1675), Pyrexia (1593), Drug ineffective (1243), Arthralgia (1188), Myalgia (1184), Malaise (1042), Pain (1021), Vaccination site pain (1004), Dizziness (942), Pain in extremity (931), Nausea (876), Chills (810), Asthenia (587), Dyspnoea (582), and Vaccination failure (575).
- Event seriousness: serious (18,814), non-serious (33,303).
- Event outcome: fatal (566), resolved/resolving (15,917), resolved with sequelae (1317), not resolved (14,900), unknown (19,549).
- In 141 cases (reporting 566 relevant events with a fatal outcome), the reported causes of death (≥ 10) included Death (15), Off label use (14), COVID-19 (13), Multiple organ dysfunction syndrome (12), Cardio-respiratory arrest, Immunisation (11 each), Pyrexia,

Sudden death, and Vaccination failure (10 each). Of note, in 25 cases, limited information regarding the cause of death was provided (PTs Death and Sudden death). Most (109 of 141 cases) of the fatal cases involved elderly subjects. The most frequently (≥10) reported medical history included diabetes mellitus (59), hypertension (46), hypothyroidism (20), atrial fibrillation (18), chronic kidney disease, COVID-19 (13 each), cardiac failure, and myocardial ischaemia (10 each).

- The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

Exacerbation or Flare-up

A focused analysis on exacerbation or flare of autoimmune or inflammatory disorders was conducted using PTs of interest (i.e., condition aggravated, disease progression), rather than all events.

- Of the 582 cases that reported PTs indicative of exacerbation or flare, 242 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (e.g., pain, hypertension, migraine, fatigue/tiredness, menstruation, COVID-19/long COVID).

Therefore, 340 cases are included in the analysis below.

Clinical Trial Data

- Number of cases: No relevant cases were retrieved, compared to 1 case (0.1%) retrieved in the PSUR #3.

Post-Authorisation Data

- Number of cases: 340 (BNT162b2 [331], BNT162b2 + BNT162b2 Omi BA.4/BA.5 [7], BNT162b2 + BNT162b2 Omi BA.1 [2]) (0.1% of 282,992 cases, the total PM dataset), compared to 771 (0.2%) retrieved in the PSUR #3.
- MC cases (152), NMC cases (188).
- Country/region of incidence: France (76), Germany (68), Japan (31), US (25), Italy (24), Norway (18), Sweden (14), Netherlands (13), Austria, UK (12 each), Belgium (10); the remaining 37 cases were distributed among 18 countries.
- Subjects' gender: female (233), male (97) and unknown (10).
- Subjects' age in years: n = 305, range: 11 – 97, mean: 53.1, median: 52.0.
- Relevant medical history; the most frequently (≥10) reported medical conditions included Rheumatoid arthritis (36), Autoimmune thyroiditis (29), Hypothyroidism (22), Ankylosing spondylitis, Multiple sclerosis, Psoriasis (16 each), Sjogren's syndrome (14),

Rheumatic disorder (13), Basedow's disease (12), Pemphigoid (11), Arthritis, and Neuropathy peripheral (10 each).

- COVID-19 Medical history (n = 39): COVID-19 (31), Coronavirus infection, COVID-19 pneumonia, Suspected COVID-19 (2 each), Asymptomatic COVID-19, Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (1 each).
- Co-suspect medications (n = 15): elasomeran (5), tofacitinib (3), methotrexate (2), alprazolam, azathioprine, betamethasone, cortisone, COVID-19 vaccine NRVV AD, ferrous sulfate, influenza vaccine, levofloxacin, loratadine, ocrelizumab, paracetamol, pneumococcal vaccine, prednisone, tamoxifen, upadacitinib, varicella zoster vaccine live (1 each).
- Number of events: 2113 (of which 342 were events of interest ie, exacerbation/flare AEs).
- Relevant event seriousness: serious (238), non-serious (104).
- Relevant PTs: Condition aggravated (258), Disease recurrence (66), Concomitant disease aggravated (13), Disease progression (4), and Symptom recurrence (1).
- Time to event onset[63]: n = 139, range: from <24 hours to 423 days, median: 5.5 days.
  - <24 hours: 19 events;
  - 1 day: 22 events (1 of which had a fatal outcome);
  - 2-7 days: 35 events;
  - 8-14 days: 18 events (1 of which had a fatal outcome);
  - 15-30 days: 15 events;
  - 31-181 days: 26 events;
  - ≥182 days: 4 events.
- Duration of relevant events[64]: n = 14, range: 1 day to 413 days, median 6.5 days.
  - 1 day: 1 event;
  - 2-7 days: 7 events;
  - 8-14 days: 1 event;
  - 15-30 days: 1 event;
  - 31-181 days: 1 event;
  - ≥182 days: 3 events.
- Relevant event outcome: fatal (4), resolved/resolving (97), resolved with sequelae (14), not resolved (122), unknown (105).

  In 4 cases (reporting 4 relevant events with a fatal outcome), the reported causes of death included Condition aggravated (3) and Disease progression (1). Additional co-reported fatal events in these 4 cases included Acute respiratory distress syndrome, Interstitial lung disease (2 each), Acute respiratory failure, Cardiac failure, Diabetic nephropathy, Pulmonary fibrosis, Pulmonary oedema, and Renal failure (1 each). All 4 cases involved male subjects with an age range of 63 to 78 years and mean of 70.5 years (n=4). The

relevant medical histories reported in these 4 cases included interstitial lung disease (2), diabetes mellitus, and rheumatoid arthritis (1 each). Review of these cases did not identify any new significant safety information.

Analysis by age group

- CT: Not applicable.
- PM: Paediatric (6), Adults (238), Elderly (78) and Unknown (18).
  - Exacerbation and/or flare of underlying autoimmune or inflammatory disorders occurred more frequently in the adult population, which is likely due to autoimmune disorders being more common in adults and the fact that adults are the largest group of vaccinated individuals reporting adverse events.

Conclusion

Overall, there were 340 PM cases (all PM cases [0.1% of the overall dataset]) that reported exacerbation/flares in subjects with autoimmune or inflammatory disorders following administration of BNT162b2, BNT162b2 + BNT162b2 Omi BA.1, or BNT162b2 + BNT162b2 Omi BA.4/BA.5. Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders occurred more frequently in the adult population which is likely due to the fact that the largest group of vaccinated individuals reporting AEs are in this age group. Also, the autoimmune or inflammatory disorders often occur during adulthood. The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

16.4. Characterisation of Risks

On 02 September 2022, EMA reminded the MAH of the legal obligation to maintain the MA for MAH' products, that includes the Risk Management Plan in module 1.8.2. of the dossier.

The safety specification and the list of safety concerns in the RMP does not seem to accurately reflect the current knowledge on the safety of your COVID-19 vaccine, as it seems to overestimate the remaining concerns for safety and missing information. Please take the next opportunity to critically appraise if the wealth of safety data accumulated during the product use can inform rationalising the safety concerns in the RMP. EMA consider that the most suitable procedure for this RMP update to be the next PSUR submission, where a summary review of the safety of the product could lead to RMP updates in Part II and more.

Response

Based on the clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, no new significant safety information has been identified that substantiates retaining VAED/VAERD as an important potential risk in the PSUR for BNT162b2. The MAH, therefore, proposes to remove the important potential risk of VAED/VAERD from the list of safety concerns.

The MAH proposes the updated list of the safety concerns, as detailed in Table 88.

Table 88. Updated Safety Concerns at the End of the Reporting Period (Proposal)

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

16.4.1. Characterisation of Important Identified and Potential Risks

A typical medicinal product has multiple risks associated with it and individual risks vary in terms of severity, effect on individual patients, and public health impact.

What constitutes an important risk depends upon several factors including the impact on the individual subject, the seriousness of the risk and its severity, and the impact on public health. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered. Risks may be related to nonclinical or clinical safety or quality issues. The intended purpose and impact of the product e.g., whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease must also be considered when characterising risks.

The following were considered in characterising risk(s) of this product:

- frequency of risk;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life or could lead to serious consequences if left untreated);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (ie, predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

Internal and external datasets were used to populate the table below with available data. In addition to literature searches for the drug itself and its class, external data sources were consulted.

Please see Appendix 8 for the characterisation of the important identified and important potential risks of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 9.0 approved on 10 November 2022.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer. The risks for BNT162b2 are well managed. No special investigations to further characterise any of these risks are necessary.

Summary information from clinical trials and post-marketing sources received by the MAH through 18 December 2022 is provided in Section 16.4.1.1 and Section 16.4.1.2.

16.4.1.1. Cumulative Characterisation of Important Identified Risks

Table 89. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
Myocarditis and Pericarditis	*Myocarditis* • No. of cases: 4 of BNT162b2 • No. of SAEs: 4 • The relevant PTs: Myocarditis, Myopericarditis (2 each) • Related SAEs: Myopericarditis (2), Myocarditis (1). *Pericarditis* • No. of cases: 3 of BNT162b2 • No. of SAEs: 3 • The most common PTs: Pericarditis (3) • Related SAEs: None. Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.	Cumulatively, there were 22,221 cases of Myocarditis and Pericarditis: 13619 cases reported myocarditis and 10725 cases reported pericarditis (in 2123 of these 22,221 cases, the subjects developed both myocarditis and pericarditis). *Myocarditis* • No. of cases: 13619 • Relevant PTs: Myocarditis (11464), Myopericarditis (2060), Carditis (184), Eosinophilic myocarditis (14), Hypersensitivity myocarditis (7), Immune-mediated myocarditis (6), Autoimmune myocarditis, Giant cell myocarditis (4 each), Chronic myocarditis (1). • Frequently reported additional PTs (≥500): Chest pain (4584), Dyspnoea (2950), Fatigue (2293), Palpitations (2173), Pericarditis (2121), Pyrexia (2008), Tachycardia (1488), Chest discomfort (1459), Headache (1160), Off label use (900), Immunisation (894), Troponin increased (864), Dizziness (844), Interchange of vaccine products (764), Malaise (644), Inappropriate schedule of product administration (633),

Table 89. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Asthenia (610), Arrhythmia (600), Nausea (556), Myalgia, Pain (517 each). • Subjects' gender: female (4645), male (8492) and unknown (482). • Subjects' age in years (n = 12278), range: 6 – 102 years, mean: 35.3 years, median: 31 years. • Age group: Paediatric (2020), Adults (9367), Elderly (1001) and Unknown (1231). • Case source: Spontaneous (13193), Literature (377), Clinical study (28), Solicited (21) • Event seriousness: serious (13744) • Event outcome: Fatal (233), Not resolved (3936), Resolved with sequelae (368), Resolved/resolving (5288), Unknown data (3931). <u>*Pericarditis*</u> • No. of cases: 10725. • Relevant PTs: Pericarditis (10644), Pleuropericarditis (81), Pericarditis constrictive (20), Autoimmune pericarditis, Pericarditis adhesive (1 each). • Frequently reported additional PTs (≥2%): Chest pain (4487), Dyspnoea (2738), Myocarditis (1982), Fatigue (1858), Palpitations (1732), Pyrexia (1223), Tachycardia (1166), Chest discomfort (1140), Pericardial effusion (838), Headache (824), Immunisation (683), Off label use (633), Dizziness (612), Interchange of vaccine products (553), Malaise (480), Myalgia (422), Pain (420), Nausea (419), Asthenia (401), Arthralgia, Pain in extremity (394 each), Inappropriate schedule of product administration (364), Paraesthesia (306), Syncope (284), Cough (261), Chills (257), Heart rate increased (252), Angina pectoris, Electrocardiogram abnormal (244 each), Lethargy (219), Back pain (207), Arrhythmia, Hyperhidrosis (194 each), Pleural effusion (193), Influenza like illness, Lymphadenopathy (192 each), Dyspnoea exertional (190),

Table 89. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Vomiting (185), C-reactive protein increased (184), Vaccination site pain (181), Troponin increased (170), Diarrhoea (168), Hypertension (167), Hypoaesthesia (166), Myopericarditis (164). • Subjects' gender: female (5047), male (5439) and unknown (239). • Subjects' age in years (n = 9908), range: 2 – 98 years, mean: 39.8 years, median: 37.0 years. • Age group: Paediatric (717), Adults (8239), Elderly (1007), and Unknown (762). • Case source: Spontaneous (10,576), Literature (96), Clinical study (44), Other solicited sources (9). • Event seriousness: serious (10,747). • Event outcome[56]: Fatal (38), Not resolved (3660), Resolved with sequelae (181), Resolved/resolving (3976), Unknown data (2903). Based on the accumulating data from post-authorisation use of the vaccine, including the consistent findings from passive and active surveillance databases of increased occurrences of myocarditis and pericarditis following vaccination with BNT162b2, myocarditis and pericarditis have been added as ADRs in section 4.8 Undesirable effects, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022.

16.4.1.2. Cumulative Characterisation of Important Potential Risks

Table 90. Cumulative Characterisation of Important Potential Risks

Risks	Clinical Study Data	Post-Marketing Data
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated	There were no cases reporting COVID-19 infection associated with one of the PTs utilized to identify potential severe or atypical cases of COVID-19.	• No. of cases: 3883. • Relevant PTs most frequently reported (>2%): Drug ineffective (2203), Vaccination failure (1680), COVID-19 pneumonia (1601), Dyspnoea (1172),

Table 90. Cumulative Characterisation of Important Potential Risks

Risks	Clinical Study Data	Post-Marketing Data
Enhanced Respiratory Disease (VAERD)	Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and VAED/VAERD.	Diarrhoea (552), Vomiting (279), Respiratory failure (206), Myocarditis (185), Abdominal pain (172), Pulmonary embolism (140), Hypoxia (129), Acute respiratory distress syndrome (118), Cardiac failure (104), Tachypnoea (101), Acute kidney injury (100), Arrhythmia (81). • Frequently reported additional PTs (>100): COVID-19 (2371), Pyrexia (746), Cough (602), Fatigue (436), Headache (423), Asthenia (352), Suspected COVID-19 (336), Nausea (213), Malaise (203), Chest pain (197), Myalgia (185), Pain (174), Dizziness (170), Oxygen saturation decreased (167), Chills (146), Decreased appetite (139), Oropharyngeal pain (137), Arthralgia (132), Anosmia (123), Pneumonia (121), Off label use (120), Ageusia (111), Palpitations (105), Pain in extremity (104), Tachycardia (103) and Immunisation (102). • Subjects' gender: female (1956), male (1835) and unknown (92). • Subjects' age in years (n = 3712), range: 2 – 104 years, mean: 65.3 years, median: 70.0 years. • Age group: Paediatric (70), Adults (1456), Elderly (2193) and Unknown (164). • Case source: Spontaneous (3716), Literature (48), Clinical study (60), Solicited (59) • Relevant event seriousness: serious (8154), non-serious (1156) • Relevant event outcome: Fatal (1507), Not resolved (1331), Resolved with sequelae (108), Resolved/resolving (3173), Unknown data (3202). Based on the cumulative PM data individual review of cases, no new significant safety information was identified for BNT162b2 and the potential risk of VAED/VAERD.

16.4.2. Description of Missing Information

Table 91 describes missing information associated with the use of BNT162b2.

Table 91. Description of Missing Information

Topic	Description
Use in pregnancy and while breast feeding	The safety profile of the vaccine in pregnant and/or breastfeeding women was not studied in the pivotal clinical trial and the maternal clinical trial was terminated early due to participant recruitment difficulties. Many pregnant women have chosen to be vaccinated despite the lack of clinical trial safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.
Use in immunocompromised patients	The vaccine is being studied in ongoing clinical trials of individuals with immunocompromised conditions. Cases involving use of BNT162b2 in immunocompromised patients received during the reporting interval are summarised in Section 16.3.5.4 *Use in Immunocompromised Patients.*
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)[97]	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 comorbidities that may compromise immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population.

[97] Search criteria: Patients with Medical history of PTs included in HLGTs (Primary Path) Bronchial disorders (excl neoplasms), Heart failures, Mental impairment disorders, Movement disorders (incl parkinsonism), Nephropathies, Pulmonary vascular disorders, Renal disorders (excl nephropathies); HLTs (Primary Path) Autonomic nervous system disorders, Diabetes mellitus (incl subtypes), Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis, Motor neurone diseases, Muscle tone abnormal, Neuromuscular disorders NEC, Pulmonary hypertensions, Respiratory failures (excl. neonatal); patients with Medical history of ongoing Tuberculosis.

Table 91. Description of Missing Information

Topic	Description	
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders *(Cont'd)*	**Clinical Study Data**	**Post-Marketing Data**
	• No. of cases: 80 Of which 61 Original, 19 Blinded. • Subjects' gender: female (30), male (50). • Subjects' age in years (n = 80), range: 1 – 86 years, mean: 52.2 years, median: 64.0 years. • Relevant PTs most frequently reported (≥2%): Respiratory syncytial virus (4), Cardiac arrest, Chronic obstructive pulmonary disease, Myocardial infarction (3 each), Asthma, Coronary artery disease, Haemorrhage intracranial, Pneumonia, Respiratory tract infection, and Thermal burn (2 each). • Relevant event seriousness: serious (91) • Relevant event outcome: Fatal (11), Not resolved (16), Resolved with sequelae (5), Resolved/resolving (59).	• No. of cases: 11,803 Of which 11033 Original, 892 Bivalent. • Subjects' gender: female (7980), male (3672), and unknown (151). • Subjects' age in years (n = 11,333), range: 2 - 102 years, mean: 53.9 years, median: 54.0 years. • Relevant PTs most frequently reported (≥2%): Fatigue (1936), Headache (1757), COVID-19 (1668), Pyrexia (1540), Drug ineffective (1152), Inappropriate schedule of product administration (1149), Myalgia (1094), Malaise (1003), Arthralgia (960), Vaccination site pain (959), Pain (856), Dyspnoea (820), Dizziness (816), Nausea (800), Chills (796), Pain in extremity (777), Off label use (760), Interchange of vaccine products (715), Vaccination failure (679), Asthenia (535), Lymphadenopathy (403), Immunisation (389), Paraesthesia (354), Diarrhoea (332), Cough (321), Vomiting (313), Vaccination site swelling (310), Rash (290), Hypoaesthesia (281), Pruritus (276), Chest pain (275), Palpitations (259), and Heavy menstrual bleeding (242). • Relevant event seriousness: serious (18,396), non-serious (29,312). • Relevant event outcome: fatal (1118), resolved/resolving (24,735), resolved with sequelae (1314), not resolved (12,898), unknown (17,803).
Use in patients with autoimmune or inflammatory disorders	There is limited clinical trial information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. Cases involving use of BNT162b2 in patients with autoimmune or inflammatory disorders received during the reporting interval are summarised in Section 16.3.5.5 *Use in Patients with Autoimmune or Inflammatory Disorders*.	
Interaction with other vaccines *Search criteria: HLT Interactions*	During the reporting interval, 3 PM cases (of which 1 serious) were originated from the same literature article[98] about the interaction with Hepatitis B vaccine. The co-reported AEs included Headache (2), Arthralgia, Chills, Fatigue, Pyrexia, Vaccination site pain, Vaccination site swelling (1 each).	

[98] Alrashdan MS, El-Kishawi M, Al Kawas S. The Co-Administration of COVID-19 and Hepatitis B Vaccines, Should Safety Be a Concern? Infect Chemother. 2022;54(3):542-4.

Table 91. Description of Missing Information

Topic	Description
Long term safety data	At the time of the initial submission, 2-month post dose 2 safety data were available for approximately half of the patients who have received BNT162b2 mRNA vaccine in Study C4591001. The pivotal clinical study is ongoing and ongoing non-interventional safety studies will collect longer term post-marketing safety data.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 6 months of age and older.[99]

17.1.1. Clinical Study Data in Individuals ≥12 Years of Age

Study C4591001 is a multicenter, placebo controlled- efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[100] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[100] 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,[101] were included as were participants with known stable infection with HIV, HCV, or HBV.[100]

Efficacy analyses were performed with confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through 13 March 2021, representing up to 6 months of follow-up after dose 2 for participants in the efficacy population, see table below.

[99] As per information reported in the CDS version 18.0 dated 05 December 2022, in effect at the end of the reporting period.

[100] Ref #12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2.

[101] Ref #21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

Table 92. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[102]			
Subgroup	**TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[103]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

[102] Ref #53 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[103] Ref #54 of the CDS. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 92. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after dose 2 (with a cut-off date of 13 March 2021) are presented in Table 93[104] and Table 94.

Table 93. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after dose 2 [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk [g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)

[104] Ref #55 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 93. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese [h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 94. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after dose 2 [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk [g]			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese [h]			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 95) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the TRADENAME and placebo groups.

Table 95. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition[105,106]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After dose 1 [d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after dose 2 [f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition[107,108]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After dose 1 [d]	1 8.427[e] (22,473)	45 8.269[e] (22,394)	97.8 (87.2, 99.9)
7 days after dose 2 [f]	0 6.514[g] (21,620)	32 6.391[g] (21,693)	100 (88.0, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

[105] Ref #57 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[106] Ref #58 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population.

[107] Ref #59 of the CDS. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population.

[108] Ref #60 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 95. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[109]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[109]

- Hospitalisation;
- Admission to the ICU;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.[110]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.[110]
g. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age

Vaccine efficacy in adolescents 12 to 15 years of age is presented in Table 96.

[109] Ref #61 of the CDS. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy.

[110] Ref #62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 96. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 to 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*,[111]			
	TRADENAME N[a]=1005 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=978 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection[112]			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1110 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In C4591001 an analysis of SARS-CoV-2 neutralising titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses comparing adolescents 12 to 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 through 25 years of age (n = 170), based on results for

[111] Ref #46 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[112] Ref #47 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

SARS-CoV-2 neutralising titers at 1 month after dose 2. The GMT ratio of the adolescents 12 to 15 years of age group to the participants 16 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the GMR >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 through 25 years of age.[113]

Efficacy and immunogenicity in participants ≥ 16 years of age after booster dose

Neutralizing SARS-CoV-2 antibody titers and S1-binding IgG antibodies were evaluated at 6 months after dose 2 for Study C4591001. The data noted the persistence of a robust immune response elicited by BNT162b2 30 µg vaccination in adults for up to 6 months; and also suggest, based on the modest decline in GMTs and GMCs from 1 month to 6 months after receiving dose 2, that vaccinees may benefit from a booster dose at 6 months or thereafter. Study C4591031 was designed to assess a booster dose in this participant population.

Study C4591031 Substudy A is a Phase 3 randomised, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 in Study C4591001, at least 6 months prior to randomisation, were enrolled and participants were randomised at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomisation was stratified by age, such that approximately 60% of participants enrolled were to be ≥16 to 55 years of age and approximately 40% of participants >55 years of age.

Considering the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards and those randomised to receive a booster dose of placebo were offered a dose of BNT162b2 30 µg to receive a booster of active vaccine.

In the 6-month interim report for Substudy A, efficacy analysis of a single booster dose of BNT162b2 30 µg from 7 days after booster dose during the blinded placebo-controlled follow-up period was evaluated; also, incidence of COVID-19 cases through the entire study follow-up period in participants who received BNT162b2 initially or subsequently after unblinding was analysed.

Demographics of participants in the evaluable efficacy populations without evidence of infection prior to 7 days after booster vaccination were similar in the BNT162b2 and placebo groups. This analysis population had similar demographics compared to the overall safety population, as did the evaluable efficacy population participants with or without evidence of infection prior to 7 days after booster vaccination and the all-available efficacy population.

[113] Ref #48 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population.

For participants without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, the median duration of blinded follow-up after booster vaccination was 2.8 months as of the data cutoff date and was similar to the safety population. Of these participants originally randomized to the BNT162b2 group, the total exposure from booster vaccination to the data cutoff date was ≥6 months for most participants (99.0%).

Follow-up times after booster vaccination for participants with or without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population were similar to the evaluable efficacy population.

After unblinding, in the all-available efficacy population, there were 7 cases meeting severe criteria; all occurred after 20 December 2021, when the Omicron variant was the predominant strain, in participants who were baseline SARS-CoV-2 negative. In original BNT162b2 participants, there were 5 severe cases: 3 met the FDA definition, 1 met the CDC definition, and 1 met both definitions. In placebo participants who later received BNT162b2, there were 2 severe cases that met the FDA definition.

These results indicate that a booster dose of BNT162b2 30 µg given ≥6 months after the primary 2-dose series of BNT162b2 30 µg vaccination provided protection against COVID-19, and protection was strongest during the Delta variant wave, and sustained up to 4 months after vaccination; longer term protection against Delta variant relative to placebo cannot be estimated from this study due to unblinding and crossover of placebo control participants. For the same reason, RVE of boosted to non-boosted participants during the Omicron variant wave cannot be estimated in this study. Although the IR during Omicron wave is much higher than that of Delta wave, the IR in those participants that were 'later' vaccinated is lower than those participants that were 'early' vaccinated, which implies better protection against Omicron with recent vaccination.

17.1.2. Clinical Study Data in Children 5 Through <12 Years of Age

Efficacy and immunogenicity after 2 doses

Study C4591007 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomized, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

A descriptive efficacy analysis of Study C4591007 has been performed in 1968 children 5 through <12 years of age without evidence of infection prior to 7 days after dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of 08 October 2021.[114]

[114] Ref #82 of the CDS. Clinical Information Amendment – COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021.

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 97. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[114]

Table 97. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population

First COVID-19 Occurrence from 7 days after dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 Infection*			
	TRADENAME± 10 mcg/dose Na=1305 Cases n1b Surveillance Timec (n2d)	**Placebo Na=663 Cases n1b Surveillance Timec (n2d)**	**Vaccine Efficacy % (95% CI)**
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

In Study C4591007, an analysis of SARS-CoV-2 50% neutralising titers (NT50) 1 month after dose 2 in a randomly selected subset of participants, demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study C4591007 to participants 16 through 25 years of age in the Phase 2/3 part of Study C4591007 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 98.[115]

Table 98. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (C4591007) to Participants 16 Through 25 Years of Age (C4591001) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n[a]=264	30 mcg/Dose 16 Through 25 Years n[a]=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

b. Protocol-specified timing for blood sample collection.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).

e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 99.[115]

[115] Ref #73 of the CDS. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults.

Table 99. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to C4591007 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		TRADENAME			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after dose 2. These values are the denominators for the percentage calculations.

b. Protocol-specified timing for blood sample collection.

c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.

d. Exact 2-sided CI based on the Clopper and Pearson method.

e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).

f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.

h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Immunogenicity after booster (3rd) dose

Administration of a booster (third) dose of BNT162b2 10-µg to children 5 through <12 years of age in Study C4591007 elicited robust neutralizing titers against the wild-type variant of SARS-CoV-2 in an evaluable immunogenicity population of 67 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

- Observed GMTs at 1-month post-dose 3 were substantially increased (2720.9) compared with those at 1-month post-dose 2 (1253.9) and prior to booster (dose 3) vaccination (271.0).

- The GMR for participants with available titers at 1-month post-dose 3 compared to those with available titers at 1-month post-dose 2 was 2.17 (2-sided 95% CI: 1.76, 2.68).
- The observed proportion of participants who achieved seroresponse (ie, ≥4-fold rise in SARS-CoV-2 neutralizing titers from pre-dose 1, or ≥4 × LLOQ for a pre-dose 1 measurement <LLOQ) was high (100.0%) at 1-month post-dose 2, waned by pre-dose 3 (77.6%), and was increased at 1 month after dose 3 (98.5%). The difference in seroresponse rates at 1-month post-dose 3 compared with at 1-month post-dose 2 was -1.5% (2-sided 95% CI: -8.0%, 2.4%).

Additionally, based on the FFRNT (a supportive assay), a third (booster) dose of BNT162b2 10-µg elicited neutralizing titers against a recombinant SARS-CoV-2 Omicron variant and recombinant wild-type (reference) strain of SARS-CoV-2 in an evaluable immunogenicity population of 29 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

- The observed 1-month post-dose 2, neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively which increased at 1-month post-dose 3 to 614.4 and 1702.8 and, respectively, representing an increase from post-two-dose primary series to post-booster vaccination of 22-fold for Omicron and 5-fold for the reference strain.
- The GMR of neutralizing titers against Omicron versus the reference strain at 1-month post-dose 2 was 0.09 (2-sided 95% CI: 0.07, 0.10) and increased to 0.36 (2-sided 95% CI: 0.28, 0.47) at 1-month post-dose 3, representing a fold-rise from 1-month post-dose 2 to 1-month post-dose 3 that was 4-times higher for the Omicron titers than for the reference strain titers obtained in the FFRNT assay.

The immune response associated with a booster (third) dose of BNT162b2 10 µg administered approximately 6 months after the second dose to children 5 to <12 years of age is expected to confer protection against COVID-19 including disease caused by Omicron. This is in the context of previously observed immunogenicity and efficacy results across pediatric, adolescent, and adult populations in the clinical development program and available real-world data, which have collectively shown that a booster (third) dose of BNT162b2 substantially increases the magnitude and breadth of neutralization and provides protection against symptomatic SARS-CoV-2 infection caused by variants including Omicron.

17.1.3. Clinical Study Data in Children 6 Months Through <5 Years of Age

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pediatric study in healthy children from 6 months to <12 years of age. The pediatric vaccination series for children 6 months to <5 years of age was initially planned as a two-dose series given 3 weeks apart. The Phase 2/3 primary immunogenicity objective in children from 6 months to <5 years of age was immunobridging the immune responses against SARS-CoV-2 wild-type strain from children 2 to <5 years and 6 months to <2 years of age in Study C4591007 compared to young adults 16 to 25 years of age in the Phase 3 efficacy Study C4591001. Immunobridging data after dose 2 met success criteria for the 6 months to <2 years group and

did not meet GMR success criteria (but met seroresponse criteria) for the 2 to <5 years of group, compared to young adults 16 to 25 years of age

Immunogenicity after 3 doses

Given emerging real-world data in the Omicron wave that two-dose protection against symptomatic infection was only modest, a third dose was evaluated for children <5 years of age. Immunobridging data after dose 3 met success criteria for the 6 months to <5 years age group, compared to young adults 16 to 25 years of age.

Immunobridging (i.e., effectiveness) data were analyzed from approximately 4500 children across the 6 months to <5 years of age groups who were randomized 2:1 to receive three doses of BNT162b2 3 µg or placebo with median follow-up of approximately 2 months after dose 3 (inclusive of blinded and open-label periods).

Immunobridging Results

Immunobridging success criteria were met for both age groups, comparing the GMR and seroresponse for each C4591007 group who received three doses of BNT162b2 3-µg to adults 16 to 25 years of age in C4591001 who received two doses of BNT162b2 30-µg. Note, the CI lower bounds of the GMRs were ≥1, indicating statistical significance.

- For children 2 to <5 years of age, the GMR for titers at 1-month post-dose 3 of BNT162b2 3 µg compared to young adults 16 to 25 years of age at 1-month post-dose 2 of BNT162b2 30 µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.30 (2-sided 95% CI: 1.13, 1.50) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -1.5%, 4.2%).
- For children 6 months to <2 years of age, the GMR for titers at 1-month post-dose 3 of BNT162b2 3 µg compared to young adults 16 to 25 years of age at 1-month post-dose 2 of BNT162b2 30 µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.19 (2-sided 95% CI: 1.00, 1.42) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -3.4%, 4.2%).

Wild-type Strain SARS-CoV-2 Neutralization

Three doses of BNT162b2 elicited robust immune responses to wild-type SARS-CoV-2 in children who received 3-µg doses and in young adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.7) was increased prior to dose 3 (401.1) and then substantially increased at 1-month post-dose 3 (1535.2). The GMFR at 1-month post-dose 3 was 73.3 and the seroresponse rate was 100%.
- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.8) was increased prior to dose 3 (317.0) and was substantially increased at 1-month post-dose 3 (1406.5). The GMFR at 1-month post-dose 3 was 68.4 and the seroresponse rate was 100%.

Patterns observed for children in wild-type SARS-CoV-2 neutralization at 1-month post-dose 3 were generally comparable to young adults 16 to 25 years of age at 1-month post-dose 2.

Omicron Variant SARS-CoV-2 Neutralization

Three doses of BNT162b2 increased neutralizing titers to Omicron and Delta variants of SARS-CoV-2 in children who received 3-µg doses and in adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, FFRNT assay results showed neutralizing titers against a recombinant Omicron variant increased from before dose 3 (14.0) to 1-month post-dose 3 (82.5). This represents a 5.9-fold increase in Omicron neutralizing titers from before dose 3 to 1-month post-dose 3.
- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, FFRNT assay results showed neutralizing titers against a recombinant Omicron variant increased from before dose 3 (16.3) to 1-month post-dose 3 (127.5). This represents a 7.8-fold increase in Omicron neutralizing titers from before dose 3 to 1-month post-dose 3.
- Substantial increases in titers against a recombinant Delta variant and a wild-type reference strain were also observed after the second and third doses in both paediatric age groups.

Efficacy

Descriptive efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <2 years of age were initially based on symptomatic COVID-19 cases accrued from dose 1 to a data cutoff date of 29 April 2022 due to the urgency of ensure an available vaccine for this age group. VE was estimated across the total population of participants 6 months to <5 years of age randomized 2:1 to receive BNT162b2 3-µg vs placebo, which included 992 BNT162b2 recipients and 464 placebo recipients who received three doses of study intervention. Based on COVID-19 cases confirmed from at least 7 days post-dose 3 to the cutoff date, observed VE was 80.3% (2-sided 95% CI: 13.9%, 96.7%). Based on cases from dose 1 onwards, observed VE was 25.5% (2-sided 95% CI: 7.7%, 39.6%). The per protocol efficacy analysis has been performed subsequently; the results can be found in Section 17.2.3.

17.1.4. Real World Data for Omicron Variant

Omicron-specific VE for the time period 01 December 2021 to 26 August 2022

Given that the US Food and Drug Administration initially authorized a third dose of the vaccine for individuals aged 65 years and older and individuals at high risk of severe COVID-19 on 22 September 2021, early estimates of real-world VE against Omicron are likely enriched for high-risk populations, including patients who are immunocompromised. Indeed, analysis of data from the early portion of the first Omicron wave showed early signs of waning effectiveness of the BNT162b2 mRNA COVID-19 vaccine against Omicron

variant-related hospital and emergency department admission at 3 months or longer after receipt of a third dose in US adults aged 18 years and older.[s]

Updated findings using an extended analysis period primarily show two things. First, waning effectiveness against Omicron-related hospitalisation observed at ≥3 months after a third dose of vaccine during the initial study period (data cutoff of 06 February 2022) was less pronounced after excluding individuals who were immunocompromised; original VE ≥3 months after a third dose of 55% (95% CI: 28−71) against hospitalisation vs 74% (95% CI: 52−86) after excluding individuals who were immune-compromised. Second, extending the analysis period through 18 March 2022, which captures the entire Omicron wave and results in the inclusion of more individuals who became eligible for booster doses on 29 November 2021, diminished the evidence of waning vaccine protection after a third dose. Specifically, after extending the analysis period, waning of VE against Omicron-related outcomes was no longer apparent, particularly in the immunocompetent population.[t]

Thus, patients who were immunocompromised likely drove much of the observed waning seen in our initial report. Another explanation may be differences in severity of illness among patients admitted to the hospital or emergency department over time, which could result from increasing levels of immunity due to natural infection and/or increased at-home COVID-19 testing during the updated study period.

A more recent study by the same group evaluated the effectiveness and durability of two, three, and four doses of BNT162b2 against hospital admissions, emergency department admissions, urgent care visits, and outpatient visits (including virtual appointments) due to SARS-CoV-2 Omicron subvariants BA.4 or BA.5 among adults aged ≥18 years. They found that two doses of BNT162b2 offered little protection against all BA.4/5 outcomes measured, including hospital admission. A booster (third or fourth dose) did provide protection against BA.4/5, but this protection probably wanes after 3 months against milder outcomes like outpatient, urgent care, or emergency department encounters and after roughly 6 months against BA.4/5- related hospitalisation.[u]

A publication from Israel[v] reports a low neutralisation efficiency against BA.4 and BA.5 even in sera obtained from BA.1-recovered from health care workers who previously received three or four vaccine doses. These findings suggest that an Omicron-specific vaccination might be indicated.

Hansen et al. evaluated the risk of reinfection, vaccine protection, and severity of infection with the BA.5 Omicron subvariant and they found a high protection against BA.5 from prior Omicron infection in triple-vaccinated individuals, and similar vaccine effectiveness for BA.5 infection as currently for BA.2. BA.5 infection was associated with an increased risk of hospitalisation which needs confirmation and continued surveillance as hospitalisations were low and stable during the study period.[w] Adapted vaccines can help slow virus circulation and emergence of variants of concern.

Additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high levels of protection against subsequent waves of SARS-CoV-2 caused by the Omicron variant or future variants with similar escape potential.[s]

17.2. Newly Identified Information on Efficacy and Effectiveness

17.2.1. Clinical Study Data for Omicron-Adapted Vaccines in Individuals ≥18 Years of Age

Substudy E of C4591031 is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 Omi (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 Omi at 60 µg (30 µg each), given as a single dose. Participants in two age groups; 18 to 55 years and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization. Participants >55 years of age were randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 Omi at 30 µg, BNT162b2 Omi at 60 µg, a combination of BNT162b2 and BNT162b2 Omi at 30 µg (15 µg each), or a combination of BNT162b2 and BNT162b2 Omi at 60 µg (30 µg each) as a fourth dose. Participants 18 to 55 years of age were randomized to receive bivalent BNT162b2 and BNT162b2 Omi at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 Omi at 30 µg (15 µg each), or BNT162b2 Omi at 60 µg as a fourth dose.

Individuals >55 Years of Age (Study C4591031 Substudy E)

For the primary and secondary immunogenicity analyses for the Omicron variant, BNT162b2 Omi 30 µg and 60 µg and the BNT162b2 +BNT162b2 Omi 30 µg and 60 µg groups met the prespecified criteria for superiority with respect to GMR and noninferiority with respect to seroresponse rate when compared to BNT162b2 30 µg group, when administered to BNT162b2-experienced participants as fourth dose.

- 'Simple' superiority of BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg were met, as the lower bound of the 2-sided 95% CI for GMR was >1 for each of the three comparisons.
- Noninferiority based on seroresponse for BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg were met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5% for each of the three comparisons. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 Omi 30 µg also had lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse (>-5%) consistent with noninferiority criterion.
- "Super" superiority of BNT162b2 Omi 60 µg to BNT162b2 30 µg for the Omicron variant was achieved based on the prespecified criterion, as the lower bound of the 2-sided 95% CI for GMR was >1.5. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 Omi 30 µg also had GMR and lower bound of 95% CI (>1.5) consistent with the super superiority criterion.
- Noninferiority for reference strain based on the GMR was met in both bivalent vaccine groups (BNT162b2 + BNT162b2 Omi 30 µg and 60 µg) as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion).

- Overall, for all BNT162b2, BNT162b2 Omi and BNT162b2 Omi + BNT162b2 recipients, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroresponse rates, for the Omicron variant except for baseline SARS-CoV-2 status. GMTs at 1 month-post-dose were substantially higher while seroresponse rates were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.

Individuals 18 through 55 Years of Age (Study C4591031 Substudy E)

For BNT162b2-experienced participants 18 through 55 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination, the GMTs for Omicron BA.1 neutralizing titers across all vaccine groups evaluated were higher when compared to participants >55 years of age:

- The ratio of GMTs for participants 18 through 55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 μg, bivalent BNT162b2 + BNT162b2 Omi 60 μg and monovalent BNT162b2 Omi 60 μg groups, respectively, to participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 μg was 1.47 (2-sided 95% CI: 1.11, 1.94), 1.68 (2-sided 95% CI: 1.26, 2.25), and 3.34 (2-sided 95% CI: 2.50, 4.46), respectively. GMRs for the reference strain were also >1 for all vaccine groups.
- Seroresponse rates to the Omicron BA.1 variant for participants 18 through 55 years of age were 87.6%, 88.5%, and 95.6% in the bivalent BNT162b2 + BNT162b2 Omi 30 μg, bivalent BNT162b2 + BNT162b2 Omi 60 μg and monovalent BNT162b2 Omi 60 μg groups, respectively. The difference in percentages of participants 18 through 55 years of age with seroresponse to Omicron BA.1 variant in the bivalent BNT162b2 + BNT162b2 Omi 30 μg, bivalent BNT162b2 + BNT162b2 Omi 60 μg and monovalent BNT162b2 Omi 60 μg groups, respectively compared with participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 μg group was 20.7% (2-sided 95% CI: 9.8%, 31.3%), 21.5% (2-sided 95% CI: 10.7%, 32.0%) and 28.6% (2-sided 95% CI: 18.9%, 38.4%), respectively. Seroresponse rates for reference strain were similarly high for all vaccine groups.
- GMTs were substantially elevated over levels observed before study vaccination for Omicron BA.1 in the bivalent BNT162b2 + BNT162b2 Omi 30 μg group (1245.3 and 80.9, respectively), while GMTs in participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 μg group at 1-month post-dose compared with prevaccination were 846.9 and 107.1, respectively. The monovalent BNT162b2 Omi 60 μg showed the highest response against Omicron BA.1 (increased from 114.9 to 2828.3) followed by the bivalent BNT162b2 + BNT162b2 Omi 60 μg group (increased from 83.2 to 1424.7). GMTs were also substantially elevated over levels observed before study vaccination for the reference strain, across all vaccine groups.
- The GMFRs from study vaccination to 1 month post dose for the Omicron BA.1 variant were higher for the bivalent BNT162b2 +BNT162b2 Omi 30 μg (15.4 [2-sided 95% CI: 12.4, 19.2]), bivalent BNT162b2 +BNT162b2 Omi 60 μg (17.1 [2-sided 95% CI: 13.7, 21.4]) and monovalent BNT162b2 Omi 60 μg (24.6 [2-sided 95% CI: 19.3, 31.4]) compared to participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi

30 µg group (7.9 [2-sided 95% CI: 6.2, 10.2]). In participants 18 to 55 years of age, monovalent BNT162b2 Omi 60 µg showed the highest Omicron BA.1 GMFR compared to bivalent vaccines at either dose level. GMFRs from study vaccination to 1 month post vaccination against the reference strain were high for participants 18 through 55 years of age across all vaccine groups than participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group.

- The proportion of participants 18 through 55 years of age who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1-month post-dose for the Omicron BA.1 variant was 87.6%, 88.5% and 95.6% in the bivalent BNT162b2 + BNT162b2 Omi 30 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and monovalent BNT162b2 Omi 60 µg groups, respectively. Proportion of participants achieving seroresponse for reference strain were similarly high for all vaccine groups.

Analysis of immunogenicity data from C4591031 Substudy E demonstrated a robust vaccine-elicited immune response to both monovalent and bivalent Omicron BA.1-modified vaccines when administered as a booster (dose 4) to BNT162b2-experienced participants 18 through 55 years of age. In vaccine-experienced individuals, a booster dose elicited robust neutralization titers to Omicron BA.1 and the reference strain.

Individuals ≥18 Years of Age (Study C4591044)

Analysis of immunogenicity data at 1 month post study vaccination from Study C4591044 Cohort 2 for BNT162b2-experienced participants 18 to 55 years and >55 years of age who received a booster (dose 4) of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg demonstrated a robust vaccine-elicited immune response.

These data show that a booster (dose 4) dose of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg elicited higher Omicron BA.4/BA.5 specific neutralization titers at 1 month after study vaccination in both age groups of 18 to 55 and >55 years compared with comparator groups of BNT162b2-experienced participants 18 to 55 years and >55 years of age from C4591031 Substudy E who received a booster (dose 4) dose of BNT162b2 Bivalent (WT/Omi BA.1) 30 µg vaccine.

Overall, immune responses against Omicron BA.1 and reference strain at 1 month after vaccination with BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg were comparable to responses observed in participants who received BNT162b2 Bivalent (WT/Omi BA.1) 30 µg vaccine. Variability in the immune responses were observed for participants in the two age groups who received BNT162b2 Bivalent (WT/Omi BA.4/BA.5) vaccine and may reflect small number of participants in each group. Additionally, longer dosing interval (time from last dose of BNT162b2 received prior to study vaccination) for participants who received BNT162b2 Bivalent (WT/Omi BA.4/BA.5) compared to participants who received BNT162b2 Bivalent (WT/Omi BA.1) could also be a contributing factor for higher GMFR and seroresponse rate for Omicron BA.1 and reference strain neutralizing titers.

Increased neutralizing responses with the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) vaccine and the BNT162b2 Bivalent (WT/Omi BA.1) vaccine were observed regardless of

baseline SARS-CoV-2 infection status, with the greatest GMFRs observed in participants without prior infection and the highest titers observed in participants with prior infection.

In summary, these data indicate the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) vaccine is more immunogenic against circulating Omicron sublineages and suggest that vaccines containing contemporary versions of SARS-CoV-2 may provide increased protection against COVID-19.

17.2.2. Clinical Study Data in Children 5 Through <12 Years of Age

A formal efficacy analysis to assess the secondary vaccine efficacy hypotheses was also performed, as the required number of SARS-CoV-2 cases for hypotheses testing has been accrued. In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days after dose 2, the observed VE was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days after dose 2 to before dose 3 through the blinded follow-up period. This VE is consistent with the primary series results of previous studies of BNT162b2 in adolescent and adult populations. Importantly, while participants were randomized 2:1 to BNT162b2 or placebo, there were fewer (10 versus 42) first cases confirmed in the BNT162b2 group than in the placebo group. Notably, most of the COVID-19 cases in this VE analysis accrued from Summer to Autumn 2021, during a time that the highly transmissible Delta variant was circulating in the US and globally. This was confirmed by next-generation sequencing which showed that the majority of cases in the BNT162b2 and placebo groups were of the Delta variant lineage. Among the small number of participants who were unblinded in late December 2021 or later, few Omicron variant cases were identified in the BNT162b2 and placebo groups. This is notable because this VE analysis captures only the earliest stages of the first global Omicron variant wave.

Among confirmed COVID-19 cases, it was more common (30.9% versus 20.0%) for participants in the placebo group to report ≥4 signs and symptoms of COVID-19 than those in the BNT162b2 group. New or increased cough, fever, and sore throat were commonly reported (greater than 46.2% overall) among cases in both the BNT162b2 and placebo groups. In contrast, new or increased muscle pain was much more common (28.6% versus 0%) in the placebo group compared to the BNT162b2 group.

Subgroup analyses identified no clinically meaningful differences in efficacy parameters; however, some subgroups had small sample sizes in the study population, so caution is warranted in extrapolating these efficacy findings to all demographic subgroups.

Taken together, these results indicate that a 2-dose series of BNT162b2 10 μg in children 5 to 12 years of age provided protection against COVID-19 during the peak of the global Delta variant wave.

17.2.3. Clinical Study Data in Children 6 Months Through <5 Years of Age

Protocol-specified efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <5 years of age were based on symptomatic COVID-19 cases accrued from dose 1 to a data cutoff date of 17 June 2022, with a median follow-up of 2.2 months post-dose 3 of the three-dose series. These analyses were based on all cases confirmed since dose 1 to the

data cutoff date, and cases confirmed from at least 7 days after dose 3 to the data cutoff date among participants without or with or without evidence of prior SARS-CoV-2 infection. These analyses were triggered by the protocol objective to evaluate VE after accrual of at least 21 confirmed cases across the combined age groups of 2 to <5 years and 6 months to <2 years of age who both previously met immunobridging success criteria.

Observed Vaccine Efficacy in Population of Children 6 Months to <5 Years

The per protocol efficacy analysis was based on cases confirmed at least 7 days post-dose 3 to the data cutoff date of 17 June 2022, observed VE in the dose 3 evaluable population was ≥72.5%, irrespective of population and/or evidence of prior SARS-CoV-2 infection. Post-dose 3 case sequence analysis identified all cases with determinant sequencing results as Omicron sublineages, with observed VE of approximately 71% to 83% against the most frequently identified sublineages (BA.2.12.1 and BA.2). Few cases were identified as BA.4 or BA.5, precluding reliable estimation or meaningful interpretation of VE against these sublineages whether considered separately or combined. Excluding cases involving coinfection with other respiratory pathogens did not meaningfully impact observed VE. This notably corresponds to a period of Omicron variant predominance, during which substantial infection surges have continued in the US and globally. This was confirmed by sequencing data and analyses showing high VE against Omicron BA.2 and BA.2.12.1 sublineages, at a time when BA.4 and BA.5 were just beginning to emerge.

The overall observed VE for each age group was generally consistent with the combined population results.

The totality of available data indicates vaccinating children 6 months to <5 years of age with three doses of BNT162b2 3-µg affords a high level of protection against symptomatic COVID-19 accrued up to a data cutoff date of 17 June 2022 in the evaluable efficacy population without evidence of prior infection.

17.2.4. Real World Data for Omicron-Adapted Vaccines

As of 18 December 2022, the real-world effectiveness of bivalent BNT162b2 + BNT162b2 Omi 30 µg has not been reported. There are, however, several early estimates for vaccine effectiveness of US-authorized mRNA Omicron-adapted BA.4/5 bivalent vaccines composed of components from the SARS-CoV-2 ancestral and Omicron BA.4/BA.5 strains.

On 02 December 2022, the Centers for Disease Control and Prevention published an Early Release report describing vaccine effectiveness of the US-authorized bivalent mRNA booster formulations manufactured by Pfizer-BioNTech or Moderna. Brand-specific effectiveness estimates were not reported. Bivalent boosters provided significant added protection against symptomatic infection in immunocompetent adults aged 18 years and older who were previously vaccinated with 2, 3, or 4 monovalent mRNA vaccine doses. Absolute effectiveness (compared to unvaccinated individuals) ranged from 19% to 50% depending on age group and number of prior monovalent doses. Relative effectiveness (compared to monovalent vaccinated-only) ranged from 14% to 61% depending on age group, number of prior monovalent doses, and time since last monovalent dose. As expected due to waning

immunity of monovalent doses, the protection provided by bivalent booster vaccination increased with time since receipt of the most recent monovalent vaccine dose.[x]

On 16 December 2022, the Centers for Disease Control and Prevention published two Early Release reports describing bivalent mRNA vaccine effectiveness of the US-authorized bivalent mRNA booster formulations manufactured by Pfizer-BioNTech or Moderna. Brand-specific effectiveness estimates were not reported. Consistent with the first report issued on 02 December 2022, both studies (released on 16 December 2022) found that bivalent boosters provided significant added protection against COVID-19 in immunocompetent adults previously vaccinated with 2, 3, or 4 monovalent mRNA vaccine doses, and that the protection provided by bivalent booster vaccination increased with time since receipt of the most recent monovalent vaccine dose. Among adults aged ≥18 years who received medical care at VISION Network sites (seven health systems across nine US states), absolute effectiveness (compared to unvaccinated individuals) was 56% against urgent/emergency care and 57% against hospitalization. Relative effectiveness (compared to monovalent vaccinated-only) ranged from 31% to 53% for urgent/emergency care, and from 38% to 45% for hospitalization, depending on time since last monovalent dose.[y] Among adults aged ≥65 years who received medical care at IVY Network sites (22 hospitals across 18 US states), absolute effectiveness (compared to unvaccinated individuals) was 84% against hospitalization. Relative effectiveness (compared to monovalent vaccinated-only) ranged from 73% to 83% for hospitalization, depending on time since last monovalent dose.[z]

In addition, on 01 December 2022, the UK Health Security Agency reported relative vaccine effectiveness for an mRNA Omicron-adapted BA.1 bivalent vaccine. In the UK, bivalent boosters manufactured by either Pfizer-BioNTech or Moderna were offered to patients in clinical risk groups and those aged 50 years and older from September 2022 onwards. Among individuals who had received at least two COVID-19 vaccine doses before 05 September 2022 and with receipt of the last dose at least six months prior to SARS-CoV-2 testing sample collection date, the relative vaccine effectiveness (compared to at least six months of waned vaccine protection) against hospitalization was 57%. Brand-specific effectiveness estimates were not reported and limited information were provided on study design details and analysis approach.[aa]

17.3. Characterisation of Benefits

Data in Section 17.1 demonstrates a high degree of efficacy against symptomatic and severe COVID-19 in non-immunocompromised people over 12 years of age, during the period at least 7 days following the second dose of vaccine. Efficacy is evident separately and at a similar level in people 12-15 years of age, 16-64 years of age, 65 to 74 years of age and 75 years of age and older. Efficacy also appears largely independent of risk factors (having at least 1 of the CMI categories) and obesity. Efficacy is also high against severe disease after the first dose. The emergence of the Omicron variant, and its sublineages, impacted the level of efficacy seen against milder disease; however, protection remained strong against severe disease, particularly after a booster dose.

Section 17.2 describes the newly identified information on immunogenicity and effectiveness of a booster dose of Omicron-modified vaccines in adults and efficacy of 3 doses of the original BNT162b2 in children 6-months through <12 years of age.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

BNT162b2 indications are provided in Section 1 *Introduction.*

Incidence

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.[bb] 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.[cc]

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.[dd]

As of 08 January 2023, the overall number of SARS-CoV-2 cases was over 668 million worldwide.[ee]

Table 100 shows the cumulative number of cases and deaths as of 08 January 2023 for the US, UK, and EU-27 countries. In the EU and the UK, by 08 January 2023, the total number of confirmed cases had accumulated to over 205 million people, or 399,661 per 1,000,000 population. Across countries in the EU, the cumulative number of confirmed cases ranged from 168,821 to 632,184 cases per 1,000,000 population. Poland, Romania, and Bulgaria reported the lowest cumulative case rates while Slovenia, Austria, and France reported the highest.

In the US, the number of confirmed cases had reached over 103 million (307,898 per 1,000,000 population) by 08 January 2023.

Table 100. Incidence, Prevalence, and Mortality of COVID-19 as of 08 January 2023

	Total Cases	Total Cases/ 1,000,000 Pop	Active Cases	Active Cases/ 1,000,000	Total Deaths	Deaths / 1,000,000	Population
Global	668,597,550	85,775	22,145,576	2,765	6,713,525	861	8,010,019,740 [a]
EU-27	181,087,628	406,773	2,754,042	6,186	1,195,398	2,685	445,181,267
UK	24,210,131	353,443	134,257	1,960	201,028	2,935	68,497,907
EU-27 + UK	205,297,759	399,661	2,888,299	5,623	1,396,426	2,718	513,679,174
US	103,086,017	307,898	2,084,458	6,226	1,121,097	3,349	334,805,269
EU-27 Countries							
Austria	5,726,287	631,573	33,945	3,744	21,487	2,370	9,066,710
Belgium	4,682,234	401,279	34,192	2,930	33,395	2,862	11,668,278
Bulgaria	1,293,216	188,940	4,046	591	38,122	5,570	6,844,597
Croatia	1,265,494	311,753	1,733	427	17,682	4,356	4,059,286
Cyprus	634,709	518,813	9,147	7,477	1,262	1,032	1,223,387
Czech Republic	4,582,935	426,844	4,881	455	42,200	3,930	10,736,784
Denmark	3,169,858	543,254	7,601	1,303	7,889	1,352	5,834,950
Estonia	612,432	463,293	84,570	63,976	2,872	2,173	1,321,910
Finland	1,446,397	260,379	16,726	3,011	8,263	1,487	5,554,960
France	39,407,727	600,869	507,822	7,743	162,643	2,480	65,584,518
Germany	37,509,539	447,162	515,051	6,140	162,688	1,939	83,883,596
Greece	5,548,487	537,819	0		34,779	3,371	10,316,637
Hungary	2,188,737	227,845	13,070	1,361	48,546	5,054	9,606,259
Ireland	1,693,847	337,406	10,738	2,139	8,339	1,661	5,020,199
Italy	25,279,682	419,491	406,182	6,740	185,417	3,077	60,262,770
Latvia	974,574	527,128	1,979	1,070	6,177	3,341	1,848,837
Lithuania	1,290,919	484,996	7,389	2,776	9,502	3,570	2,661,708
Luxembourg	297,757	463,528	7,633	11,883	1,133	1,764	642,371
Malta	116,655	262,717	793	1,786	821	1,849	444,033
Netherlands	8,574,631	498,193	25,255	1,467	22,989	1,336	17,211,447
Poland	6,371,259	168,821	916,733	24,291	118,586	3,142	37,739,785
Portugal	5,557,941	548,090	8,407	829	25,805	2,545	10,140,570
Romania	3,312,085	174,033	7,037	370	67,408	3,542	19,031,335
Slovakia	1,859,692	340,591	1,001	183	20,845	3,818	5,460,193
Slovenia	1,313,700	632,184	13,496	6,495	7,025	3,381	2,078,034
Spain	13,693,478	293,102	73,259	1,568	117,413	2,513	46,719,142
Sweden	2,683,356	262,586	41,356	4,047	22,110	2,164	10,218,971

a. World population based on https://www.worldometers.info/world-population/#:~:text=7.9%20Billion%20(2022),Nations%20estimates%20elaborated%20by%20Worldometer. Accessed January 08, 2023

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested, as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported.[ff] Further, as at-home rapid testing kits have become more readily available[gg] and formal testing resources reach capacity due to the Omicron variant, the true estimate of cases is expected to be larger than formally reported counts. The numbers should therefore be interpreted with caution. While there is limited information on number of cases attributable

to specific variants, case counts for the majority of months in 2022 through current are likely to reflect the Omicron variant, which is currently the predominant strain in many countries, including in the US[hh] where Omicron BQ.1.1 was responsible for 34.4%, XBB.1.5 was responsible for 27.6%, BQ.1 was responsible for 21.4%, XBB was responsible for 4.9%, and BA.5 was responsible for 3.7% of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 07 January 2023.

The main existing treatment options:

Through 18 December 2022, other COVID-19 vaccines were authorised[ii] in the European Union including COVID-19 Vaccine (inactivated, adjuvant; EU/1/21/1624), Spikevax (EU/1/20/1507), JCOVDEN (EU/1/20/1525), Vaxzevria (EU/1/21/1529), Nuvaxovid (EU/1/21/1618), and VidPrevtyn Beta (EU/1/21/1580).

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 to 45% of patients, across age groups[jj,kk,ll,mm] 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.[mm] A meta-analysis has estimated that 46.7% of infections in children are asymptomatic.[mm] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults.[nn,oo] Confirming these observations in a 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 in 37%, and any nasopharyngeal symptom in 22%.[pp]

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.[qq,rr] 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.[rr] Data on rates of re-infection are limited but variants that are not neutralised by immune antisera, such as the Beta, Delta, and Omicron variants, may lead to increased risk of re-infection in the future.[rr,ss]

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 06 January 2023, there were 5,781,017 total hospital admissions for patients with confirmed COVID-19 in the US.[tt] For the week ending 18 December 2022, 7.6 per 100 000 population

(country range: 1.3–19.5) were hospitalised due to COVID-19 in 14 countries of the EU/EEA with available data.[uu]

The most common symptoms in patients are fever (42-80%), shortness of breath (35-71%), fatigue (33-62%), cough (77-84%), chills (63%), myalgias (63%), headache (59%), and diarrhea (33%)[vv,ww,xx,yy] COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[zz] Among unhospitalised 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.[xx] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[aaa,bbb,ww] 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.[ccc] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[ddd]

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.[qq] In 9 countries of the EU/EEA with available data, 0.5 per 100,000 population (country range 0.1-1.3) were in the ICU due to COVID-19 for the week ending 18 December 2022.[uu] 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.[kk] A study of 82 cases in three pediatric hospitals noted that older children and those with higher body mass index or multiple comorbidities were more likely to receive respiratory support.[eee]

Mortality

As of 04 January 2023, there were 1,091,184 deaths reported in the US for all age groups among 101,094,670 COVID-19 cases, equating to a mortality rate of 1.1% of cases.[fff] As of the week ending on 18 December 2022, the mortality rate was 10.4 per million population (country range: 1.1–28.6) in the EU.[uu] As of 08 January 2023, the UK has seen 214,723 deaths from COVID-19 in all age groups among 24,442,197 cases (0.9% of cases).[ggg]

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

As of 08 January 2023, the overall SARS-CoV-2 mortality for the EU + UK was 1,396,426 deaths, or 2,718 per 1,000,000 population. Reported mortality among EU countries and the UK ranged from 1,032 to 5,570 deaths per 1,000,000 population. Cyprus, Denmark, and Netherlands reported the lowest mortality; Bulgaria, Hungary, and Croatia reported the highest.[ee]

In the US, as of 08 January 2023, the mortality was 1,121,097 deaths (3349 per 1,000,000 population). Mortality in the US was higher than that of the UK (2935 per 1,000,000).[ee]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK and US.[bbb,hhh,iii,jjj]

Complications of COVID-19 and Post-acute COVID

Evidence has shown that a range of persistent symptoms can remain long after the acute SARS-CoV-2 infection. This condition has been called long COVID or post-acute COVID by some recognised research institutes; a universally accepted definition of long COVID has yet to be established.

Studies have shown that long COVID can affect individuals with COVID-19 across a wide spectrum of severity, from those with very mild acute disease to the most severe forms.

Studies around the world have reported various incidence rates for long COVID with different follow-up examination times after the acute infection, including 76% of people at 6 months, one study reporting 32.6% at 60 days while another reporting 87% at 60 days, and 96% at 90 days. Findings are not fully consistent nor comparable across studies, but they do show that a substantial proportion of people who have had COVID-19 may develop long COVID.[kkk]

Assuming at least 10% of COVID-19 survivors develop long COVID, it is estimated that 5 million people are facing long COVID globally.[lll]

This illness is poorly understood as it affects COVID-19 survivors at all levels of disease severity, even younger adults, children, and those not hospitalised. While the precise definition of long COVID may be lacking, the most common symptoms reported in many studies are fatigue and dyspnoea that last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues.

Presently, there is limited literature discussing the possible pathophysiology, risk factors, and treatments in long COVID, which the current review aims to address. In brief, long COVID may be driven by long-term tissue damage (e.g., lung, brain, and heart) and pathological inflammation (e.g., from viral persistence, immune dysregulation, and autoimmunity). The associated risk factors may include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific systemic inflammatory or pro-inflammatory biomarkers (e.g., D-dimer, CRP, and lymphocyte count), although more research is required to substantiate such risk factors.[lll]

Studies that have evaluated a potential impact of SARS CoV-2 vaccination on long COVID include:

Ayoubkhani et al. described that a first dose of COVID-19 vaccine was associated with a reduction in long COVID symptoms of 12.8% (95% confidence interval −18.6% to −6.6%, P<0.001), and evidence suggested a sustained improvement after a second dose, with an initial 8.8% decrease (95% confidence interval −14.1% to −3.1%, P=0.003) in the odds of long COVID, with a subsequent decrease by 0.8% per week (−1.2% to −0.4% per week, P<0.001), at least over the median follow-up of 67 days in this study.

No evidence was found of differences in this relationship by sociodemographic characteristics, health related factors, vaccine type, or duration from infection to vaccination.

Although causality cannot be inferred from this observational evidence, vaccination may contribute to a reduction in the population health burden of long COVID.[mmm]

Furthermore, Kuodi et al.[nnn] showed that two doses of BNT162b2 vaccine reduced the risk of the most common long COVID symptoms after COVID-19 infection, in a cross-sectional study preformed between 15 March 2020–15 November 2021. They found that patients who received 2 doses of BNT162b2 were 54% to 82% less likely to report 7 of the 10 most commonly reported symptoms compared with unvaccinated patients (all P<0.04).

Post COVID has also been described in children. A national survey in the UK found 7-8% of children with COVID-19 reported continued symptoms at >12 weeks.[ooo]

Long COVID can appear after mild to severe infections, and after MIS-C. Most common symptoms: similar to adults and include fatigue, headache, insomnia, trouble concentrating, muscle and joint pain, and cough. Impact on quality of life: limitations of physical activity, feeling distressed about symptoms, mental health challenges, decreased school attendance/participation.

Post-COVID conditions may be less likely to occur after vaccine breakthrough in adolescents.[ppp,qqq]

Persons who were previously vaccinated were less likely to have symptoms between 12 and 20 weeks after infection compared to persons who were unvaccinated (OR 0.22; 95% 0.20, 0.25) with a lower occurrence of post-COVID conditions after infection compared to persons who were unvaccinated.[ppp,qqq]

Further research is needed, but vaccination may contribute to a reduction in the population health burden of long COVID.

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

Non-interventional (observational) study data:

a) There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.

b) Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also inherent limitations.

Post-marketing data:

a) Reports originate from multiple sources (consumer and healthcare professional) and they can be poorly characterised from a medical perspective.

b) Limited or incomplete information is common, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.

c) Difficult to contextualise quantitatively, as voluntary and sporadic reporting do not allow complete knowledge of total exposure or total number of events ever experienced in the exposed population. These data are generally not suitable to make between-drug comparisons.

18.2.1. Benefits

Please refer to Section 17 *Benefit Evaluation*.

18.2.2. Risks

An assessment of the important risks, identified and potential, was performed using the following data sources: pre-clinical studies, clinical studies, post-marketing experience, and literature as applicable. Interval findings are summarised in Table 101.

Based on pharmacovigilance monitoring activities, there has been no new safety information contributing importantly to the risks of BNT162b2.

No actions have been taken upon review of safety topics:

- Dyspnoea, Palpitations and Tachycardia/Heart rate increase
- Multisystem Inflammatory Syndrome, and
- Thyroiditis subacute.

Table 101. Summary of Important Risks

Risks	Clinical Study Data	Post-Marketing Data	Literature Sources	Conclusion
Important Identified Risks				
Myocarditis and Pericarditis	No new data from clinical studies were identified during the reporting interval.	Based on the review of post-marketing data, no new safety information was identified for BNT162b2 and myocarditis and pericarditis.	During the reporting significant information on myocarditis was reviewed. Please refer to Section 11 *Literature* for details.	The risk is communicated through the CDS in the Section 4.4 *Special warnings and precautions for use* and EU SmPC in the Section 4.8 *Undesirable effects*. It is also included as an Important identified risk in the EU RMP and in the US PVP. Considering the accumulating data from post-authorisation use of the vaccine, myocarditis and pericarditis have been added as ADRs in the Section 4.8 *Undesirable effects*, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022. Based upon review of the available information, no additional change to the RSI is warranted at this time.
Important Potential Risks				
VAED/VAERD	No new data from clinical studies were identified during the reporting interval.	Based on the review of post marketing data, no new safety information was identified for BNT162b2 and VAED/VAERD.	No new significant data received from literature sources.	VAED-VAERD 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. It is included as an Important Potential Risk in the EU RMP and in the US-PVP. Based upon review of the available information, no additional change to the RSI is warranted at this time. The MAH proposes to remove the important potential risk of VAED/VAERD from the PSUR on the basis that accumulated scientific and clinical data are not supportive of the initial theoretical supposition that VAED/VAERD may be a risk of vaccination with the COVID-19 mRNA vaccine.

The important identified risk Anaphylaxis was removed as an important risk during the reporting interval and is not included in this table.

18.2.3. Overall Benefit-Risk

The important risks associated with the use of BNT162b2 are minimised through provision of relevant product information in the RSI to support safe use of the product. Risks have been evaluated in the context of the enumerated benefits of the product. Based on the available safety and efficacy/effectiveness data for BNT162b2 (original and bivalent presentations), the overall benefit-risk profile of BNT162b2 remains favourable for all age groups in which it is authorised.

Table 102. Overall Benefit-Risk for BNT162b2

Consideration	Favourable Benefit-Risk	Non Contributory	Unfavourable Benefit-Risk
Severity of condition	The severity of the condition being treated, as well as comorbidities and outcomes in the population to be treated were considered. (See Section 18.1)	NA	NA
Unmet medical need	BNT162b2 meets an unmet medical need because there is - lack of alternative therapies, or - although alternative products are available in this class, this product may be the preferred therapeutic option or preferred in a select group of patients. (See Section 18.1)	NA	NA
Clinical benefit	The nature, clinical importance, duration, and generalizability of benefits were considered. (See Section 18.1)	NA	NA
Risk associated with treatment	The nature, seriousness, frequency, predictability, reversibility, impact on patients and public health of the product's risks were considered. (See Section 18.2.2)	NA	NA
Risk management	Risk minimisation measures currently in place for this product support a favourable benefit-risk balance. (See Section 18.2.2)	NA	NA

Table was adapted from European Medicines Agency. Benefit-risk Methodology Project – Working package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010.

19. CONCLUSION AND ACTIONS

Risks been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2 (original and bivalent vaccines Omi BA.1 and BA.4/BA.5), the overall benefit-risk profile of BNT162b2 remains favourable. No further changes to the BNT162b2 RSI or additional risk minimisation activities are warranted in addition to those above mentioned.

Based on the clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, no new significant safety information has been identified that substantiates retaining VAED/VAERD as an important potential risk in the PSUR for BNT162b2. The MAH proposes to remove the important potential risk of VAED/VAERD from the PSUR on the basis that accumulated scientific and clinical data are not supportive of the initial theoretical supposition that VAED/VAERD may be a risk of vaccination with the COVID-19 mRNA vaccine.

The MAH will continue to review the safety of BNT162b2, including all reports of adverse experiences and will revise the product documents if an evaluation of the safety data yields significant new information.

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