COMIRNATY : Periodic safety update report assessment

19 June 2022 to 18 December 2022

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period 19th June 2022 to 18th December 2022, and;

2. The Comirnaty PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

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)

ATC CODE: J07BX03

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD)[2]: 19 DECEMBER 2020

EUROPEAN UNION REFERENCE DATE (EURD): 19 DECEMBER 2020

INTERVAL COVERED BY THIS REPORT:

19 JUNE 2022 through 18 DECEMBER 2022

DATE OF THIS REPORT: 17 FEBRUARY 2023

SIGNATURE: [redacted] **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

[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.

data published on the ECDC websites for doses of BNT162b2 vaccines (original and 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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APPENDICES

LIST OF ABBREVIATIONS

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

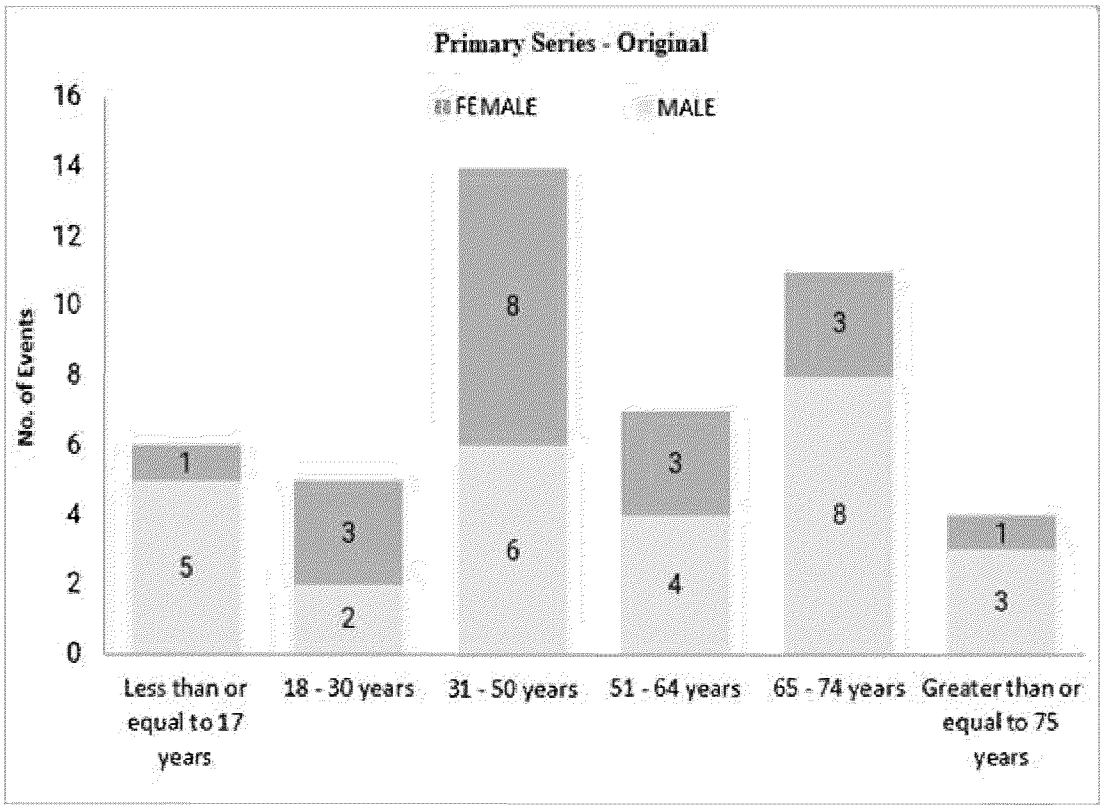
Characteristics		All No. of Cases (%[a]) N=309	BNT162b2 No. of Cases (%[a]) N=223	Blinded Therapy No. of Cases (%[a]) N=81	Placebo No. of Cases (%[a]) N=5
Vaccine series	Primary	85 (27.5%)	36 (16.1%)	44 (54.3%)	5 (100%)
	Booster[30]	224 (72.5%)	187 (83.9%)	37 (45.7%)	-

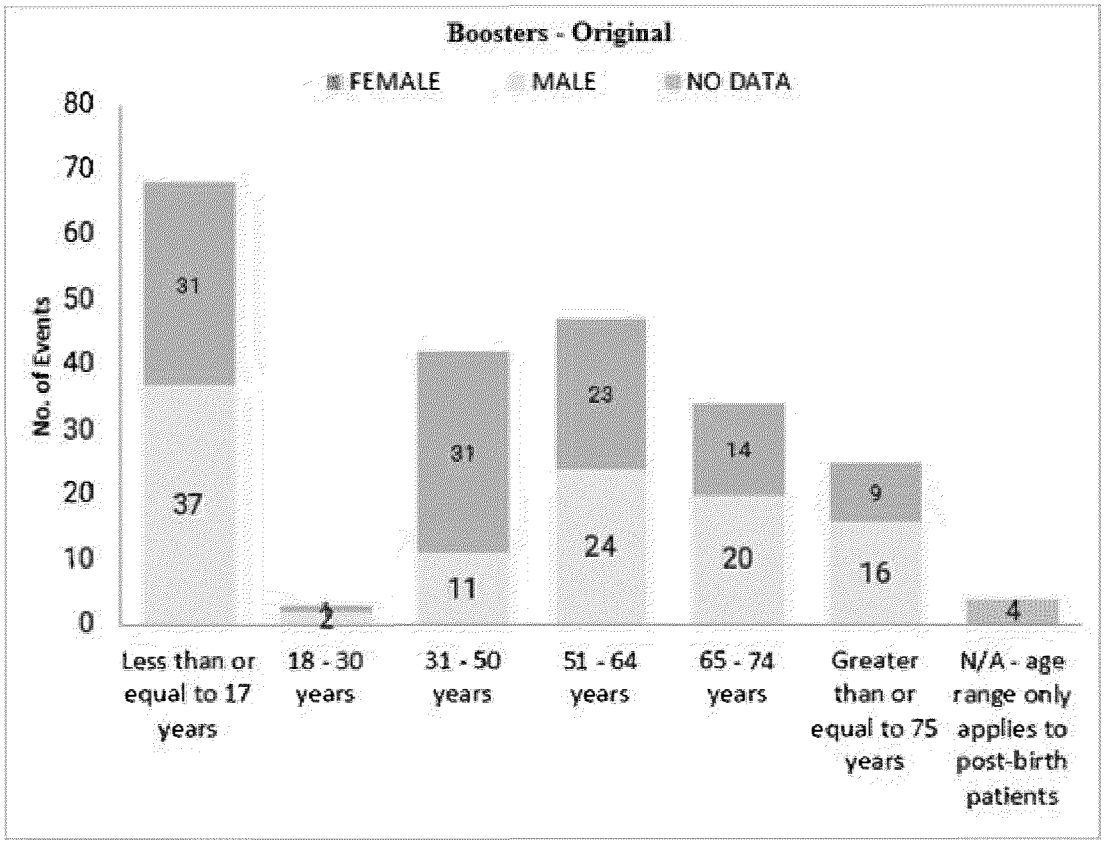
a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Foetus cases: Age range only applies to post-birth subjects.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (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

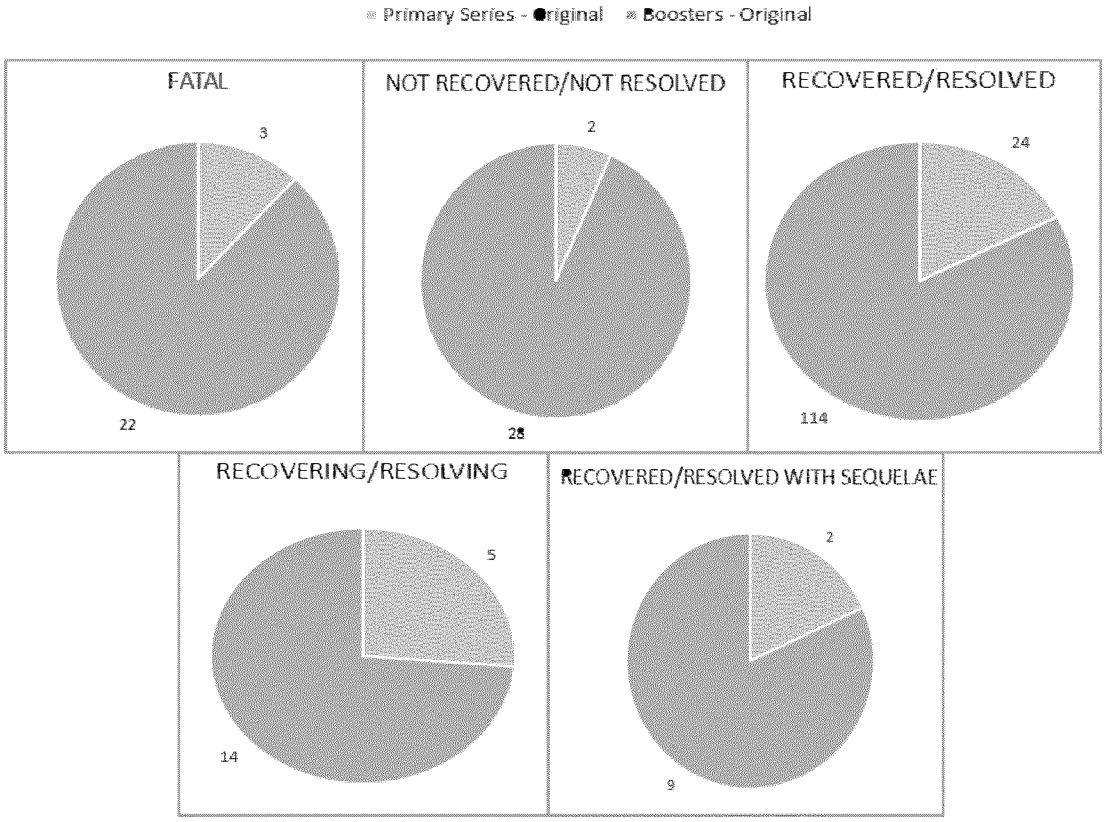


Figure 3. Clinical Trial Data: Overall Case Outcome by Gender in Primary Series Cases and Boosters Cases by Vaccine Type

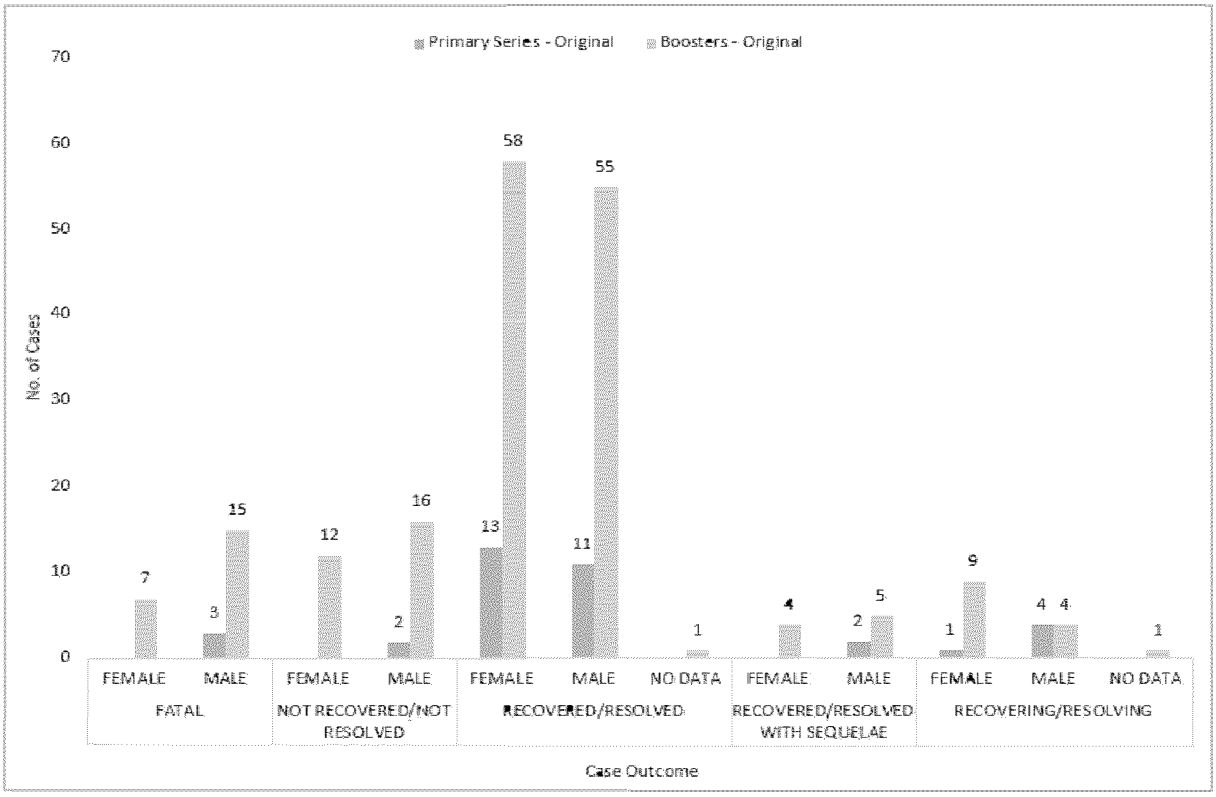
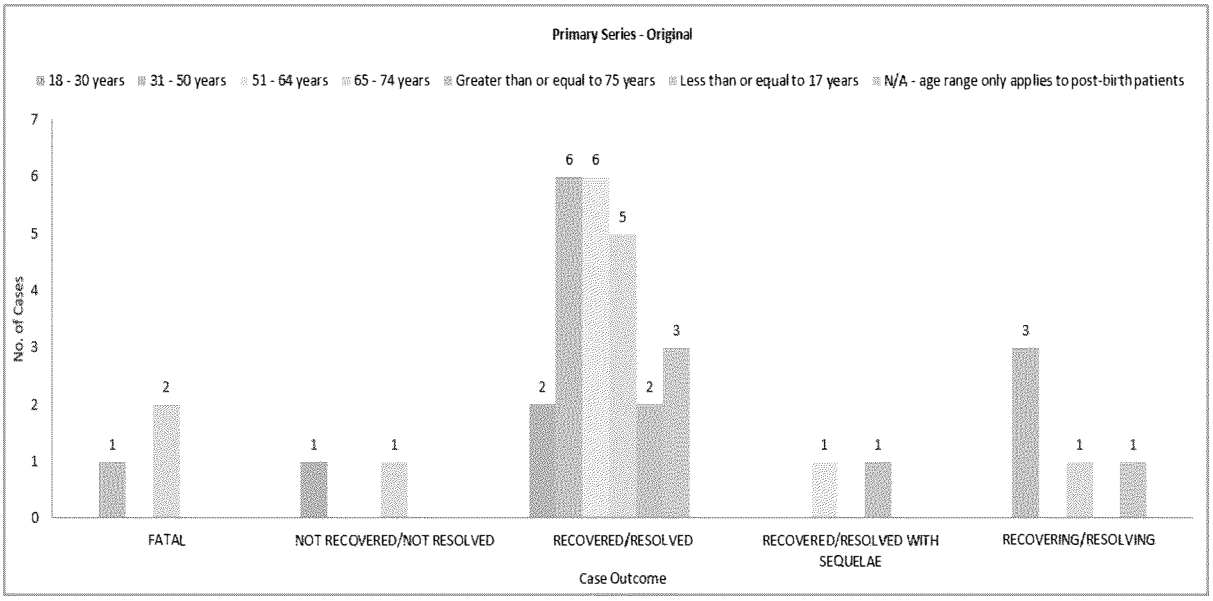
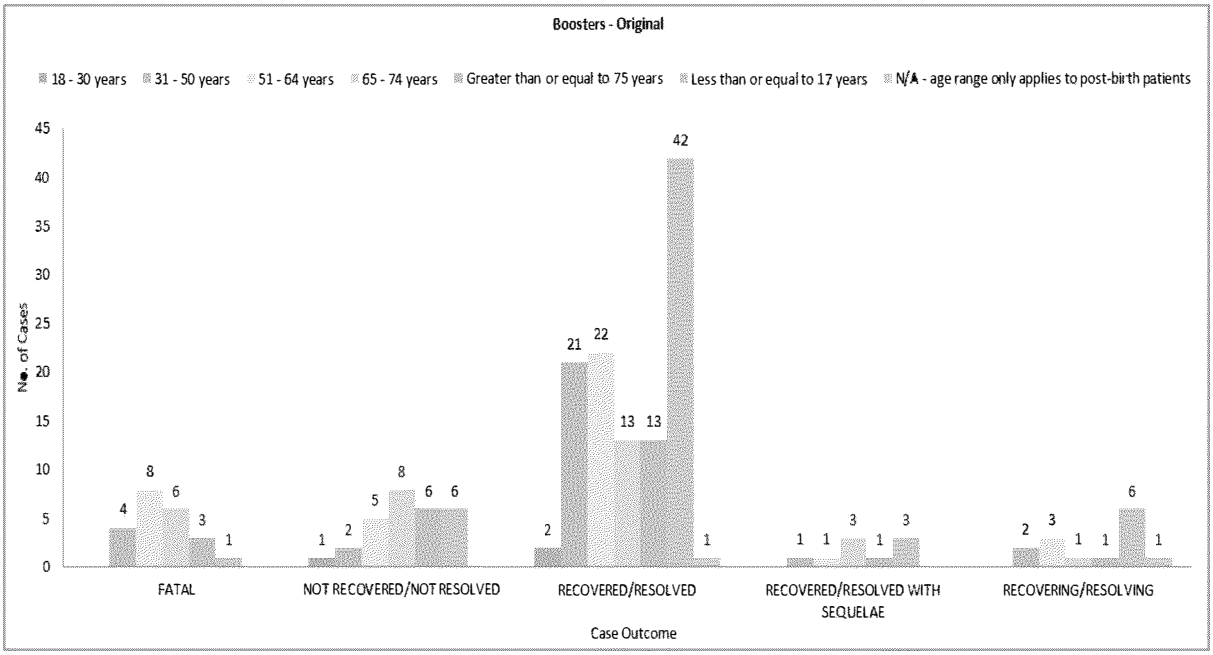


Figure 4. Clinical Trial Data: Overall Case Outcome by Age Group and Vaccine Type





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/b2s 01/BT Cases (N=304) AEs (n=376)**	**All Cases [c] (N=2724) AEs (n=3578)**	**BNT162b1/BNT1 62b2/BNT162b2s 01/BNT162b3/BN T162c2/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

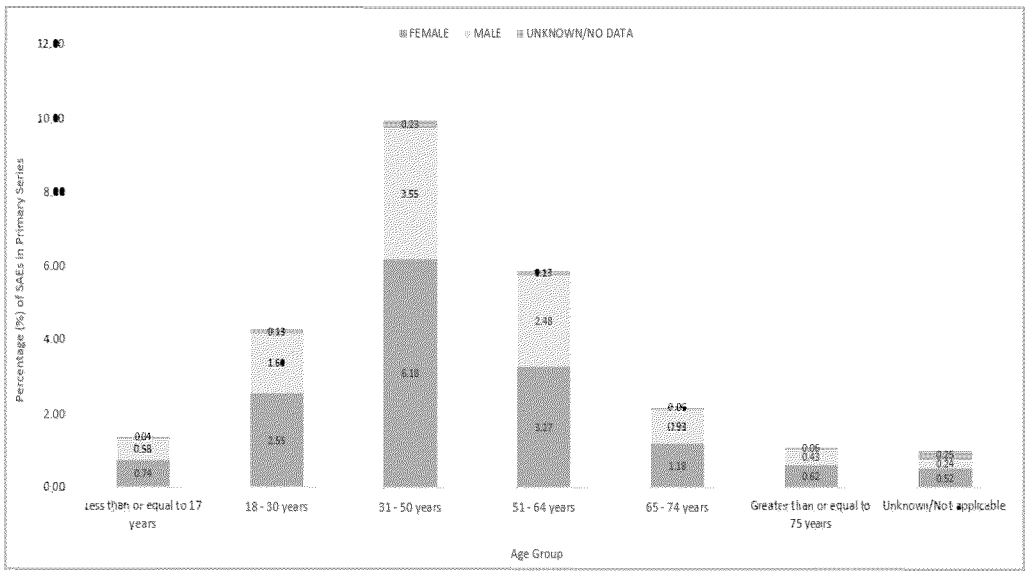
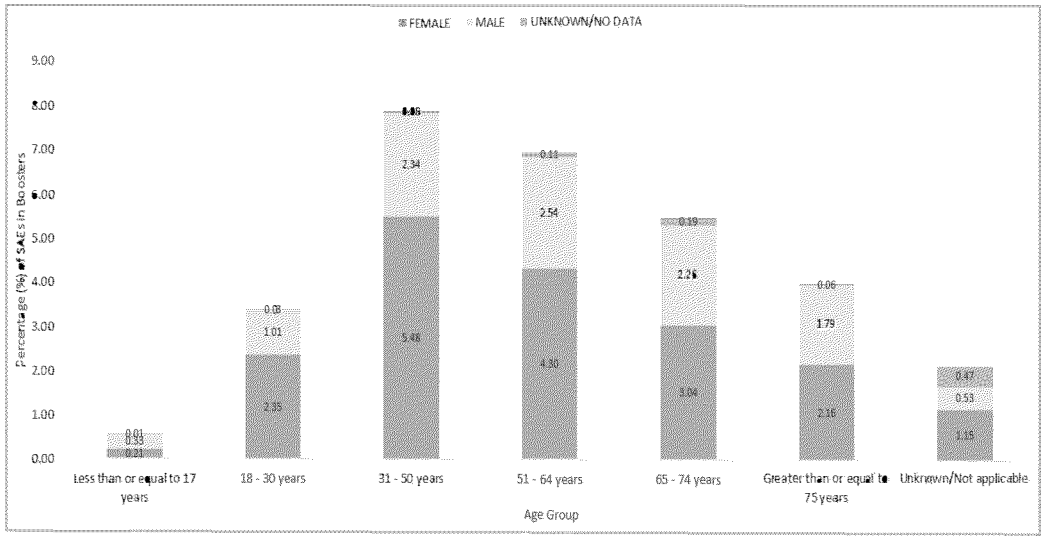
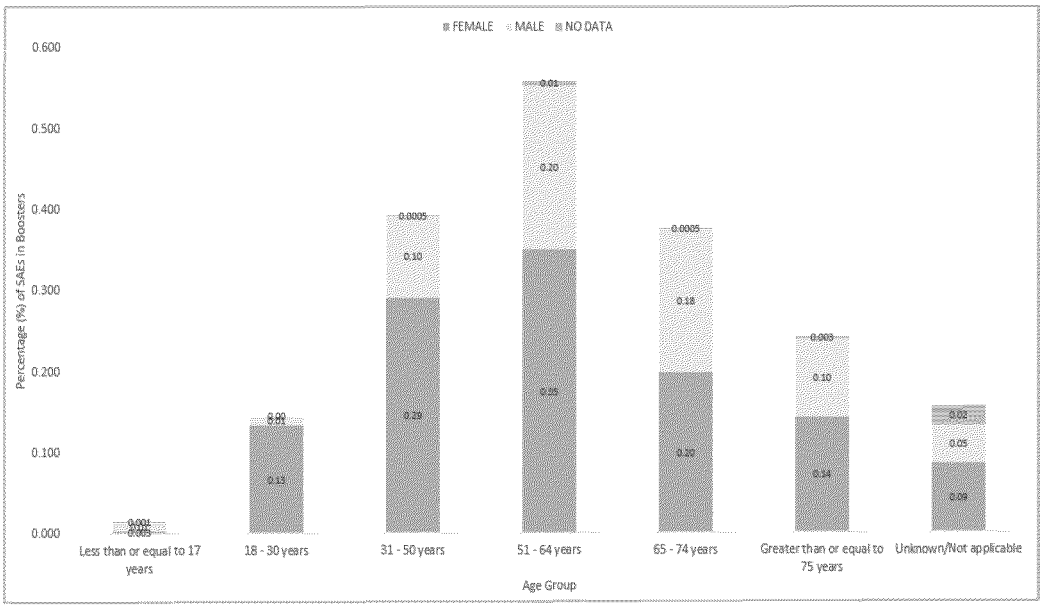
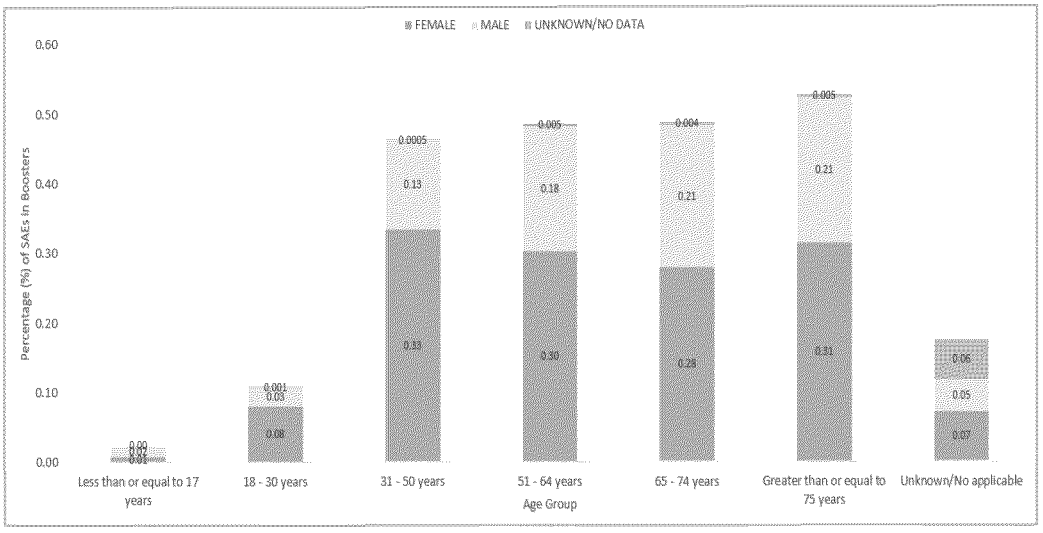
Primary series	
Original	
Boosters	
Original	

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.

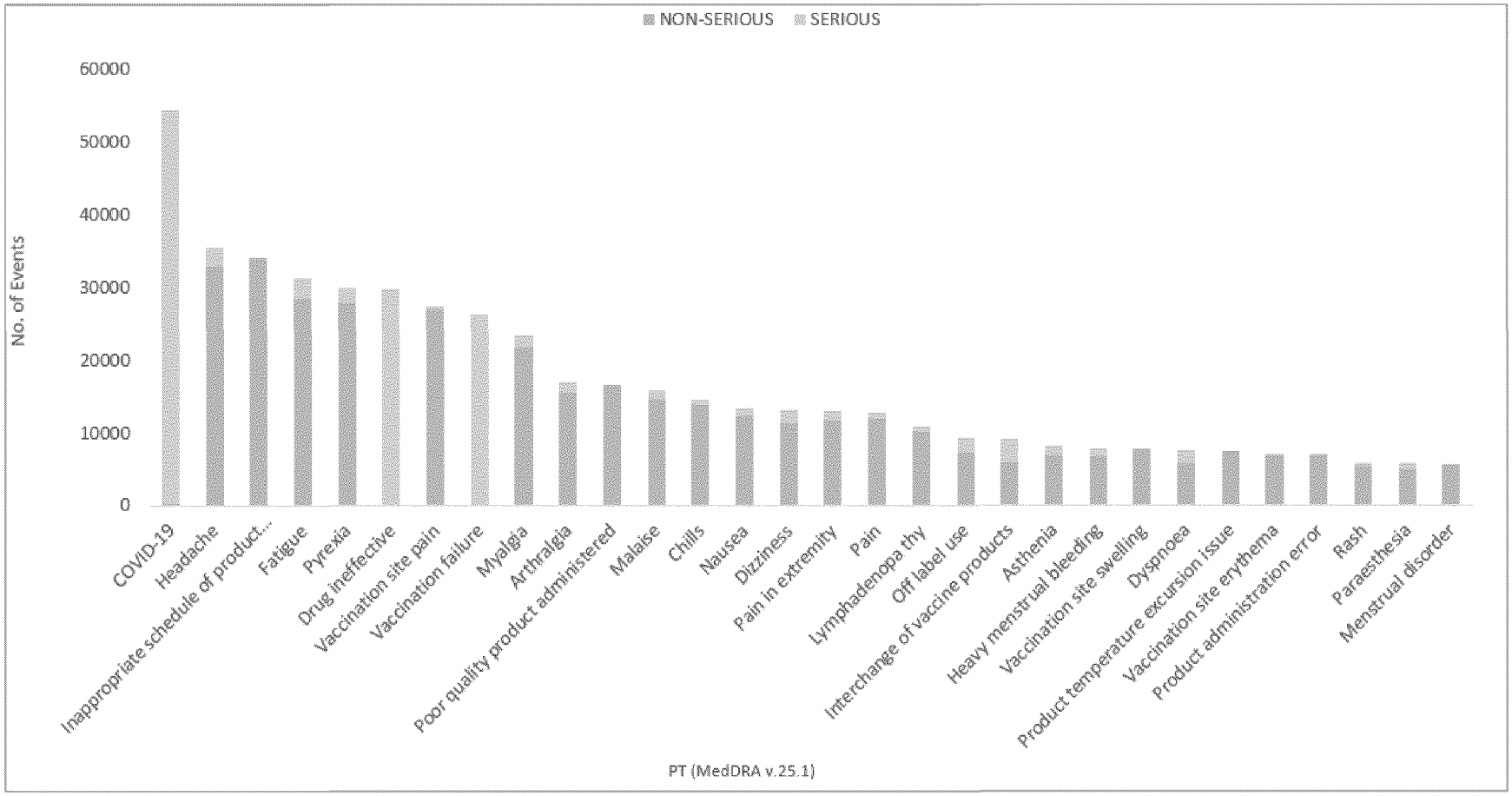
The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (261,953), Nervous system disorders (94,886), Injury, poisoning and procedural complications (84,718), Musculoskeletal and connective tissue disorders (77,153), Infections and infestations (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

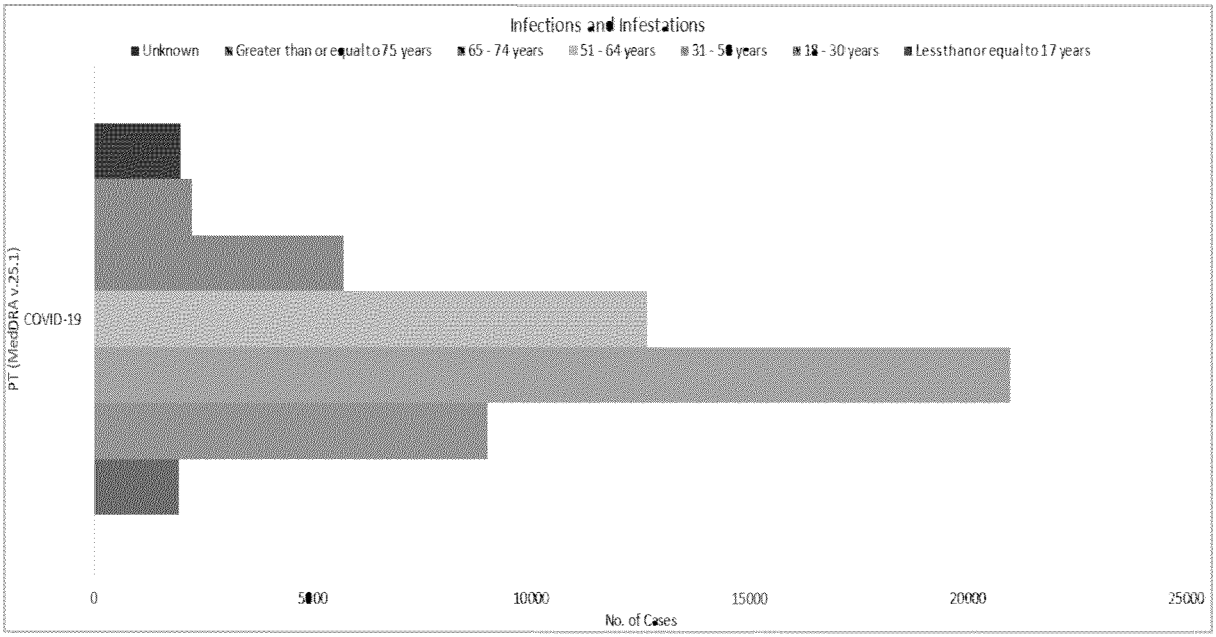
	Reporting Period 19 Jun 2022 - 18 Dec 2022				Cumulatively through 18 Dec 2022			
MedDRA SOC MedDRA PT	**All Cases (N=282,992) AEs (n=838,865)**	**BNT162b2 (N=271,848) AEs (n=800,366)**	**BNT162b2 + BA.1 (N=4861) AEs (n=19,777)**	**BNT162b2 + BA.4/BA.5 (N=8802) AEs (n=23,397)**	**All Cases (N=1,766,357) 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%)

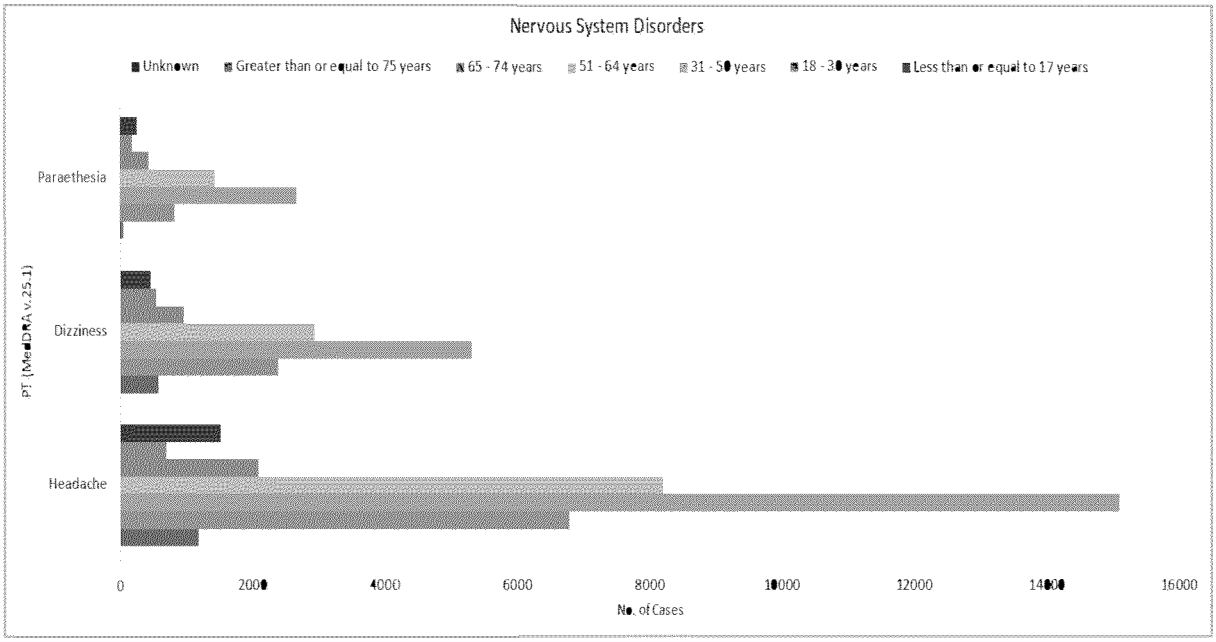
a. Reporting proportion calculated as n/N (% of all incremental cases, incremental serious cases and all cumulative cases).
b. The sum of percentages may not exactly match 100% due to rounding in calculations.
c. Listed per case processing conventions, except for fatal cases.
d. Drug ineffective represents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

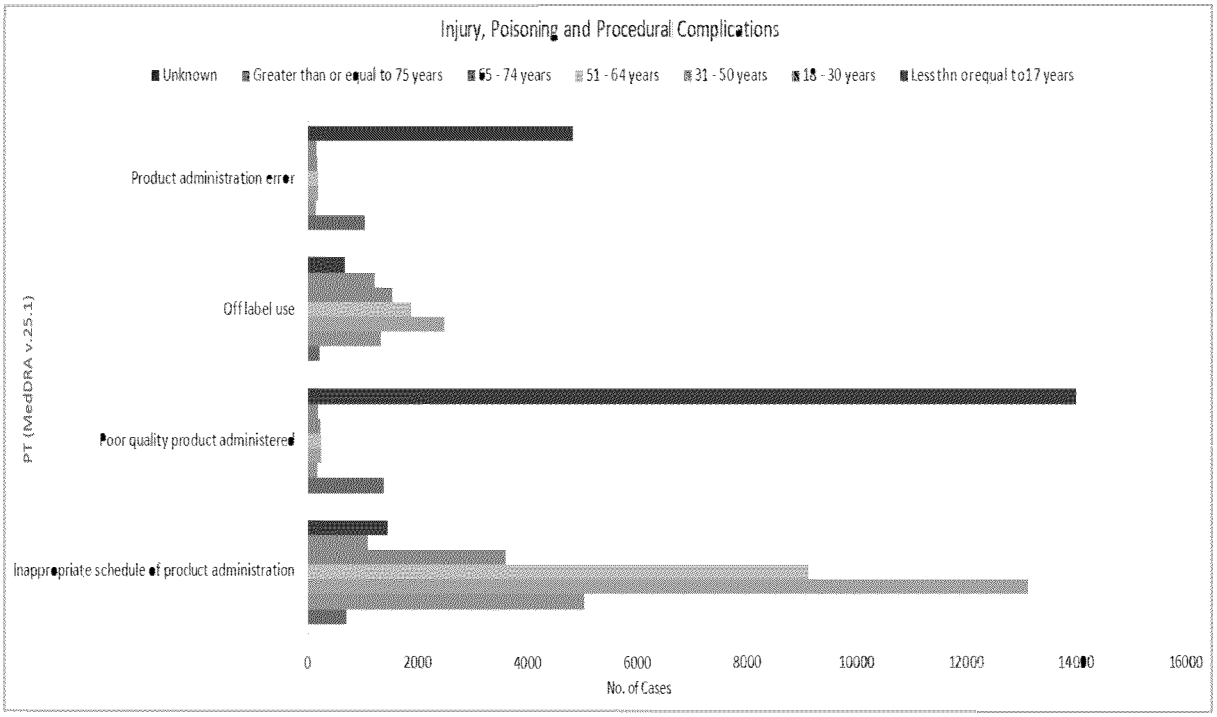
N = Number of cases; n = Number of events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; PT = Preferred Term; AE = Adverse Event; AERP = Adverse Event Reporting Proportion

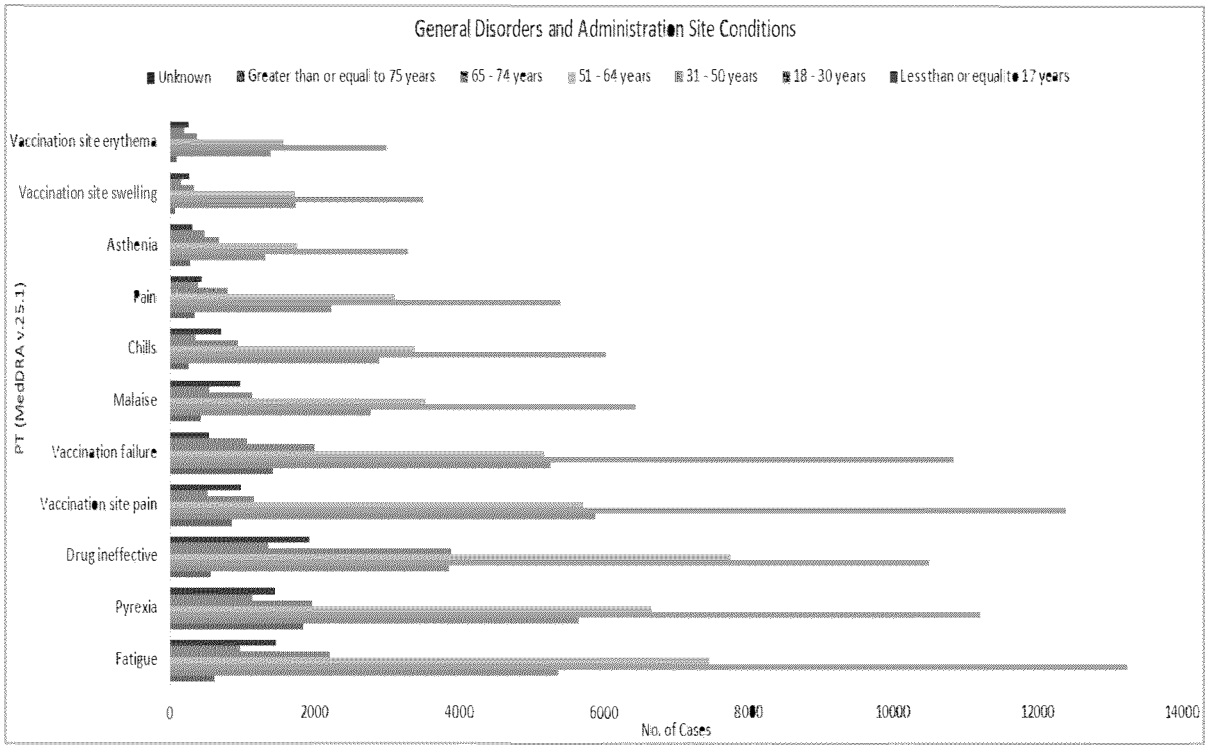
Figure 6 provides information about the age breakdown in the clinical AEs reported in more than 2% of the cases by SOC in the overall PM dataset; the age group 31-50 years is the one reporting higher proportion of events than other age groups except for PTs Product administration error, Poor quality 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.

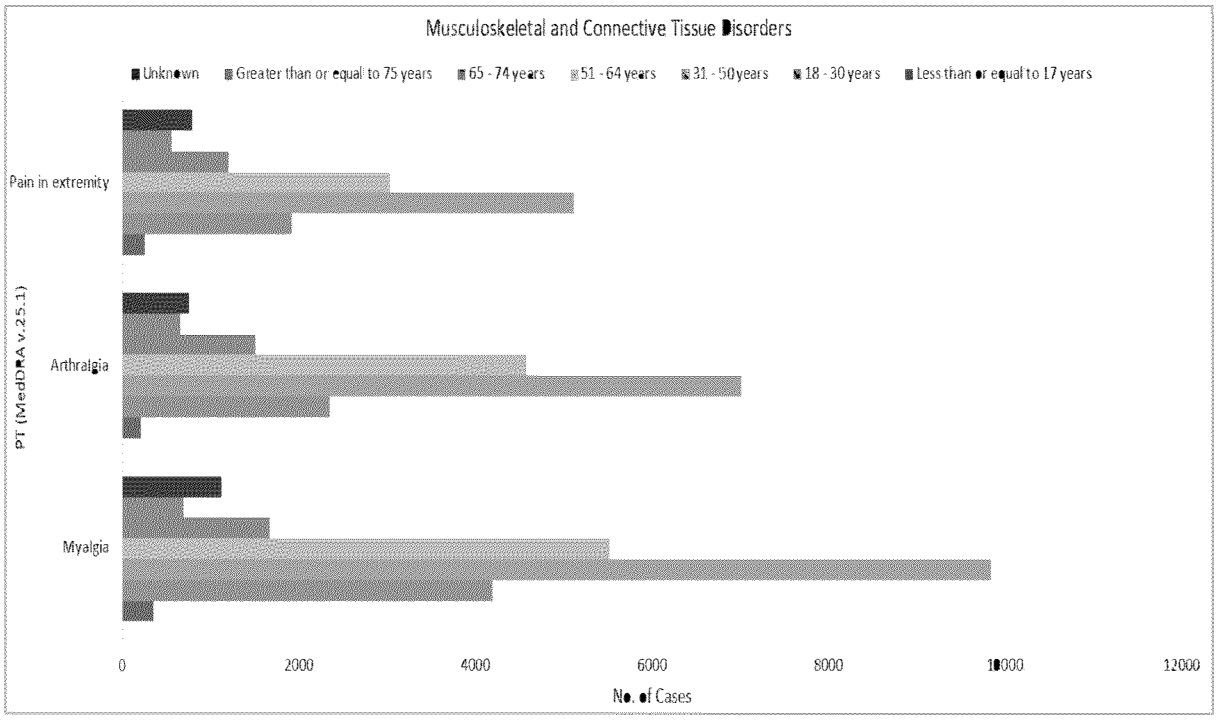
Figure 6. Clinical AEs Reported in More Than 2% of the Cases by SOC and Age Group

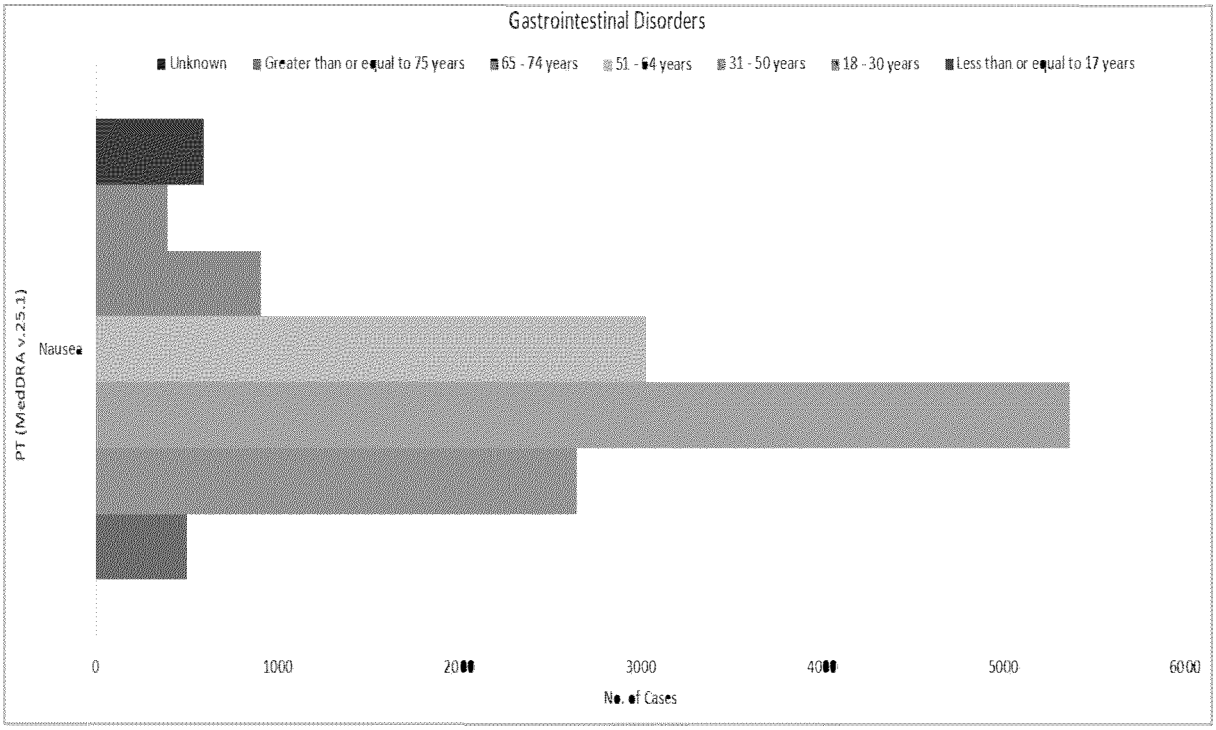


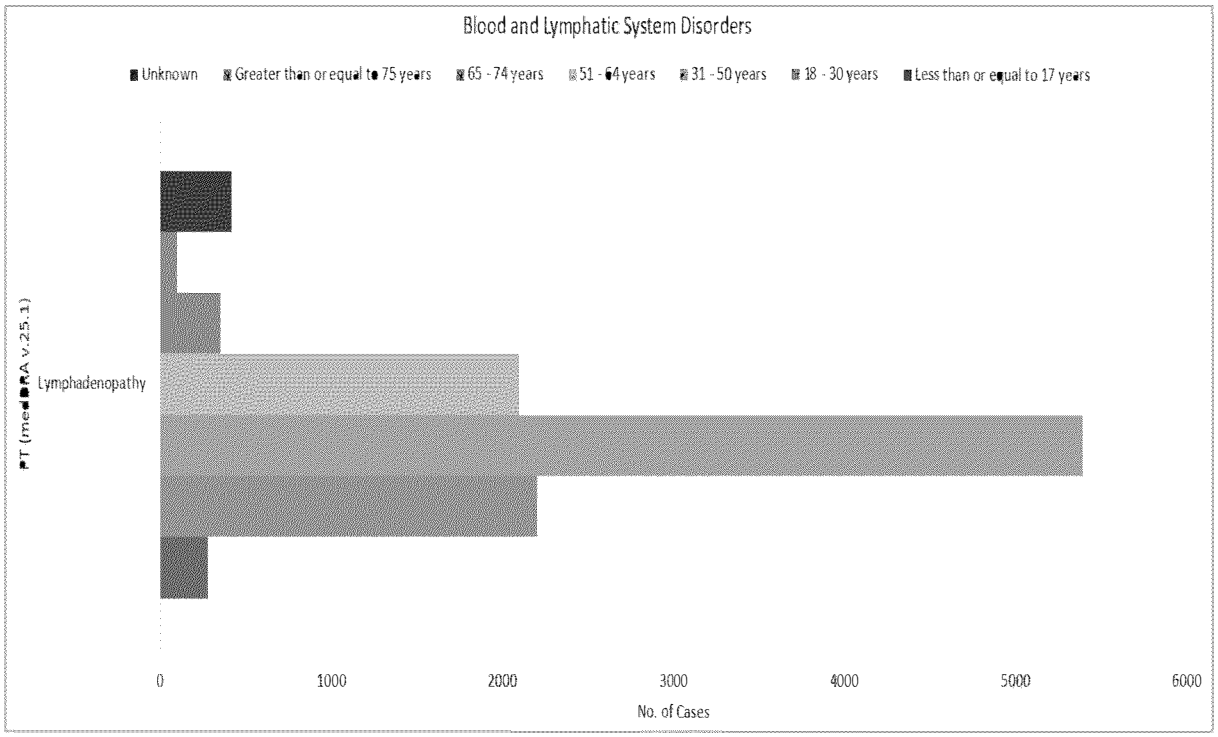


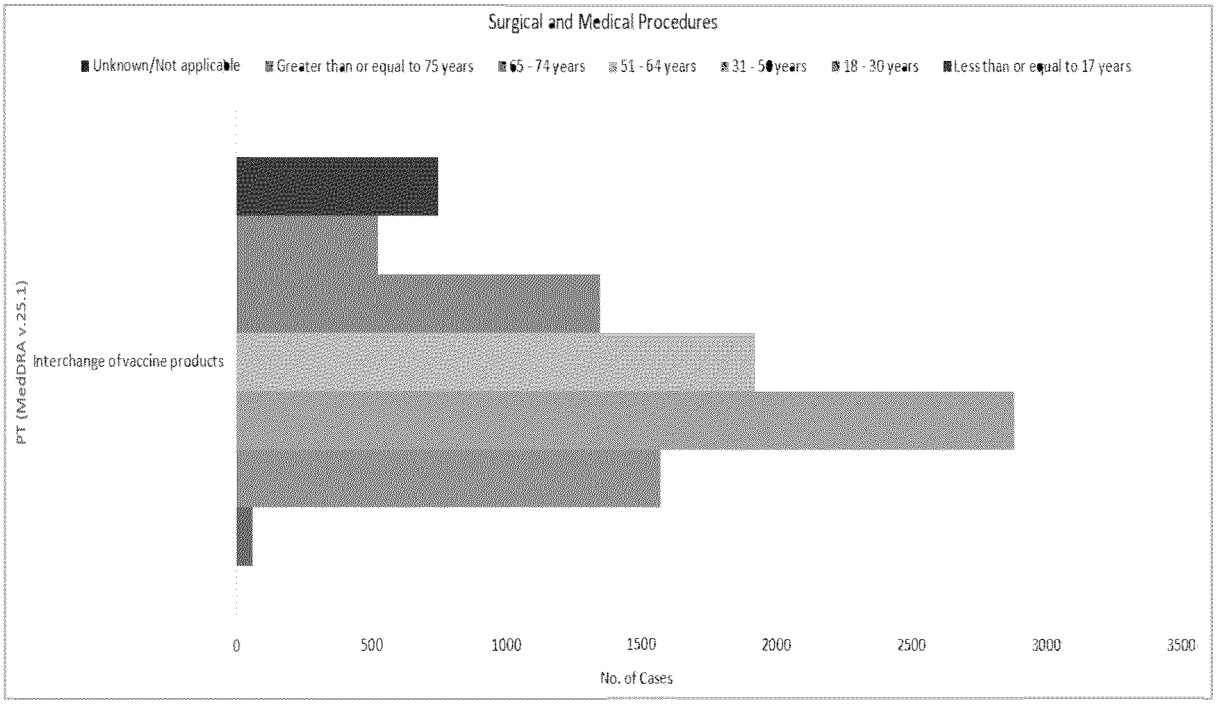


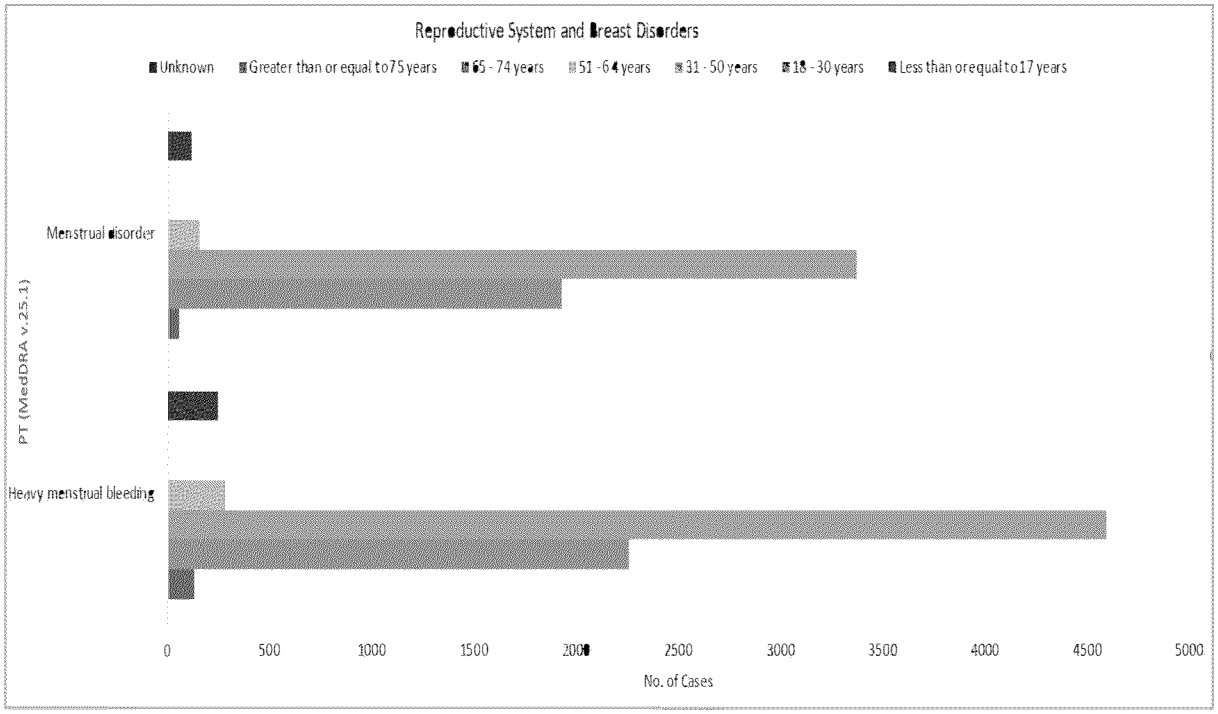


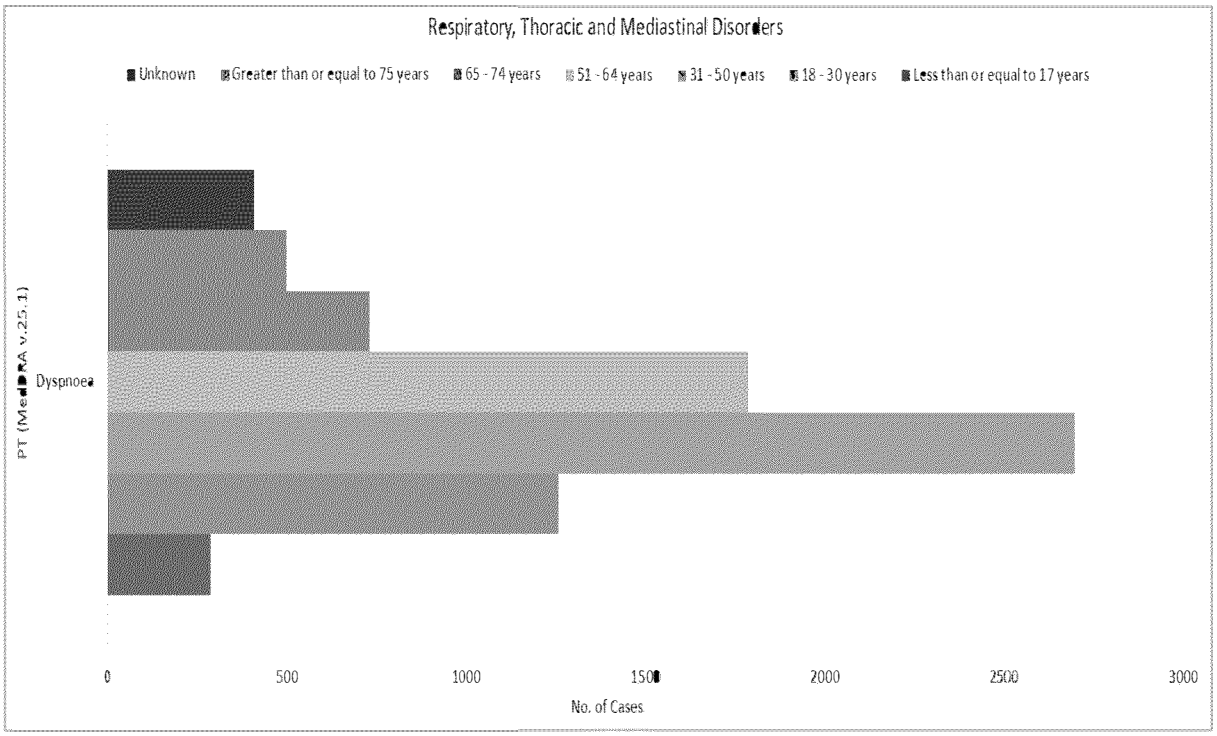


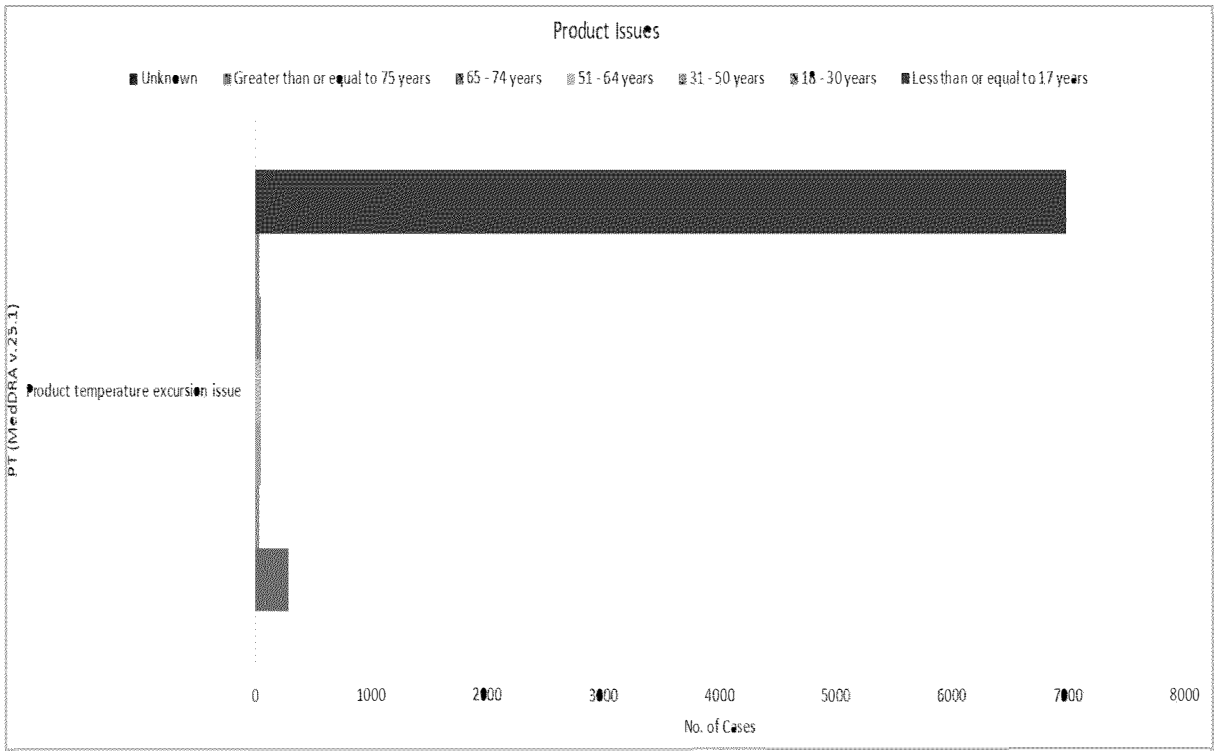


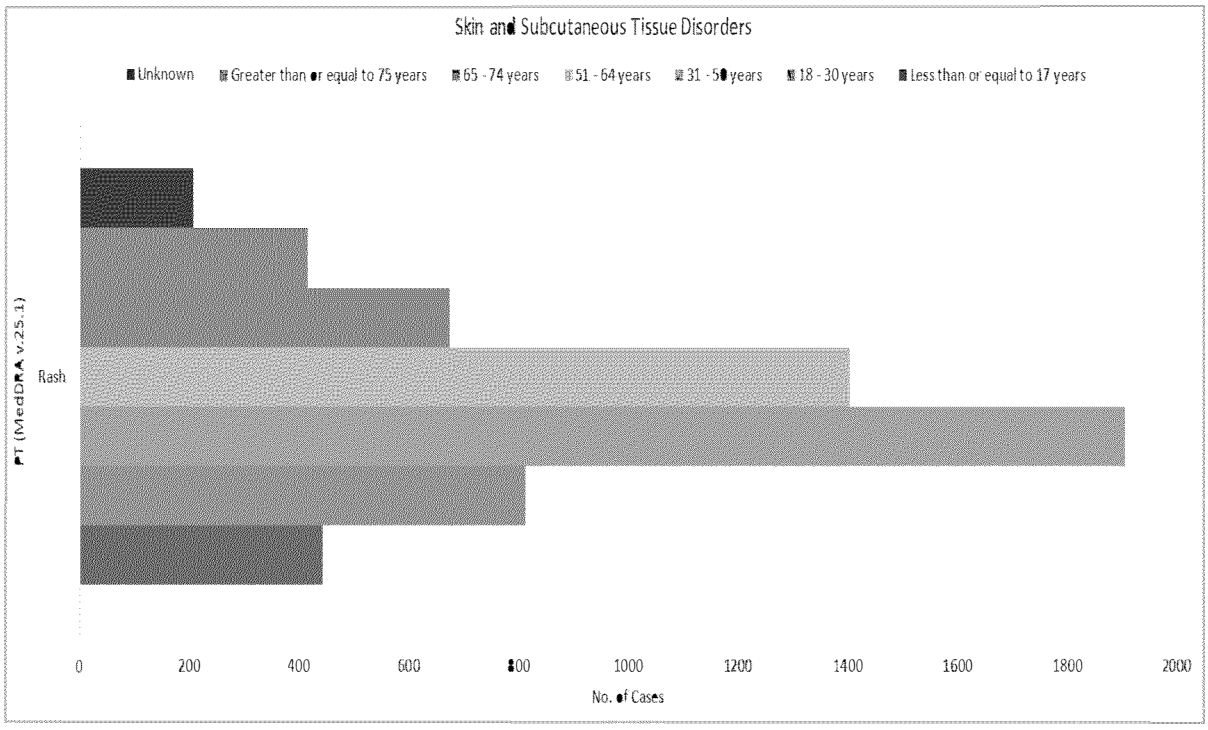












Conclusion

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[c]	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 35-year-old female subject who received BNT162b2 on 24 November 2021 and 16 December 2021 (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 April and continued until June. The pain was treated with painkillers and yoga. On 04 June 2022, the subject experienced COVID-19. On 09 June 2022, 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”. She 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 82-year-old male subject who received BNT162b2 on 10 March 2021 and 31 March 2021. 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 he has had vaccines, he 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 32-year-old female subject received BNT162b2 on 21 June 2021 and 26 July 2021. 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.*

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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), Brazil, Costa Rica and Puerto Rico (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 her 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 6-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), Australia, Austria, Japan, New Zealand, UK, US (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 8-year-old female subject, dose 2, medically confirmed, Taiwan:

- 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 17-year-old male subject, dose 1, non-medically confirmed, United States:

- 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 [redacted] 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)

A 23-year-old male subject, dose 3 (with dose 2 being a vector vaccine), medically confirmed, Norway:

- 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.

A 24-year-old male 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 his 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 he 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 '[redacted]' suggests that the case did not result in a fatal outcome.

A 22-year-old female subject, dose unknown, medically confirmed, Israel:

- 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 22-year-old female 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 19-year-old male subject, dose 3, medically confirmed, Japan:

- 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)

A male subject in his 3rd decade, dose unknown, medically confirmed, Korea:

- 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 27-year-old male subject, dose unknown, non-medically confirmed, United States:

- 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.

A 26-year-old male subject, dose 2, medically confirmed, Italy:

- 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)

A 35-year-old male subject, dose 1, non-medically confirmed, Canada:

- 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.

A 35-year-old male subject, dose unknown, medically confirmed, Israel:

- 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 38-year-old male subject, dose 3 (first 2 Moderna vaccine), Non-medically confirmed, United States:

- 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 30-year-old male subject, dose 2, medically confirmed, Japan:

- 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 32-year-old male subject, dose 1, medically confirmed, Portugal:

- 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 46-year-old male subject, dose 1, medically confirmed, Germany:

- 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 55-year-old female subject, dose 4, medically confirmed, Japan:

- 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 87-year-old female subject, dose 4, medically confirmed, Japan:

- 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 elderly 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), Australia, Spain, UK (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), Chile, Latvia, Slovenia, US (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), France, Italy, Malaysia (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), Austria, Denmark, Japan, Malaysia, Norway, Poland, Taiwan, Province of China, UK (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), Austria, Belgium, Denmark, Hong Kong, Israel, Luxembourg, Netherlands, New Zealand, Poland, South Africa, Spain and US (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), Finland, Ireland, Luxembourg, Malaysia, Mexico, Switzerland (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):

A 78-year-old female subject from Australia.

- 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.

A 95-year-old male subject from Japan.

- 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):

An 83-year-old female subject, from Greece.

- 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.

A 77-year-old male subject from New Zealand.

- 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), Belgium, Philippines (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), Chile, Finland, Ireland, Israel, Slovakia (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 74-year-old female 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, a 69-year-old male subject was administered 3 doses of the BNT162b2 vaccine. He experienced bilateral pneumonia due to SARS-CoV-2 (infection confirmed via positive PCR test) with severe respiratory failure. Despite treatment, his condition worsened, and he 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), Belgium, Finland, South Korea, Malaysia, Philippines, and UK (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: male (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), Canada, Hungary, Ireland, New Zealand (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.

[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).

- Relevant event outcome: fatal (1), resolved (3), resolved with sequelae (1), not resolved (4).

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,

[67] Some cases reported more than 1 suspect drug.

Thrombocytopenia (164 each), Dermatitis (144), Neuralgic amyotrophy (130), Alopecia areata (128), and Autoimmune thyroiditis (125).

- 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), Brazil, Finland, Germany (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), Argentina (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: male (2)
- Subjects' age in years: n = 2, range: 6 – 66, 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), Austria, Estonia, Greece, Italy, Philippines, Poland, Portugal, Serbia, UK (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), Czech Republic, Italy, Slovenia, Sweden, UK (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: female.
- Subjects' age in years: 2.
- 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

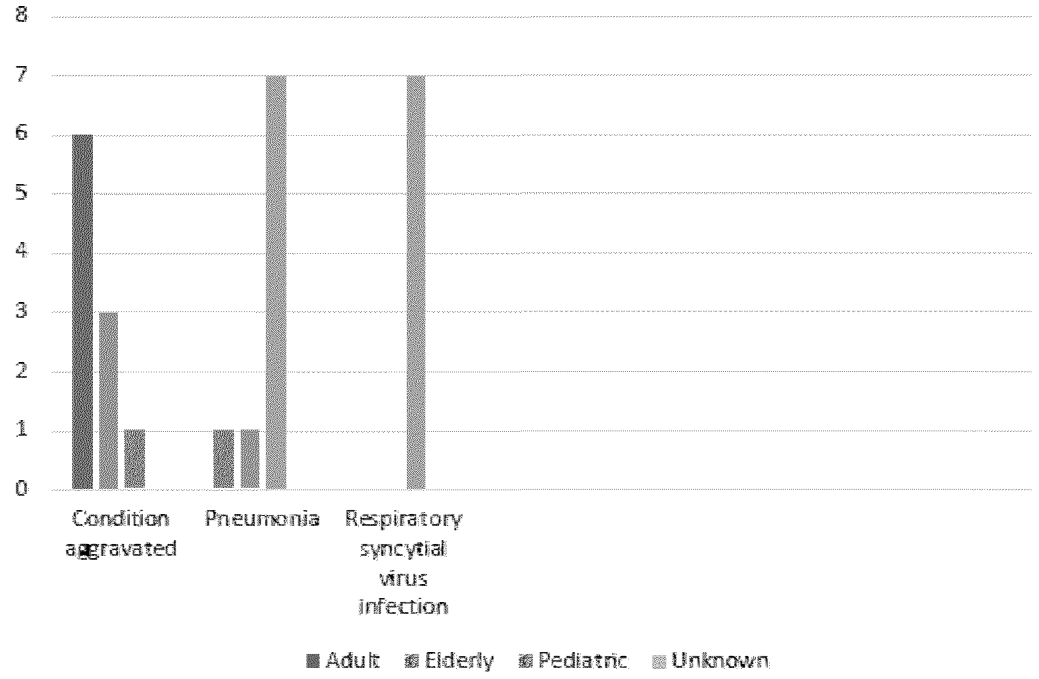
SOC	Paediatric	Adult	Elderly	Unknown
Infections and infestations	57	21	11	0
Injury, poisoning and procedural complications	13	18	6	0
Nervous system disorders	12	10	8	0
Respiratory, thoracic and mediastinal disorders	12	10	3	0
General disorders and administration site conditions	7	13	5	0

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

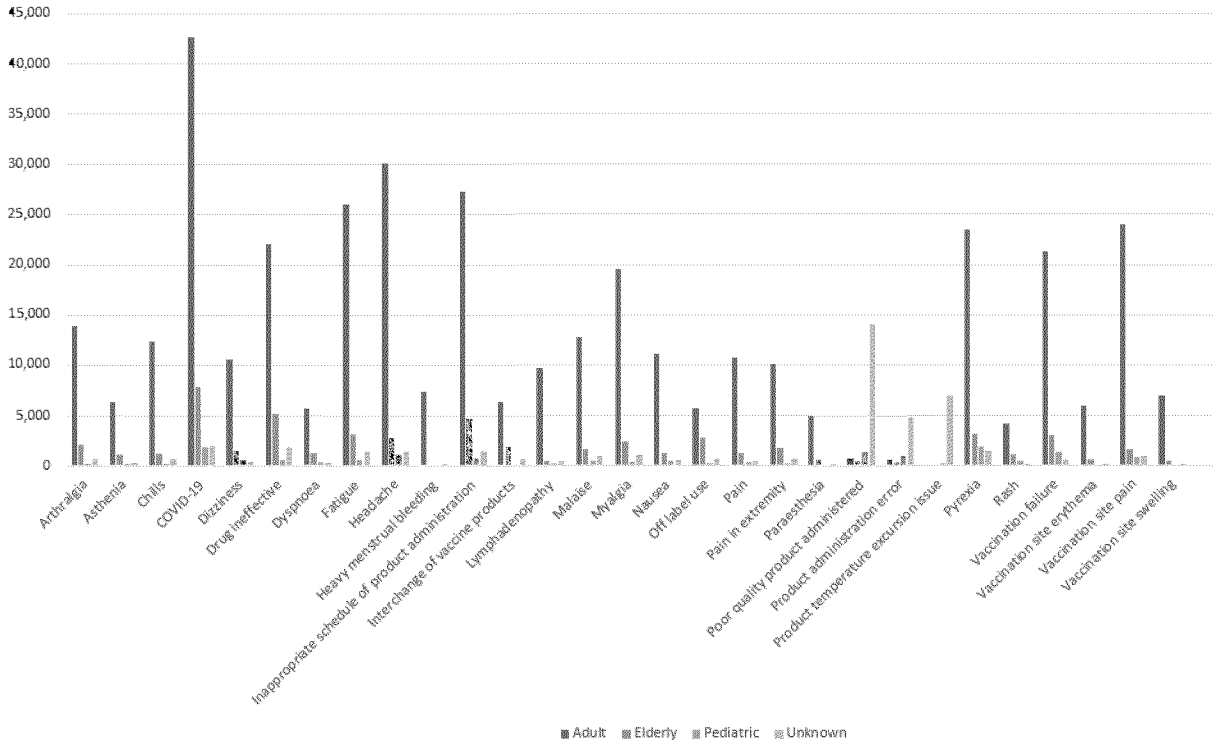
SOC	Paediatric	Adult	Elderly	Unknown
General disorders and administration site conditions	8256	211,602	29,175	12,886
Injury, poisoning and procedural complications	7148	39,173	10,758	27,398
Nervous system disorders	3207	75,758	11,500	4402
Infections and Infestations	2450	51,063	10,752	3165
Gastrointestinal 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).

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[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).

[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.*

- 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, 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), France and Italy (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), Brazil, Germany, Israel (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: 7 months (1), 2 years (2).

- MC case (1), NMC cases (2).
- Gender: males (2), unknown (1).
- Country: US (2), Taiwan, Province of China (1).
- 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 Germany (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)

- Age: 5 years (2), 6 years (2), 7 years (3), 8 years (3), 9 years (1), 10 years (3), 11 years (2), unknown (2).
- MC cases (12), NMC cases (6).
- Gender: females (11), males (5), unknown (2).

- Country: Philippines (11), Japan, US (2 each), Brazil, Malaysia, and Taiwan, Province of China (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 Mexico (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: 12 years (3), 13 years (1), 14 years (5), 15 years (3), 16 years (8), 17 years (7), unknown (1).
- 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: 16 years; gender: female; 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: 14 years; gender: female; 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: 16 years; gender: female; 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: 14 years; gender: male; 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

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– 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., 43 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). *Pericarditis* • 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** • 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).	**Post-Marketing Data** • 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

[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.

immune response in participants 16 through 25 years of age (n = 170), based on results for 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

[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.

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.

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]

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 N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	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

[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.

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

[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.

(children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 99.[115]

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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EMA/PRAC/304118/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202212

Active substance(s): tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5)

Period covered by the PSUR: 19/06/2022 To: 18/12/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
COMIRNATY	BioNTech Manufacturing GmbH

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	9 March 2023	9 March 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	8 May 2023	8 May 2023
☐	MS/PRAC members and MAH comments	7 June 2023	7 June 2023
☐	PRAC Rapporteur's updated assessment report following comments	22 June 2023	22 June 2023
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	6 July 2023	6 July 2023

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5).

2. Assessment conclusions and actions

The MAH submitted the 4th EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 17 Feb 2023) covering the period 19 Jun 2022 to 18 Dec 2022.

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in people aged 6 months and older.

During the reporting period of the PSUR:

- A booster dose of Comirnaty 10 µg in children 5 to 11 years of age was recommended (procedure EMEA/H/C/005735/II/0129)
- The indication of Comirnaty was extended to children 6 months - 4 years old (tozinameran; Tris/Sucrose presentation 3 micrograms per dose). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose. (procedure EMEA/H/C/005735/X/0138)
- Two adapted Comirnaty vaccines became available:
    - Comirnaty Original/Omicron BA.1 that contains tozinameran and riltozinameran:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0140)
    - Comirnaty Original/Omicron BA.4-5 that contains tozinameran and famtozinameran:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0143)
        - Booster dose (5/5 micrograms per dose) for people aged from 5 years to 11 years at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/X/0147)

During the reporting interval, 813,783,710 doses of Comirnaty original and bivalent vaccines were shipped worldwide. Cumulatively, 4,369,782,515 doses of Comirnaty original and bivalent vaccines were shipped worldwide.

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

During the reporting interval, Dizziness (with frequency Uncommon) and Heavy menstrual bleeding (with frequency Unknown) were added as ADRs to the Comirnaty product information.

During the reporting interval, the following signals were evaluated, not to be determined risks, and no new important safety issue was identified based on the data provided in the PSUR:

- Haemophagocytic lymphohistiocytosis (HLH); Dermatomyositis; Histiocytic necrotizing lymphadenitis (HNL); Genital (e.g., vulvovaginal) ulceration.

The following were ongoing signals during the reporting interval:

- Pemphigus and Pemphigoid (EPITT 19859).

During the reporting interval, there were post-approval regulatory requests for the following topics for which no safety signal was identified based on the information provided in the PSUR:

- Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Subacute thyroiditis; Amenorrhea.

There was a new aspect of a previously recognised important safety issue identified, which included the clinical course (including intensive care support) and outcome (including fatal outcome) of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months). Therefore, the wording of the warning concerning myocarditis and pericarditis in the Comirnaty PI should be amended accordingly (please refer to section 3 Recommendations below).

During the reporting interval, the important identified risk Anaphylaxis was removed from the list of safety concerns in the Comirnaty RMP.

The important potential risk VAED/VAERD can be removed from the list of safety concerns in both RMP and PSUR, as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance.

Taking into account the extensive use of the vaccine and the relatively well-established safety profile, the PRAC endorses the proposal to move the PSUR cycle to 1 year. As the MAH has expressed a wish to keep the cycle aligned with the EURD, two additional 6-monthly PSURs will be submitted, followed by the yearly PSUR.

The benefit-risk balance for the use of Comirnaty (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran and riltozinameran), and Comirnaty Original/Omicron BA.4-5 (tozinameran and famtozinameran) in its authorised indications remains unchanged.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on myocarditis and pericarditis from the literature and spontaneous reports, the PRAC considers that the current warning on this risk should be amended to reflect the clinical course and outcome (including very rare fatal outcome) of Comirnaty associated myocarditis/pericarditis. The PRAC concluded that the product information of products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran should be amended accordingly.

Precise scope:

Update of section 4.4 of the SmPC to amend the warning/precaution regarding myocarditis and pericarditis and section 2 of the package leaflet accordingly.

The following changes to the product information of medicinal products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran are recommended (new text **underlined and in bold,** deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males **(see section 4.8)**. Available data **indicate** ~~suggest~~ that **most cases recover. Some cases required intensive care support and fatal cases have been observed.** ~~the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general (see section 4.8).~~

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Package Leaflet

- Section 2

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. **Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen.** Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

In addition, MAH should address the issue concerning the removal of the important potential risk VAED/VAERD, as detailed in section 2 of the Assessment report, in the next RMP update to be submitted within the next upcoming regulatory procedure affecting the RMP.

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM)

The MAH should also address the following issues in the next PSUR:

1. For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition;

HIV infection should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.

2. For future PSURs in the section 'Evaluation of Other Risks (not categorised as important)', the reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
3. For future PSURs in the section 'Evaluation of special situations', death (cases reporting fatal outcome) should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
4. For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
5. The MAH should present a case level analysis for all cumulative positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a TTO of <2 days. The MAH should discuss whether these events should be added in section 4.8 of the Comirnaty SmPC and PIL accordingly.

5. PSUR frequency

☒ Changes of PSUR frequency are proposed.

The current frequency of submission should be changed from 6 months to 1 year at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

Noting that the MAH has expressed a wish to stay aligned with the EURD, two additional 6-monthly PSURs (DLP June 2023 and DLP December 2023 respectively) will be submitted, then a first yearly PSUR (DLP December 2024), to be followed by further yearly PSURs.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the 4th PSUR for BNT162b2 (Comirnaty) covering the period 19 June 2021 to 18 December 2022, which is assessed in this report.

The active substance of BNT162b2 is highly purified single-stranded, 5'-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the viral spike 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 neutralizing antibody and cellular immune responses to the spike antigen, which may contribute to protection against COVID-19.

BNT162b2 was approved in the EU through a centralised procedure (conditional approval) on 21 December 2020 and is currently indicated for 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

No changes to the Comirnaty product information were proposed as part of the submission of the PSUR.

Rapporteur assessment comment:

During the interval period of the current 4th PSUR:

The Comirnaty Original indication was extended to children 6 months - 4 years old (Tris/Sucrose formulation, 3 micrograms per dose). (procedure EMEA/H/C/005735/X/0138).

Comirnaty became available as two adapted vaccines (only to be used in people who have received at least a primary vaccination course against the SARS-CoV-2 virus):

- In persons of 12 years and older, Comirnaty Original/Omicron BA.1 contains tozinameran and riltozinameran (another mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2), 15/15 mcg. (procedure EMEA/H/C/005735/II/0140)
- In persons of 12 years and older; Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran (another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2), 15/15 mcg. (procedure EMEA/H/C/005735/II/0143)
- In persons of 5 to 11 years, Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, 5/5 mcg. (procedure EMEA/H/C/005735/X/0147)

1.2. Worldwide marketing authorisation status

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK 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 countries for primary series and in 50 countries for booster;
  - in individuals aged between 12 and 15 years in 81 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.

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.

Rapporteur assessment comment: The provided information regarding the worldwide marketing authorisation status is noted.

1.3. Overview of exposure and safety data

1.3.1. 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.

Rapporteur assessment comment: The provided information is noted.

1.3.2. Changes to reference safety information

The reference safety information (RSI) for this PSUR is the Core Data Sheet (CDS) version 18.0 dated 05 Dec 2022, which is located in Appendix 1 of the PSUR. The 5 previous CDS versions (version 13.0 dated 10 May 2022, version 14.0 dated 26 Jul 2022, version 15.0 dated 31 Aug 2022, version 16.0 dated 08 Sep 2022, version 17.0 dated 06 Oct 2022) were also in effect during the reporting interval.

Safety-related changes to the RSI are presented in Appendix 1.1 of the PSUR (not reproduced here).

Rapporteur assessment comment: The EU SmPC of Comirnaty (version 24 Mar 2023 which is after the PSUR DLP of 18 Dec 2022) is in line with the CDS.

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively, 68,997 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates:

- BNT162b2: 57,505 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/ Seasonal inactivated influenza vaccine (SIIV); 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); 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); 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 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.
- Blinded therapy: 8958 participants.
- Placebo: 4018 participants.
- SIIV/placebo: 7 participants.

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;
- 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.

Post-marketing exposure

The number of doses cumulatively administered (as per public available data for the EU-EEA countries, the US, and Japan) 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, 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.

Worldwide exposure:

- Cumulative exposure:
    - Approximately a total of **4,369,782,515 doses of BNT162b2 (original and bivalent) were shipped** worldwide from the receipt of the first temporary authorisation for emergency supply on **01 Dec 2020 through 18 Dec 2022**, of which 3,974,026,615 were original and bivalent adult presentations (including PBS and Tris/Sucrose); 395,755,900 were original and bivalent paediatric 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 rest of world.
    - Table 8 below displays the cumulative EU/EEA published data with number of doses administered for each age group and by vaccine type:

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

- Table 9 through Table 11 of the PSUR (not reproduced here) 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).

- Interval exposure:
  - Approximately **813,783,710 doses of BNT162b2 original and bivalent vaccines were shipped** worldwide during the current reporting interval from **19 Jun 2022 through 18 Dec 2022**, of which 142,687,310 were original adult presentations (including PBS and Tris/Sucrose); 155,236,800 were original paediatric 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 rest of world.
  - Table 18 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

  - Table 19 (not reproduced here) 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).

Rapporteur assessment comment:

The MAH stated that 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 (ECDC website for Comirnaty original and bivalent doses administered in the EU-EEA countries).

Cumulatively, worldwide a total of 4,369,782,515 doses of Comirnaty were shipped.

During the reporting period, in the EU-EEA countries a total of 39,687,303 doses of Comirnaty were administered and cumulatively 520,820,597 doses.

The MAH should continue to report on the administered 1st, 2nd, 3rd ,4th , etc. doses of Comirnaty as presented in future PSURs.

1.3.4. Data in summary tabulations

Response to the PRAC request 8 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *After the DLP of the 3rd PSUR, Comirnaty has been variant updated (bivalent vaccines), approved and is currently being used in the EU. In light of this, 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. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent Comirnaty or, indeed, when comparing the two different variant updated bivalent Comirnaty vaccines, should be discussed.*

MAH's response: In Section 6.3.1.1 General Overview – All Cases, the incremental data are presented by original and bivalent presentations. Across the entire PSUR document, where possible, data are detailed by original and bivalent presentations.

Rapporteur assessment comment:

Noted.

A total of 283,301 case reports (309 from clinical trials and 282,992 from post-marketing) containing 839,246 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 508,351 case reports retrieved in the PSUR#3.

Clinical trial data (CT)

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.

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.

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 Dec 2022 (Table 23).

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/b2s 01/BT Cases (N=304) AEs (n=376)	All Cases [c] (N=2724) AEs (n=3578)	BNT162b1/BNT1 62b2/BNT162b2s 01/BNT162b3/BN T162c2/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 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).

MAH's conclusion: Based on the review of the CT cases, no new safety issues were identified.

Rapporteur assessment comment:

During the interval period, there were 309 cases reporting 381 adverse events (668 case reports in the previous 3rd PSUR). The most frequently reported serious adverse events (≥2% of the cases) in the clinical trials were unexpected: the proportion of Pneumonia (2.9%) and Respiratory syncytial virus infection (2.3%) was higher compared to their proportions in the cumulative dataset of 2.4% and 0.3%, respectively. However, all these serious adverse events were assessed as unrelated.

MAH's conclusion is endorsed that no new important safety information could be identified from the clinical trial data.

Post-authorisation data (PM)

Response to the PRAC request 1 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

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.

MAH's response: 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. There were 512 cases (0.2%, 26 serious and 486 non-serious) not included in the PSUR.

Rapporteur assessment comment:

The MAH stated that the number of processed cases downloaded from Eudravigilance was 99.8% of the total downloaded cases.

The MAH should continue only report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases decreases below 99%.

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%)

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.

A total of 838,865 AEs (of which 232,740 were serious and 606,521 non-serious) 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 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, 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 (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

MAH's 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.

Rapporteur assessment comment:

During the interval period, there were 282,992 cases reporting 838,865 adverse events (507,683 case reports in 3rd PSUR).

It is noted that all cases reporting adverse events were assigned to Comirnaty Original and/or bivalent BA.1 and/or bivalent BA.4/BA.5, and there were no case reports coded Comirnaty with 'not otherwise specified' (NOS) variant.

Also, noted is that of the most frequently reported serious adverse events (≥2% of the cases) in MAH's safety database the proportion of COVID-19 (19.2%), Drug ineffective (10.5%), and Vaccination failure (9.3%) was higher compared to their proportions in the cumulative dataset of 7.2%, 4.0% and 3.7%, respectively. However, less higher proportions than in the previous 3rd PSUR: COVID-19 (31.3%), Drug ineffective (17.6%), and Vaccination failure (16.1%).

Please refer concerning reports of COVID-19 and Drug ineffective/Vaccination failure to the COVID-19 AESIs (section Adverse events of special interest of this AR) and Lack of therapeutic efficacy (section Evaluation of special situations of this AR).

MAH's conclusion is endorsed that no new important safety information could be identified from the post-marketing data.

During the reporting period, the safety signal procedure concerning **Pemphigus and Pemphigoid** (EMEA/H/C/005735/SDA/061 - EPITT 19859) was ongoing. After DLP of this PSUR, PRAC (April 2023) considered that currently there is insufficient evidence to establish a causal association between Comirnaty and pemphigus and/or pemphigoid. The signal is closed and in the next PSUR, the MAH

should perform a review of all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to the vaccine, including data from clinical trials, post-marketing exposure and new scientific literature.

The safety signal procedures concerning **Corneal graft rejection** (EMEA/H/C/005735/SDA/055- EPITT 19789; continue closely monitoring through routine pharmacovigilance), **Histiocytic necrotizing lymphadenitis** (EPITT 19835; cumulative review in current PSUR#4), **Heavy menstrual bleeding** (EMEA/H/C/005735/SDA/053- EPITT 19783; added as an ADR in Comirnaty PI), **Angioimmunoblastic T-cell lymphoma (AITL)** (EPITT 19875; not confirmed signal, continue closely monitoring through routine pharmacovigilance), **Vulval ulceration** (EPITT 19840; continue closely monitoring through routine pharmacovigilance) were closed.

After DLP of the current PSUR, the safety signal procedure concerning **Myocarditis leading to disabling decompensated heart failure requiring heart transplantation** (EPITT 19712; not confirmed signal, continue closely monitoring through routine pharmacovigilance) was closed. The safety signal procedure concerning **Myositis** (EPITT 19883) is ongoing.

Booster dose

First booster is 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 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).

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).

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.

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.

Rapporteur assessment comment:
No new important safety information could be identified from the booster doses.

Batch-related issues

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

Rapporteur assessment comment:
MAH's conclusion is noted that no new important safety information could be identified from the batch-related issues.

Product quality analysis

MAH's 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.

Rapporteur assessment comment:
MAH's conclusion is noted that no new important safety information could be identified from the product quality analysis.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Clinical trials

Completed clinical trials

- Safety trials: During the reporting period, no interventional safety studies were completed with a final CSR.
- Efficacy trials: During the reporting period, no trials that reported new significant efficacy information were completed with a final CSR.

- Other 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.

Ongoing clinical trials

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

Safety trials:

- 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 information has emerged from this ongoing PASS.
- PASS C4591024 [A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age] is an ongoing PASS. No clinically important 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, 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, A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.
  - BNT162-01, A multi-site, phase I/II, 2-Part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults.
  - BNT162-14: 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.

  Bivalent vaccine

  - C4591031: 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 a SARS-CoV-2 monovalent and multivalent RNA vaccine 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.

Long-term follow-up

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

Other therapeutic use of medicinal product

BNT162b2 was also administered as study vaccine in another MAH-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.

New safety data related to fixed combination therapies

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

Rapporteur assessment comment:

No new important safety information was identified by the MAH from the clinical (safety and efficacy) trials concerning long-term follow-up, other therapeutic use of the product, or related to fixed combination therapies.

1.3.5.2. Findings from non-interventional studies

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

Completed non-interventional study

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 study

- During the reporting period, the study C4591019 was completed. No new safety information emerged from this non-interventional study.

Ongoing non-interventional studies

Safety Studies:

- The non-interventional studies C4591008,C4591009, C4591010, C4591012, C4591021 and C4591022 are PASS. No clinically important information has emerged from PASS.

Other Studies, 5 ongoing non-interventional studies:

- C4591006, General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).
- C4591014, Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.
- C4591025, 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.

Rapporteur assessment comment:

No new important safety information was identified by the MAH from non-interventional studies.

1.3.5.3. Information from other clinical trials and sources

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.

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

Rapporteur assessment comment: No new important safety information was identified by the MAH from other clinical trials.

Medication errors

Clinical trial data

- 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.

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.

MAH's 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.

Rapporteur assessment comment:

Clinical trial data

No cases indicative of a medication error were reported.

Post-marketing data

During the reporting period, an increased number of medication errors resulting in adverse reaction(s), 1670 cases (2.9%) compared to 1326 cases (2.0%) in the previous reporting period, were reported. However, no specific trend or pattern was observed.

No new important safety information could be identified regarding reported medication errors. Current risk minimisation measures are considered sufficient to minimize the potential for medications errors.

1.3.5.4. Non-clinical data

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

1.3.5.5. Literature

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.

Rapporteur assessment comment:

The MAH identified 18 clinical trials that presented important new safety findings for myocarditis after Comirnaty exposure, grouped as a) Booster (n=6); b) Special patient population (n=3); c) Clinical characteristics, severity, investigations (n=2) and d) Long-term data (n=7).

Please refer regarding the assessment of literature concerning new safety findings for myocarditis and pericarditis to section 2.3.1. 'Evaluation of important identified risks: Myocarditis and Pericarditis' of this AR.

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.

1.3.5.6. Other periodic reports

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

1.3.5.7. Lack of efficacy in controlled clinical trials

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

1.3.5.8. 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 Literature.

Rapporteur assessment comment:

Please refer regarding myositis to the separate ongoing safety signal procedure (EPITT 19883).

It is noticed that the study of Hause et al (2023) reported 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.

2. Signal and risk evaluation

2.1. Summary of safety concerns

The important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU RMP version 5.0 adopted 10-03-2022:

Ongoing Safety Concerns

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

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

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).

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]).

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.

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.

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.

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).

Rapporteur assessment comment:

During the reporting period, the important identified risk Anaphylaxis was removed from the list of safety concerns in the Comirnaty RMP.

2.2. Signal evaluation

Tabular overview of signals: new, ongoing or closed during the reporting interval 19-06-2022 to 18-12-2022:

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Pemphigus and Pemphigoid	25Nov22	Ongoing		Enquiry from a competent authority (EMA PRAC).	Signal opened following receipt of EMA PRAC Dec 2022 agenda alert that pemphigus and pemphigoid were to be discussed for Comirnaty at the upcoming PRAC meeting. Subsequently, EMA PRAC request was received to perform a cumulative review of cases of pemphigus and pemphigoid.	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Under evaluation.
Dizziness	23Jun22	Closed	27Jul22	Enquiry from a competent authority (EMA PRAC)	In PSUR #2 AR, EMA PRAC requested a cumulative review of cases reporting dizziness after Comirnaty exposure outside the context of anxiety/stress-related reactions.	Postauthorization safety data and clinical study safety data review.	MAH concluded that dizziness should be considered a reaction (an identified risk) Section 4.8 of the CDS was updated to add Dizziness as an ADR Note, this review of dizziness was included in PSUR #3 (Appendix 6A.1) and EMA PRAC endorsed the MAH conclusion. Procedure EMEA/H/C/005735/II/0152.
Haemophagocytic lymphohistiocytosis (HLH)	21Oct22	Closed	09Nov22	Routine signal detection activity for clinical trials.	Serious adverse event reported in a participant of a Pfizer sponsored COVID-19 vaccine clinical trial and of a participant of a dermatomyositis study who was reported to have received BNT162b2 (see Dermatomyositis below).	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis	Based on the totality of data, there is insufficient evidence to conclude a causal association between BNT162b2 and HLH. An update to product labeling is not warranted at this time. Routine monitoring will continue.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Dermatomyositis	23Sep22	Closed	16Nov22	Routine signal detection activity for clinical trials.	Information was shared from Pfizer colleagues about an SAE in a Pfizer-sponsored non-vaccine placebo-controlled clinical trial of an IMP for the treatment of dermatomyositis in which the study participant had attributed the dermatomyositis to BNT162b2 vaccination (see HLH above).	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and dermatomyositis. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Histiocytic necrotizing lymphadenitis (HNL)	26Aug22	Closed	31Aug22	Enquiry from a competent authority (EMA PRAC).	Signal opened following receipt of EMA PRAC Aug- Sep 2022 meeting agenda alert that HNL was to be discussed for Comirnaty at the upcoming PRAC meeting. Subsequently on 02 Sep 2022, MAH received an adopted PRAC recommendation that requested within the next PSUR (#4), a cumulative review HNL.	Postauthorization safety data, clinical study safety data, and literature review.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and HNL. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Genital (e.g., vulvovaginal) Ulceration	26Aug22	Closed	30Aug22	Enquiry from a competent authority (TGA and EMA PRAC).	In July 2022, opened as a safety topic and reviewed in response to TGA request to update the Adverse Effects section of the Comirnaty Australia PI to include nonsexually acquired genital ulceration as an adverse reaction. It was determined not to be a validated signal at that time. On 26 Aug 2022, re-opened as a validated signal in response to EMA PRAC request for a cumulative review in PSUR #4.	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and genital (e.g., vulvovaginal) ulceration. An update to product labeling is not warranted at this time. Routine monitoring will continue. Procedure EMEA/H/C/005735/SDA/056.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
IgA nephropathy	14Jul22	Closed	10Aug22	Enquiry from a competent authority (EMA PRAC).	In the PSUR #2 AR, EMAPR AC requested a cumulative review of cases reporting IgA nephropathy to be provided in PSUR #3.	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and IgA nephropathy. An update to product labeling is not warranted at this time. Routine monitoring will continue. Note, a cumulative review for glomerulonephritis/ nephrotic syndrome (Appendix 6A) was submitted with PSUR #3 and the EMA PRAC endorsed the MAH's conclusion.
Acquired Hemophilia	27Jun22	Closed	20Jul22	Enquiry from a competent authority (EMA PRAC).	In PSUR #2 AR, EMA PRAC requested a cumulative review of acquired haemophilia reported with the administration of Comirnaty.	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and acquired hemophilia. An update to product labeling is not warranted at this time. Routine monitoring will continue. Note, the review of acquired hemophilia was included in PSUR #3 (Appendix 6A.2) and EMA PRAC endorsed the MAH conclusion.
Hearing Loss	31May22	Closed	20Jul22	Enquiry from a competent authority (EMA PRACHealth Canada).	Following their review of the 3rd Bimonthly Safety Report, Health Canada requested MAH to provide a cumulative review of tinnitus and hearing loss. Following their review of the 3rd Bimonthly Safety Report, EMA PRAC requested MAH to perform a cumulative review on sudden sensorineural hearing loss and Comirnaty exposure, to be provided in PSUR #3.	Postauthorization safety data, clinical study safety data, medical literature, and O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and hearing loss. An update to product labeling is not warranted at this time. Routine monitoring will continue. Note, a review of hearing loss was included in PSUR #3 (Appendix 6A.3) and EMA PRAC endorsed the MAH conclusion.

Rapporteur assessment comment:

During the interval period, the safety signal procedure concerning heavy menstrual bleeding (EMEA/H/C/005735/SDA/053- EPITT 19783) was closed and Heavy menstrual bleeding with frequency Not known was added as an ADR in Comirnaty PI.

After DLP of the current PSUR, the safety signal procedure concerning **Myocarditis leading to disabling decompensated heart failure requiring heart transplantation** (EPITT 19712; not confirmed signal, continue closely monitoring through routine pharmacovigilance) was closed. The safety signal procedure concerning **Myositis** (EPITT 19883) is ongoing.

Other safety topics not considered signals

Multisystem Inflammatory Syndrome (MIS-C/-A)

Response to the PRAC request 2 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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.*

MAH's response

Introduction (Appendix 5.6.1 of the PSUR)

In August 2021, the EMA issued a signal assessment report on MIS-C with SARS-CoV-2 vaccination and requested all MAH of these vaccines perform cumulative review of MIS-C and MIS-A.

A cumulative review of cases reported within MAH's global safety database was performed with a DLP of 02 September 2021. Analysis of these cases, in conjunction with observed to expected analysis did not support a causal relationship between Comirnaty and MIS-C/-A. In concordance with MAH's assessment the PRAC agreed that the signal be closed and that no update to the product information is currently warranted.

PRAC requested the MAH continue to closely monitor MIS-C/-A and report on new cases in the MSSR and PSUR. Cases were requested to be assessed using the Brighton Collaboration (BC) case definition[1] with MIS-C defined as patients age <21 years and MIS-A those age ≥21 years.

Interval cases have subsequently been analysed and discussed in the following aggregate safety documents:

- MSSR #11 (interval 03 September through 26 October 2021),
- SBSR #1 (interval 27 October through 15 December 2021)
- PSUR#2 (interval 19 June through 18 December 2021)
- SBSR #2 (interval 16 December 2021 through 15 February 2022)
- SBSR #3 (interval 16 February through 15 April 2022)
- PSUR #3 (interval 19 December 2021 through 18 June 2022)

In accordance with the PRAC request, retrieved cases meeting BC level 1 (definitive), 2 (probable) and 3 (possible) case definition criteria are presented in this review.

Methodology

The safety database was searched for all BNT162b2; BNT162b2, BNT162b2 OMI BA.1 and BNT162b2, BNT162b2 OMI BA.4-5 cases reporting MedDRA v25.1 PTs; Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Multiple organ dysfunction syndrome, Systemic inflammatory response syndrome, Cytokine release syndrome, Distributive shock reported through 18 December 2022.

Results

A cumulative total of 710 cases have been retrieved using the search strategy outlined above through 18 December 2022; 106 new cases since the DLP of PSUR#3 (18 June 2022). In 12 cases, the original ICSR was received prior to the PSUR#4 data period however follow-up information received allowed coding of new PTs which then identified them in the current database search for PSUR#4 (7 BC level 5, 3 BC level 4 and 2 insufficient information). Two literature cases ([redacted] and [redacted]) although not processed to completion in the safety database by the time of data-lock for PSUR#4, are summarised below in order to present and analyse the totality of available data.

AER # [redacted] (15-year-old male, [redacted], pre-print literature article)[2]

Fifty days after receiving dose 2 the patient attended hospital complaining of fever and chest pain. Body temperature 39.8°C, BP 109/69mmHg, bilateral conjunctival hyperemia. ECG showed "suspected myocarditis" with ST abnormalities in leads II, III, aVF, V5 and V6. Echocardiography showed no pericardial effusions and no coronary dilatation. Cardiac MRI showed a LVEF 49%. "SARS-CoV-2 from a nasopharyngeal swab was negative for the nucleocapsid protein antibody and positive for the SARS-CoV-2 spike protein antibody". Initial PCR of blood samples; negative for enterovirus, adenovirus, parvovirus B19. Per the reporter, the possibility of Yersinia infection could not be eliminated. CRP 7.12 mg/dl, AST 70, ALT 173, BNP 5.8pg/ml, troponin I <0.007ng/ml, WBC 11.2x103/l (neutrophils 73.9%, lymphocytes 17.1%), platelets 14.7x104/l. After admission the patient also complained of abdominal pain and diarrhoea, with fever disappearing the day after admission. The patient's chest pain persisted with increased troponin (1.664ng/ml) and subsequent echo revealing global longitudinal strain of 13% and abnormal wall motion in the anteroseptal at the base. The troponin peaked the day after admission and gradually decreased. The chest pain was improved by acetaminophen without need for IVIG administration. On the 8th day of admission, a cardiac MRI revealed EGE in the anteroseptal at the base in a similar region as echocardiography. One month after discharge the chest pain had not recurred, and ECG changes were improved.

MAH comment; this case has been classified as BC level 2b, a probable case of MIS-C. The statement in this pre-print article regarding SARS-CoV-2 testing is unclear but it appears that the patient may be negative for anti-nucleocapsid antibodies. A significant confounding element in this case is that Yersinia infection could not be excluded; gastrointestinal symptoms, fever, and rarely myocarditis, have been associated with Yersinia infection.

Rapporteur assessment comment:
MAH conclusion is endorsed, the case should be considered MIS-C BC level 2b which is confounded by an Yersinia infection.

AER #202201392709 (15-year-old, male, Turkey, literature article)[3]

The patient, reported to be previously healthy, presented to the ED with fatigue, myalgia, fever (38.3°C) and pain in the chest five days after dose 2 of BNT162b2. He had no history of recent viral illness symptoms and no known COVID-19 exposures. ECG revealed ST elevation and an elevated troponin I of 1410ng/l (NR <14ng/L). Inflammatory markers were elevated: CRP 103.2mg/l, ESR 51mm/h, ferritin 530ug/l with D-dimer 0.78mg/l (NR <0.55mg/L), AST 11U/L (NR <40U/L), ALT 54 (NR <41U/L). Echocardiography was normal with an EF of 68% and a "fractional shortening of 33%". A nasopharyngeal swab was PCR negative for SARS-CoV-2, "all other viral diagnostic studies were negative". Serology reports negative SARS-CoV-2 spike antibody, anti-nucleocapsid antibody is not reported. The patient received IVIG, IV methylprednisolone (3 days) then a 2-week oral prednisolone taper. On day 3 of hospitalization the patient was well and ST elevation had resolved. On day 9 of hospitalization the patient's troponin I and inflammatory markers had returned to normal.

MAH comment; this literature case is reported as MIS-C however, the duration of fever is unclear and fatigue is the only clinical feature reported so the case does not meet the diagnostic criteria of a level 1-3 case. It is therefore classified as BC level 4. Anti-nucleocapsid antibody is not reported and there is a limited description of the patient's clinical examination or investigations for alternative aetiologies.

Rapporteur assessment comment:

MAH conclusion is endorsed, the duration of the fever is unclear and the case should be considered BC level 4.

Ninety-two cases met the PSUR criteria and are included in the analysis of the post-marketing data of the PSUR period. In six cases the patient's age was not reported; 4 of these reported such insufficient information as to preclude a meaningful assessment of the case, and 2 cases were categorised as BC level 5.

MIS-C

Twenty-three cases occurred in patients aged <21 years and therefore were classified in consideration for MIS-C:

Table 1. BC classification of potential MIS-C cases

BC classification	Number of cases
1	9
2	3
3	2
4	6
5	3

BC Level 1 cases: definitive cases of MIS-C

Nine cases were classified as BC level 1 and are presented in Table 2 (see below in comment box). There were no cases retrieved in association with BNT162b2, BNT162b2 OMI BA.1 or BNT162, BNT162b2 OMI BA.4-5 in patients <21 years old.

Rapporteur assessment comment:

Please refer regarding the assessment of the 9 MIS-C BC level 1 cases to the PRAC Rapporteur's comments in:

MIS-C Table2.pdf

The 9 MIS-C BC level 1 cases were considered possible related to Comirnaty exposure (n=2), unlikely related (n=6) or unassessable (n=1).

BC Level 2 cases: probable cases of MIS-C

Three cases were classified as BC level 2b and are presented in Table 3 (see below in comment box).

Rapporteur assessment comment:

Please refer regarding the assessment of the 3 MIS-C BC level 2b cases to the PRAC Rapporteur's comments in:

MIS-C Table3.pdf

The 3 MIS-C BC level 2b cases were considered possible related to Comirnaty exposure (n=1) or unlikely related (n=2).

Cases classified as BC Level 3: possible cases of MIS-C

Two cases were classified as BC level 3b, possible cases of MIS-C and are presented in Table 4 (see below in comment box).

Rapporteur assessment comment:

Please refer regarding the assessment of the 2 MIS-C BC level 3b cases to the PRAC Rapporteur's comments in:

MIS-C Table4.pdf

The 2 MIS-C BC level 3b cases were considered unlikely related to Comirnaty exposure (n=1) or unassessable (n=1).

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 23 potential new MIS-C cases. Of these, 9 were classified as BC level 1, 3 as BC level 2, 2 as BC level 3, 6 as BC level 4, and 3 as BC level 5.

Of the 9 MIS-C BC level 1 cases, 2 cases were considered possible related to Comirnaty exposure, 6 cases unlikely related and 1 case unassessable.

Of the 3 MIS-C BC level 2b cases, 1 case was considered possible related to Comirnaty exposure and 2 cases unlikely related.

Of the 2 MIS-C BC level 3b cases, 1 case was considered unlikely related to Comirnaty exposure and 1 case unassessable.

MIS-A

Sixty-three cases were in patients aged greater than or equal to 21 years and were classified in consideration of MIS-A. Seven cases reported insufficient information, precluding a meaningful assessment of the case.

Four cases were retrieved for Bivalent BNT162b2, BNT162b2 OMI BA.4-5 and three cases for Bivalent BTN162b2, BNT162b2 OMI BA.1, all were classified as BC level 5. Table 5 demonstrates the BC classification of the 56 cases classified in consideration of MIS-A.

Table 5. BC classification of potential MIS-A cases

BC level	Number of cases
1	2
2	1
3	0
4	11
5	42*

*3 cases BNT162b2, BNT162b2 OMI BA.1, 4 cases BNT162b2, BNT162b2 OMI BA.4-5

BC Level 1 cases: definitive cases of MIS-A

Two cases were classified as BC level 1 cases, both from literature sources. The cases are presented below:

AER #: [redacted]

52/male, [redacted] Literature source[12]

Reported PTs: Multisystem inflammatory syndrome. No significant medical history or concomitant medications.

Dose 2: 20 days before onset of symptoms. The patient presented with a 4-day history of fever, headache, dizziness, vomiting and complained of anterior chest pain. He had no prior history of confirmed or suspected COVID-19 and no close contact with a known COVID-19 case within 12 weeks. Physical examination revealed bilateral nonexudative conjunctivitis. No rash/erythema. The patient was hypotensive (BP 66/47 mmHg), tachycardic (HR 110 beats/min), respiratory rate of 22/min, and body temperature of 38.2° C. Laboratory findings showed leukocytosis (neutrophilia) with left shift and lymphopenia, an increase in inflammatory markers (PCT 0.92ng/ml, ESR 49mm/h), hepatic enzymes, NT-proBNP (941 pg/mL, NR 5-900), and D-dimer. Normal troponin. Negative SARS-CoV-2 PCR test following a nasopharyngeal and throat swab. Respiratory virus panel, including RSV and influenza, was also negative. CT imaging of the chest and abdomen revealed enlarged lymph nodes with soft tissue infiltrations in the left axilla and mesentery. Hypotension persisted despite adequate fluid resuscitation and norepinephrine infusion was required. The patient was admitted to the ICU and treated with antibiotics (ceftriaxone) and high-flow oxygen therapy. Despite empirical antibiotics and supportive therapy, on HD 3 he was hypoxic, his laboratory tests deteriorated and urine output decreased to less than 0.5 mL/kg/h. Transthoracic ECHO showed normal cardiac chamber dimension, preserved LV contractility without regional wall motion abnormalities (global LVEF 53%), and no evidence of

vegetations, a moderate amount of pericardial effusion was found. Lower extremity CT angiography and lung perfusion scan revealed no thrombosis.

The initial blood cultures, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and serology for various viral infections, leptospirosis, and rickettsial disease were all negative. Peak transaminitis on hospital day 6 (ALT 5151 IU/l, AST 8556 IU/l), peak CRP 139.06mg/l, serum ferritin peak 30165ng/ml (NR 23-336.2).

The patient was commenced oral prednisolone, colchicine and LMWH thromboprophylaxis. Within the first 24 hours, all clinical symptoms and signs showed dramatic improvement. On HD 7, a repeated transthoracic ECHO showed a decrease in pericardial effusion to a small amount, and no other new findings were observed. The laboratory findings also gradually normalized over 2 weeks and the patient was discharged on HD 15. Prednisolone was tapered over 2 months and colchicine was administered for a total of 3 months. At the 2-month follow-up after discontinuation of all medications, the patient was still in good condition and all laboratory findings were within normal range.

MAH's comment: Onset 20 days from dose 2 and although SARS-CoV-2 PCR test was negative there is no report on serology. Given that COVID-19 is the current known precipitant of MIS-A the absence of detail on serology precludes a meaningful assessment of causality. There are some unusual features reported; a markedly elevated serum ferritin (30165ng/ml) and imaging evidence of enlarged lymph nodes and "soft tissue infiltrations" in the left axilla and mesentery. The transaminases are also markedly elevated which may reflect hepatic shock secondary to hypotension but a search for other aetiologies (e.g., liver US) have not been reported.

Rapporteur assessment comment:

Although MAH's comment is acknowledged, the presented MIS-A case is considered BC level 1 and considered probably related with Comirnaty (no history of COVID-19, negative tests COVID-19 and other infections). However, a coincidental finding cannot be excluded either, given the extensive exposure of Comirnaty in adults.

AER #[redacted]

22-year-old, female, United Kingdom. Literature source[13]

Reported PT: Multisystem inflammatory syndrome in adults. Medical history and concomitant medications were not reported.

The patient presented to hospital with headache, neck pain, vomiting, diarrhoea, abdominal pain, photophobia and malaise two days after dose 2 BNT162b2. She had no history of previous COVID-19 infection. On presentation to ED: tachycardic and pyrexial, BP normal. Suspected to have meningitis and treated with ceftriaxone and acyclovir. CSF sampling was unremarkable. The patient deteriorated on day 3 with persistent fever, tachycardia, severe hypoxia, lactatemia and hypotension unresponsive to IV fluids. She was admitted to ICU and managed with high-flow nasal oxygen and vasopressors, she quickly fatigued and was intubated and ventilated. Rapid and progressive multisystem failure occurred over the next 18 hours manifesting as hypotension, hypoxia, azotemia with oliguria, non-absorption of feeds and diarrhoea. An ECHO showed well filled but poorly contracting right and left ventricles so she was commenced on dobutamine. Renal dysfunction was initially managed conservatively but in view of severe metabolic acidosis, oliguria, azotemia and progressive severe hyperpyrexia she was commenced on hemofiltration. CT chest/abdomen was performed as the working diagnosis was severe sepsis. This

showed multiple enlarged mesenteric lymph nodes but no other abnormalities. The patient was moribund and after discussion with the surgical team a diagnostic laparoscopy was performed; this showed multiple enlarged mesenteric lymph nodes, minimal ascites and a small ovarian cyst. Lymph node biopsy: " suggestive of marked suppurative inflammation with background acute vasculitic changes though to be secondary to the initial inflammatory insult. It was felt this was compatible with a diagnosis of MIS-A" . No source of sepsis could be identified and all microbiological sampling was negative. Three negative PCR tests excluded active COVID-19 infection. CMV and EBV IgG and IgM were both positive but thought to be nonsignificant. Broad-spectrum antibiotics (ciprofloxacin, vancomycin and meropenem) had been administered for > 24 hours without clinical improvement. Following MDT discussion it was decided that the presentation correlated with a diagnosis of MIS-A and the patient was commenced on treatment with IVIG and methylprednisolone for 5 days. There was rapid improvement in the clinical picture with resolution of hyperpyrexia, cardiovascular instability and decreasing oxygen requirements within 36 hours of commencing treatment. The patient significantly improved and was successfully extubated on day 7 of ICU admission. Repeat ECHO showed return of normal ventricular function and she made a full recovery and was discharged home on day 13 postadmission. COVID-19 antibodies "were positive - possibly from the vaccination or representing previous infection". Macrophage activation syndrome was considered in view of the mildly elevated ferritin but there was no evidence of hypofibrinogenemia or cytopenias in more than two lineages.

MAH's comment: Although PCR tests were negative, it is unclear from the reported SARS-CoV-2 serology whether the patient had anti-nucleocapsid antibodies. The report states that COVID-19 antibodies COVID-19 antibodies "were positive - possibly from the vaccination or representing previous infection". Given that COVID-19 is the current known precipitant of MIS-C the absence of detail on these casts doubts on vaccine causality. The lymph node biopsy results may suggest an alternative inflammatory/infectious aetiology.

Rapporteur assessment comment:
MAH's comment is acknowledged, the presented MIS-A case is considered BC level 1 and considered unlikely related with Comirnaty. COVID-19 antibodies were reported positive and the lymph node biopsy results may suggest an alternative inflammatory/infectious aetiologies.

BC Level 2 case: probable case of MIS-A

One case, from a literature source[14], was classified as BC level 2 - a probable case of MIS-A:

AER # PV202200020010. Male, "in his forties" , United States.

Dose 2; 4 weeks prior to onset of symptoms. The patient presented to hospital complaining of 1 day of fever, sore throat, abdominal pain associated with loose stools and a diffuse erythematous rash. The rash was non-tender, non-pruritic, blanching, and had progressed from his right thigh to include diffuse areas of his chest, abdomen, back, and the palms and soles of his hands and feet. He denied prodromal symptoms prior to the onset of rash and denied prior COVID-19 infection. SARS-CoV-2 RT-PCR assay of a nasopharyngeal swab specimen was negative. A presumptive diagnosis of bacterial pharyngitis was considered and throat specimens were obtained for culture. He was prescribed a short course of oral amoxicillin and released without hospital admission.

Three days later, the patient returned to the hospital complaining of persistent fever, sore throat, non-productive cough, ongoing abdominal pain and loose stools, worsening rash, and new onset painful joint swelling in the hands and feet. He reported full compliance with recently prescribed amoxicillin.

Examination revealed extension of the erythematous rash to encompass both thighs and approximately half of the torso and chest surface. Symmetric involvement of the palms and soles of the hands and feet was present. Conjunctival injection without exudate was present bilaterally and oral examination revealed angular cheilitis, erythematous strawberry tongue, dry mucous membranes without ulceration and enlarged tonsils without exudate. Diffuse cervical lymphadenopathy was present. Joint examination revealed bilateral shoulder pain on passive range of motion testing, swelling and tenderness in bilateral wrists, bilateral proximal phalangeal joints associated with inability to make a fist, bilateral ankles and bilateral metatarsophalangeal joints associated with difficulty walking. Laboratory results on admission: lymphopenia, transaminitis, increased alkaline phosphatase and GGT. Increased fibrinogen and D-Dimer. Increased ferritin (858ng/ml). Elevated ESR (58mm). Normal troponin. Normal BNP. Negative ANA, mildly elevated RF (17.1 IU/ml - NR 0-14). Blood and urine cultures: no growth. SARS-COV-2 serology: positive anti-spike, negative anti-nucleocapsid antibodies.

Empiric antibiotic therapy with oral doxycycline was initiated on the first day of hospitalisation. Symptoms persisted despite antibiotic treatment, including fever to a maximum temperature of 38.9° C. Daily aspirin and a 3-day course of IVIG were initiated on the second day of hospitalisation. Over the ensuing 6 days sustained defervescence and progressive abatement of rash were observed, marked by desquamation of the palms and soles. Reduced swelling and return of full range of motion in the joints of hands and feet accompanied resolution of the rash. Tongue erythema and conjunctival injection resolved over a period of 5 days following initiation of IVIG. Oral prednisone was initiated on the fifth day, following completion of IVIG. Laboratory analysis on the fifth day of hospitalisation revealed reduced inflammatory markers and mild thrombocytosis that peaked on the seventh day. A transthoracic ECHO performed on the second day revealed no evidence of cardiac dysfunction, and CT coronary angiogram performed on the seventh day did not demonstrate coronary aneurysms or stenosis. On discharge from acute care on the seventh day of hospitalisation, the patient reported significant improvement in symptoms including complete resolution of fever, joint pain, abdominal pain and erythematous rash. Painless desquamation of the palms and soles of the hands and feet was present. The patient was instructed to continue daily aspirin and complete a taper of oral prednisone over 3 weeks. One month after discharge the patient reported sustained resolution of symptoms, though did demonstrate ongoing painless desquamation of the palms and soles. Two months after discharge the patient reported resolution of desquamation. Laboratory analysis revealed resolution of thrombocytosis and normalisation of inflammatory markers.

MAH's comment: This is classified as a BC level 2a case as there is only one measure of disease activity (normal cardiac biomarkers and echo). SARS-CoV-2 serology showed a negative antinucleocapsid antibody, and negative PCR tests, suggesting no prior COVID-19 infection. It is noteworthy that the patient was initially considered for a bacterial pharyngeal infection; the results of throat swab are not reported and the constellation of symptoms would be compatible with a Streptococcal infection/reactive arthritis; strawberry tongue, rash (with subsequent desquamation), reactive arthritis.

Rapporteur assessment comment:

MAH's comment is acknowledged, the presented MIS-A case is considered BC level 2a and considered possible related with Comirnaty. SARS-CoV-2 serology showed a negative anti-nucleocapsid antibody, and negative PCR tests, suggesting no prior COVID-19 infection. However, alternative diagnoses/causes were not excluded.

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 63 potential new MIS-A cases. Of these, 2 was classified as BC level 1, 1 as BC level 2, 0 as BC level 3, 11 as BC level 4, and 42 as BC level 5 (of which 3 cases after Comirnaty Original/Omicron BA.1, 4 cases Comirnaty Original/Omicron BA.4-5.

Of the 2 MIS-A BC level 1 cases, 1 case was considered probable related to Comirnaty exposure and 1 case unlikely related.

The MIS-C BC level 2a case was considered possible related to Comirnaty exposure.

MAH's conclusion

In summary, 92 cases were analysed for potential MIS for the PSUR period 19 June through 18 December 2022. Two additional literature cases were analysed to provide the totality of available post-marketing data. Twenty-three cases were classified as BC Level 1-3 MIS-C cases and three as BC level 1-3 MIS-A cases. As highlighted in the individual case commentaries, in the majority of cases there are either confounding elements or important clinical detail is missing which would facilitate causality assessment.

Considering the totality of the data, including the number of reports received in the context of the billions of doses of vaccine administered, the MAH does not consider that the currently available information supports a causal association between MIS-C/A and Comirnaty. No updates to current labelling or the Risk Management Plan are warranted at this time. Routine pharmacovigilance on this topic will continue and further updates will be provided if warranted.

Rapporteur assessment comment:

MIS-C

During the reporting period, the MAH identified a total of 23 potential new MIS-C cases. Of these, 9 were classified as BC level 1, 3 as BC level 2, 2 as BC level 3, 6 as BC level 4, and 3 as BC level 5.

Of the 9 MIS-C BC level 1 cases, 2 cases were considered possible related to Comirnaty exposure, 6 cases unlikely related and 1 case unassessable.

Of the 3 MIS-C BC level 2b cases, 1 case was considered possible related to Comirnaty exposure and 2 cases unlikely related.

Of the 2 MIS-C BC level 3b cases, 1 case was considered unlikely related to Comirnaty exposure and 1 case unassessable.

Cumulatively, there are still only 2 MIS-C BC level 1 cases (Danish index case and literature case from New-Zealand) which are considered probably related to Comirnaty exposure which is given the extensive exposure of Comirnaty (in children) not to be considered unexpected and does not present a new safety concern.

MIS-A

During the reporting period, the MAH identified a total of 63 potential new MIS-A cases. Of these, 2 was classified as BC level 1, 1 as BC level 2, 0 as BC level 3, 11 as BC level 4, and 42 as BC level 5 (of which 3 cases after Comirnaty Original/Omicron BA.1, 4 cases Comirnaty Original/Omicron BA.4-5.

Of the 2 MIS-A BC level 1 cases, 1 case was considered probable related to Comirnaty exposure and 1 case unlikely related.

The MIS-C BC level 2a case was considered possible related to Comirnaty exposure.

Cumulatively, two BC level 1 MIS-A cases (MIS-A BC level 1 case from the 3rd PSUR and current BC level 1 case) are considered probably related with Comirnaty, due to the absence of other aetiologies or confounding. However, given the extensive exposure of Comirnaty in adults this is not considered unexpected and does not present a new safety concern.

Based on the data provided, no new important information could be identified concerning MIS-C/-A. The data is currently insufficient to support regulatory action and therefore no update of the product information in relation to MIS-C/-A is currently warranted.

The MAH should continue to closely monitor this safety issue as outlined in PRAC's signal recommendation (EPITT 19732) and all new cases of MIS-C/-A including a WHO causality assessment should be reported in the future PSURs.

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Dyspnoea; Palpitations, Tachycardia/Heart Rate Increase

Response to the PRAC request 9 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *The MAH should present cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase, with special focus on the duration of the events not considered stress/anxiety-related reactions. The MAH should evaluate whether these events should be added in the section 4.8 of the Comirnaty SmPC.*

MAH's response (Appendix 5.6.2 of the PSUR):

Methodology

In order to focus on events of dyspnoea, palpitations, and tachycardia/increased heart rate reported to the MAH safety databases that are least likely to represent an immediate or stress/anxiety related event, the analysis focused on cases describing these events from 2 through 21 days post vaccination. An overview of all cases coded with any of these PTs is presented initially.

The duration of each event is calculated as the difference between the onset and cessation dates and, therefore, can only be calculated for events having a clinical outcome of resolved or resolved with sequelae.

The latency or TTO of the event from vaccination is the difference in days between the last vaccine administration date and the event onset date; similar to duration, TTO can only be calculated for events with full dates reported. Section 4.4 of the EU-SmPC provides the following information about stress or anxiety based reactions to the process of vaccination:

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g., dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

While the events of dyspnoea, palpitations and tachycardia/increased heart rate may occur in the setting of vaccination stress/anxiety, they may also occur as symptoms of a hypersensitivity reaction to the vaccine. Both anxiety-related responses and hypersensitivity responses to vaccine/vaccination are adequately addressed in the EU-SmPC. This review was undertaken to determine if the events should be considered causally-associated vaccine reactions outside of those scenarios.

Clinical trial database review

Clinical trial adverse events reported from dose 1 to 1 month after dose 2 in the placebo-controlled phase of the large pivotal MAH-run study (C4591001) showed the following in placebo (N=21,921):

- Dyspnoea was reported in 6 (<0.01%) of participants in the COMIRNATY group and 10 (<0.01%) of participants in the placebo group.
- Palpitations was reported in 6 (<0.01%) of participants in the COMIRNATY group and 14 (0.1%) of participants in the placebo group.
- Tachycardia was reported in 13 (0.1%) of participants in the COMIRNATY group and 6 (<0.01%) of participants in the placebo group.
- Heart rate increased was reported in 4 (<0.01%) of participants in the COMIRNATY group and 2 (<0.01%) of participants in the placebo group.

Overall, these events were reported very rarely in the pivotal clinical trial with no meaningful difference between the vaccine and placebo groups. Because these events may be attributed to vaccination stress/anxiety reactions, their very rare occurrence in the trial and lack of differentiation between vaccine and placebo groups is what one would expect in voluntary study participants (i.e., no anxiety around the vaccination process). If, on the other hand, these events were attributable to the vaccine product, one would expect the events to have occurred more frequently and to see a difference in occurrence frequency between participants receiving vaccine versus those receiving placebo in this large clinical trial.

Rapporteur assessment comment:

The large randomised placebo controlled clinical trial C4591001 (n=21,921) showed no meaningful differences between the vaccine and placebo groups concerning dyspnoea, palpitations, tachycardia and increased heart rate.

Safety database review

Overall Cases: Dyspnoea, Palpitations, Tachycardia and/or Heart rate increased

Search criteria - The search of the safety database was conducted for all BNT162b2 vaccines (original and bivalent presentations) for cases with any of the following PTs (MedDRA v. 25.1): Dyspnoea, Palpitations, Tachycardia, Heart rate increased.

The search retrieved 117,173 cases (17 CT cases and 117,156 PM cases); upon review, 6 PM cases involving babies were excluded from further consideration because they reflected indirect exposure (transplacental/trans-mammary) to vaccine.

Clinical Trial Data

- Number of cases: 17 (BNT162b2 [10] and Blinded therapy [7], representing 0.6% of 2724 cases of the total CT dataset).
- Subjects' gender: female (8), male (9).
- Subjects' age in years: n=17, range: 18-84, mean: 62.2, median: 64.0.
- Country/region of incidence: US (13), Argentina (2), Israel and South Africa (1 each).
- Number of relevant events: 17.
- Reported relevant PTs: Dyspnoea (12), Tachycardia (3) and Palpitations (2). Out of these, only one occurrence of Tachycardia was considered related to BNT162b2 by the Investigator.
- Case outcome: fatal (1), resolved (15), resolved with sequelae (1).

Post-Authorisation Data

- Number of cases: 117,150 (6.6% of 1,766,357 cases of the total PM dataset).
- MC cases (45,896), NMC cases (71,254).
- Subjects' gender: female (82,155), male (32,550) and unknown (2445).
- Subjects' age in years: n=110,358, range: 0.12-111, mean: 44.4, median: 43.0.
- Country/region of incidence (≥2%): Germany (24,320), UK (14,723), France (8623), US (8498), Australia (7265), Netherlands (5873), Italy (5702), Japan (5426), Sweden (3575), Mexico (3181), Norway (2536); the remaining 27,428 cases were distributed among 100 countries.
- Number of relevant events: 141,737.
- Reported relevant PTs: Dyspnoea (64,781), Palpitation (35,021), Tachycardia (28,636), Heart rate increased (13,299).
- Case outcome: fatal (1782), resolved/resolving (50,457), resolved with sequelae (3466), not resolved (48,525).

Summary

Cases of dyspnoea, palpitations, tachycardia and increased heart rate comprised <1% of CT cases and 6.6% of post-authorization reports. In both the CT and PM setting, dyspnoea was the most commonly reported of the PTs of interest. Males and females reported the PTs equally in the CTs however, similar to most non-serious AEs reported spontaneously, females were more likely than males to report.

Rapporteur assessment comment: Retrieved were 17 clinical trial cases and 117,150 post-marketing cases reporting dyspnoea, palpitations, tachycardia and/or increased heart rate.

Dyspnoea

Search criteria - PT: Dyspnoea.

The search of the safety database retrieved 64,797 relevant cases (12 CT cases and 64,785 PM cases); upon review, 4 PM cases involving babies were excluded from further consideration because they reflected indirect exposure (transplacental/trans-mammary) to the vaccine.

Clinical Trial Data

- Number of relevant cases: 12 (BNT162b2 and Blinded therapy [6 each]).
- Subjects' gender: female (6), male (6).
- Subjects' age in years: n=12, range: 45-84, mean: 66.2, median: 66.5.
- Country/region of incidence: US (10), Israel and South Africa (1 each).
- Medical history (n=11): the reported relevant2 medical conditions included Seasonal allergy (4), Myocardial infarction and Obesity (3 each), Anxiety, Chronic obstructive pulmonary disease and Coronary artery disease (2 each), Angina pectoris, Asthma, Asthma exercise induced, Cardiac failure congestive, Coronary artery bypass, Dyspnoea, Myocardial ischaemia, Obstructive sleep apnoea syndrome, Oesophageal stenosis and Restrictive pulmonary disease (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of Dyspnoea events: 12, all assessed by investigator as unrelated to BNT162b2 or blinded therapy. In 11 cases, it was the only SAE reported.
- Time to dyspnoea onset: n=11, range: 1-231 days, mean: 141.1 days, median: 152 days.
- Duration of dyspnoea: n=9, range: 4-72 days, mean: 20.2 days, median 10 days:

- 4-7 days: 3 events;
- 8-14 days: 3 events;
- 15-21 days: 1 event;
- ≥22 days: 2 events.

- Dyspnoea outcome: fatal (1), resolved/resolving (10), resolved with sequelae (1).

This case was of a 47-year-old male in Substudy D of C4591031 in South Africa who had no reported medical history. He received BNT162b2 vaccine as follows: Dose 1 (17 Sep 2021), dose 2 (15 Nov 2021), dose 3 (28 Mar 2022), dose 4 (25 Apr 2022). He also had 3 potential COVID-19 illness visits: Visit 1 (10 May 2022) due to moderate cough, headache and nasal congestion which resolved 12 May 2022, his vitals were normal and COVID-19 test was negative; Visit 2 (16 Jun 2022) due to moderate shortness of breath, headache, fever and sore throat which resolved on 23 Jun 2022, his nasal swab was positive for COVID-19; Visit 3 (17 Jul 2022) due to moderate dyspnoea especially at night, fever, sore throat which resolved on the same date, vitals were normal and nasal swab was negative for COVID-19. The participant' s first available imaging studies appear to be associated with a hospital admission in early October 2022 when he had a chest X-ray consistent with pulmonary oedema and an echocardiogram (dated 28 Sep 2022) that showed dilated cardiomyopathy with an ejection fraction of 26%. Shortly following admission, the participant died, and his reported cause of death was dilated cardiomyopathy and pulmonary oedema; no autopsy was performed. The investigator reported that it was likely the participant had viral myocarditis post COVID-19 infection on 16 Jun 2022; he assessed the death as not related to vaccine.

Overall, there were limited reports of dyspnoea in the clinical trials during the reporting period. Most events occurred at least 21-days post vaccination; duration, when reported, had a wide range of 4-72 days. The information is not supportive of dyspnoea being caused by the vaccine or the act of vaccination mainly due to the long latency between vaccination and dyspnoea and lack of biological plausibility.

Post-Authorisation Data

- Number of cases: 64,781 (BNT162b2 original [64,4746], BNT162b2 original + Omi BA.1 [164], BNT162b2 original + Omi BA.4/BA.5 [167]) (3.7% of 1,766,357 cases of the total PM dataset).
- MC cases (26,455), NMC cases (38,326).
- Subjects' gender: female (43,804), male (19,653) and unknown (1324).
- Subjects' age in years: n=61,046, range: 0.12-111, mean: 45.2, median: 43.0.
- Country/region of incidence (≥2%): Germany (12,294), UK (8402), US (4829), France (4486), Australia (4464), Netherlands (3381), Japan (3144), Italy (2877), Sweden (2022), Norway (1612), Malaysia (1478); the remaining 15,792 cases were distributed among 88 countries.
- Medical history (n=28,144): 43.4% of reports contained some medical history information. The most frequently (≥200) reported relevant medical conditions included Asthma (4325), Drug hypersensitivity (2316), Seasonal allergy (2074), Hypersensitivity (1843), Food allergy (1801), Chronic obstructive pulmonary disease (892), Depression (787), Obesity (774), Atrial fibrillation (744), Anxiety (588), Dyspnoea (586), Mite allergy (574), Allergy to animal (560), Myocardial infarction (326), Pulmonary embolism (294), Pneumonia (256), Dust allergy (255), Anaphylactic reaction and Sleep apnoea syndrome (252 each), Arrhythmia (246), Myocardial ischaemia (241), Rhinitis allergic (233), Allergy to plants (217), Contrast media allergy (215), Allergy to chemicals (214) and Coronary artery disease (202).
- COVID-19 Medical history (n=4336): COVID-19 (2615), Suspected COVID-19 (1621), Post-acute COVID-19 syndrome (121), SARS-CoV-2 test positive (43), COVID-19 pneumonia (40),

Coronavirus infection (27), Exposure to SARS-CoV-2 (20), Asymptomatic COVID-19 (16), SARS-CoV-2 antibody test positive (5), Coronavirus test positive (3), COVID-19 treatment and Occupational exposure to SARS-CoV-2 (1 each).

- Co-suspects (n=904); the most frequently (≥10) reported co-suspects included elasomeran (143), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) and influenza vaccine (69 each), COVID-19 vaccine (41), adalimumab (25), influenza vaccine inact SAG 4V (23), influenza vaccine inact SPLIT 4V and mepolizumab (21 each), treprostinil sodium (16), apixaban and macrogol (10 each).
- Number of Dyspnoea events: 64,781. In a relatively low number (2408) of cases, dyspnoea was the only event reported.
- Dyspnoea seriousness: The event of dyspnoea was non-serious in a majority of the cases: serious (24,631) and non-serious (40,211).
- Co-reported relevant PTs: the most frequently (≥5%) co-reported relevant PTs included Fatigue (18,413), Headache (15,521), Chest pain (13,629), Pyrexia (11,477), Dizziness (10,976), Palpitations (9378), Nausea (8380), Chest discomfort (8276), Myalgia (7792), Malaise (7508), Tachycardia (6808), Cough (6552), Chills (6389), Asthenia (6278), Arthralgia (5823), Vaccination site pain (5008), Pain in extremity (4805), Pain (4704), Paraesthesia (3720).
- Dyspnoea time to onset: n=46,764, range: <24 hours to 738 days, mean: 8.7, median: 1 day:
    - <24 hours: 16,561 events (107 of which had a fatal outcome);
    - 1 day: 10,061 events (116 of which had a fatal outcome);
    - 2-3 days: 6937 events (114 of which had a fatal outcome);
    - 4-7 days: 4825 events (89 of which had a fatal outcome);
    - 8-14 days: 3211 events (73 of which had a fatal outcome);
    - 15-21 days: 1486 events (34 of which had a fatal outcome);
    - ≥22 days: 3672 events (151 of which had a fatal outcome.
- Dyspnoea duration: n=8105, range: <24 hours to 607 days, mean: 17.8 days, median: 2 days:
    - <24 hours: 2607 events;
    - 1-7 days: 3545 events;
    - 8-14 days: 573 events;
    - 15-21 days: 268 events;
    - ≥22 days: 1112 events;
    - 22-30 days (170); 31-60 days (311); 61-120 days (256); 121-239 days (259); 240-607 days (116).
- Event (Dyspnoea) outcome: fatal (896), resolved/resolving (26,659), resolved with sequelae (1662), not resolved (20,630), and unknown (15,413).

Fatal cases: Of 1587 PM fatal cases, 896 cases recorded a fatal outcome for the event dyspnoea. Where a cause of death was reported, the most frequently reported causes of death (≥45 cases) included Dyspnoea as the sole cause of death (69), Pyrexia (137), Cough (90), Cardiac arrest (75), Malaise (69), COVID-19 (68), Fatigue and Pulmonary embolism (62 each), Chest pain and Pneumonia (60 each), Cardiac failure and Death (57 each), Oxygen saturation decreased (56 each), Vomiting (50) and Asthenia (49).

Medical history was provided in 578 out of 896 fatal cases. Significant cardiac medical conditions (including mainly cardiac arrhythmias, coronary artery disorders and heart failures) were reported in 222 cases and significant respiratory disorders (including mainly bronchial disorders [excluding neoplasms], respiratory disorders NEC and lower respiratory disorders [excluding obstructions and infections]) were reported in 193 cases; the most frequently (>15) reported single medical conditions included COPD (78),

Atrial fibrillation (70), Cardiac failure (57), Myocardial ischaemia (36), Asthma (35), Obesity (32), COVID-19 (27), Myocardial infarction (23), Pneumonia (20), and Tobacco user (18).

Dyspnoea Duration and Time to Onset

Duration of dyspnoea was calculable for 8105 events; the distribution of the duration values is shown in Figure 1 (not reproduced here). About 65% of the events (5275 out of 8105) lasted between 0 and 3 days and about 86% of the events (6993 out of 8105) lasted between 0 and 21 days. The mean is 17.8 days and the median is 2 days with a range between 0 and 607 days.

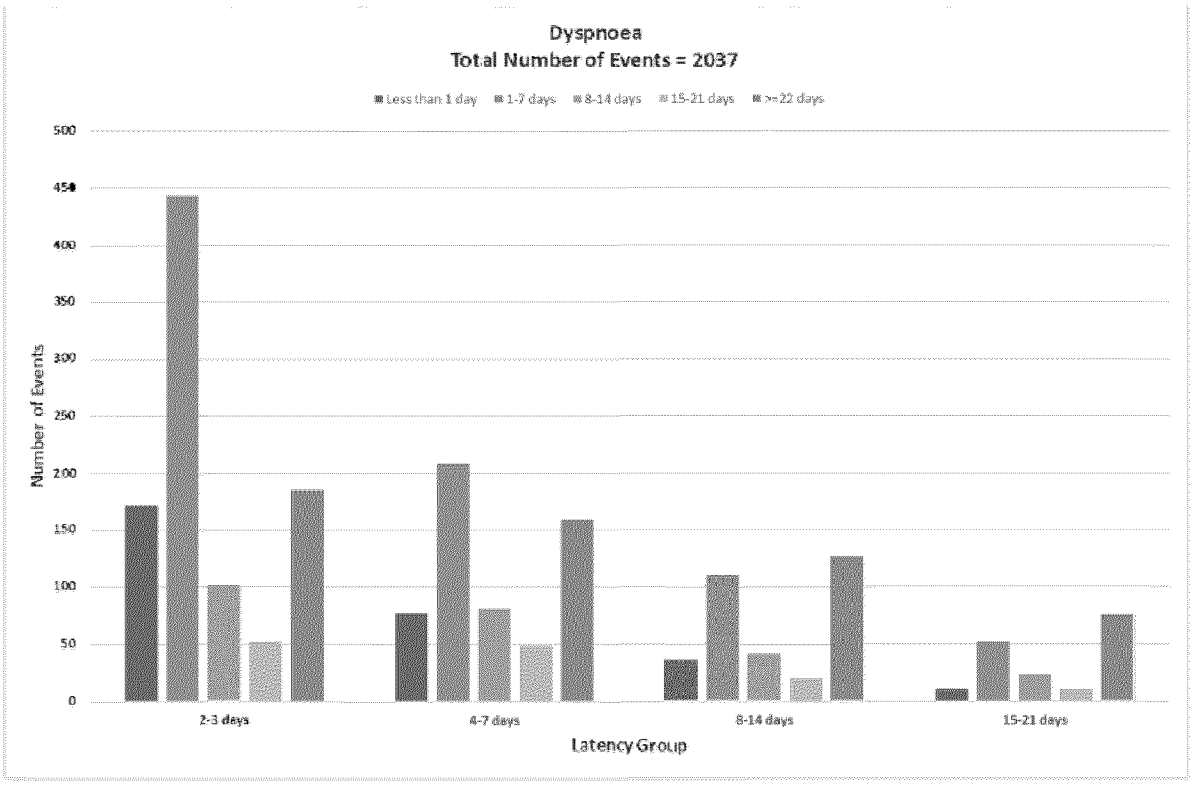
To focus on reports of dyspnoea least likely to be vaccination related stress responses, further analysis concentrated on the 2030 cases (2037 Dyspnoea events) with TTO between 2 and 21 days after vaccination for which duration could be calculated.

The most commonly experienced TTO from vaccination for the 2030 subjects was within 2-3 days of vaccination followed by 4-7 days. The 2037 events of dyspnoea were grouped into the following duration ranges:

- Less than 1 day (296),
- 1 to 7 days (814),
- 8 to 14 days (246),
- 15 to 21 days (134), and
- ≥22 days (547).

Figure 2 shows duration of dyspnoea by the TTO subgroups. Whether dyspnoea occurred within 2-3 days or 4-7 days of vaccination, the duration of dyspnoea was limited to 1-7 days in most subjects.

Figure 2. Duration of Dyspnoea Events with TTO between 2 and 21 Days



Co-Reported Events

Among the 16,406 dyspnoea cases with TTO between 2 and 21 days, the top 15 co-reported events for each duration are provided in Table 1 (not reproduced here). The co-reported events are similar across the different duration ranges and mostly reflect local and systemic reactogenicity events.

Similarly, in the subset of 2030 cases with TTO 2-21 days, an event outcome of resolved/resolved with sequelae and a calculable duration, the co-reported events are largely reactogenicity events as shown in Table 2.

Table 2. Dyspnoea Events (n = 2034) with TTO 2-21 Days and a Duration Value: Co-reported Events by Duration Range

PTs	Duration					
	Less than 1 Day	1-7 Days	8-14 Days	15-21 Days	≥22 Days	All
Chest pain	38	130	45	16	48	277
Fatigue	9	62	25	16	119	231
Chest discomfort	18	82	28	19	63	210
Palpitations	21	69	24	17	76	207
Headache	15	79	31	14	56	195
Dizziness	25	46	12	11	75	169
Tachycardia	22	56	14	15	56	163
Pyrexia	17	75	17	5	18	132
Arrhythmia	4	21	15	10	77	127
Cough	11	40	15	13	33	112
Asthenia	3	35	10	13	47	108
Nausea	15	49	14	7	20	105
Myalgia	5	49	13	5	29	101
Malaise	13	36	12	6	24	91
Chills	14	41	6	4	9	74

Overall, most post-authorization reports of dyspnoea were non-serious and not medically confirmed. Dyspnoea was reported to occur for a wide range of days following vaccination, but the majority of the cases were within 1 week of vaccination and lasted a week or less. Dyspnoea was rarely the only AE reported in a case and some of the commonly co-reported events are events that may precipitate dyspnoea (e.g., fatigue, chest pain, tachycardia, cough). In the cases providing medical history, conditions that often have dyspnoea as a symptom were the most frequently reported (e.g., asthma, seasonal allergies, other hypersensitivities, COPD, obesity).

MAH's conclusion

Overall, the analysis of CT data for the event of dyspnoea does not support a causal association with vaccination based on the very low numbers reported during the placebo-controlled portion of the study and the lack of differentiation between the vaccine and placebo groups. The PM data is more difficult to evaluate, however, while most cases of dyspnoea occur within 1 week of vaccination and last up to 1 week, there is not a dominant trend in the parameters of the PM cases that allow better characterization of the event. Furthermore, a mechanism by which the vaccine could cause dyspnoea is not evident, rather the most commonly reported medical histories, including various respiratory and allergic conditions, cardiac conditions and obesity) and/or co-reported events that may have dyspnoea as a symptom are a more likely explanation for the dyspnoea reported.

Rapporteur assessment comment:

Concerning dyspnoea, retrieved were 12 clinical trial cases and 64,781 post-marketing cases.

Clinical trial data

The 12 clinical trial cases were all considered unrelated to Comirnaty or blinded therapy.

Post-marketing

Duration of dyspnoea was available for 8,105 (12.5%) of the total 64,781 events, and analysis concentrated on the 2,030 cases least likely to be vaccination related stress responses (2,037 dyspnoea events [3.1%]) with TTO between 2 and 21 days after vaccination. If dyspnoea occurred within 2-3 days or 4-7 days of vaccination (most commonly experienced TTO), the duration of dyspnoea was limited to 1-7 days in most cases (n=1,110 [54.7%]).

There were 547 (26.9%) of the 2,037 events reporting a duration of ≥22 days of which a detailed evaluation was not provided by the MAH. This could be accepted because 547 events are a relative low number of dyspnoea reports compared to the background incidence and high Comirnaty exposure and therefore considered not unexpected and coincidence reports.

The MAH stated that a mechanism by which the vaccine could cause dyspnoea is not evident.

Based on the data provided, no new important information could be identified concerning dyspnoea. There is not sufficient evidence to conclude a causal association between dyspnoea and Comirnaty exposure.

Palpitations

Search criteria - PTs: Palpitations. The search retrieved 35,023 cases (2 CT cases and 35,021 PM cases).

Clinical Trial Data

- Number of relevant cases: 2 (BNT162b2).
- Subjects' gender: female (1), male (1).
- Subjects' age in years: n=2, both aged 56 years.
- Country/region of incidence: Argentina (2).
- Medical history (n=2): the reported relevant medical conditions included Angina unstable, Angioplasty, Aortic bypass, Asthma, Cardiac ablation, Insomnia, Salpingo-oophorectomy bilateral, Stent placement and Ventricular extrasystoles (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of Palpitations events: 2, both assessed by investigator as unrelated to BNT162b2.
- Palpitations time to onset: n=2, 38 and 87 days, respectively.
- Palpitations duration: n=2, 2 and 7 days, respectively.
- Palpitations outcome: resolved (2).

Palpitations in these 2 clinical trials occurred at least 21-days post vaccination; and duration, had a range of 2-7 days. The information is not supportive of palpitations being caused by the vaccine or the act of vaccination.

Post-Authorisation Data

- Number of cases: 35,021 (BNT162b2 original [34,887], BNT162b2 original + Omi BA.1 [67], BNT162b2 original + Omi BA.4/BA.5 [74]) (2.0% of 1,766,357 cases of the total PM dataset).
- MC cases (12,351), NMC cases (22,670).
- Subjects' gender: female (25,317), male (8923) and unknown (781).

- Subjects' age in years: n=32,723, range: 0.17-109, mean: 42.8, median: 41.0.
- Country/region of incidence (≥2%): UK (6900), Germany (5969), Australia (2832), Netherlands (2195), France (2181), US (2008), Japan (1892), Sweden (1285), Austria (848), Malaysia (847); the remaining 8066 cases were distributed among 69 countries.
- Medical history (n=14,108): the most frequently (≥200) reported relevant medical conditions included Hypothyroidism (592), Palpitations (466), Depression (336), Atrial fibrillation (278), Arrhythmia (202).
- COVID-19 Medical history (n=2484): COVID-19 (1304), Suspected COVID-19 (1162), Post-acute COVID-19 syndrome (58), SARS-CoV-2 test positive (22), Asymptomatic COVID-19, Coronavirus infection and COVID-19 pneumonia (8 each), Exposure to SARS-CoV-2 (6), SARS-CoV-2 antibody test positive (3), COVID-19 treatment and Occupational exposure to SARS-CoV-2 (1 each).
- Co-suspects (n=269): the most frequently (≥5) co-suspects included elasomeran (81), influenza vaccine (26), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (22), COVID-19 vaccine (16), levothyroxine sodium (8), adalimumab and influenza vaccine inact SPLIT 4V (6 each), hepatitis A vaccine, ibuprofen, and ramipril (5 each).
- Number of Palpitations events: 35,021. In 1935 cases it was the only event reported.
- Palpitations seriousness: serious (11,762) and non-serious (23,283).
- Co-reported relevant PTs: the most frequently (≥5%) co-reported relevant PTs included Fatigue (9959), Dyspnoea (9378), Headache (8441), Dizziness (7478), Chest pain (7135), Tachycardia (5279), Pyrexia (4903), Nausea (4860), Chest discomfort (4320), Malaise (4283), Myalgia (3713), Chills (3308), Arthralgia (2847), Asthenia (2718), Pain in extremity (2686), Vaccination site pain (2663), Heart rate increased (2624), Paraesthesia (2557), Arrhythmia (2088), Pain (2018), Hypoaesthesia (1956), Myocarditis (1952), Off label use (1802).
- Palpitations Time to onset: n=24,433, range: <24 hours to 417 days, mean: 6.8, median: 1 day.
    - <24 hours: 9643 events (6 of which had a fatal outcome);
    - 1 day: 4992 events (2 of which had a fatal outcome);
    - 2-3 days: 3365 events (3 of which had a fatal outcome);
    - 4-7 days: 2459 events (3 of which had a fatal outcome);
    - 8-14 days: 1646 events (2 of which had a fatal outcome);
    - 15-21 days: 734 events (1 of which had a fatal outcome);
    - ≥22 days: 1594 events (2 of which had a fatal outcome).
- Palpitations duration: n=5058, range: <24 hours to 544 days, mean: 16.3 days, median: 1 day.
    - <24 hours: 1743 events;
    - 1-7 days: 2198 events;
    - 8-14 days: 309 events;
    - 15-21 days: 164 events;
    - ≥22 days: 644 events.
- Palpitations outcome: fatal (30), resolved/resolving (15,061), resolved with sequelae (768), not resolved (11,586), and unknown (8021).

Fatal cases: the most frequently reported causes of death (≥3 cases) in these 30 fatal cases included Palpitations (25), Dyspnoea (11), Syncope (7), Chest pain, Myocardial infarction and Pyrexia (6 each), Fatigue, Myocarditis and Tachycardia (5 each), Cardiac arrest and Death (4 each), Chest discomfort, Hyperhidrosis and Pulmonary embolism (3 each). When the medical history was provided (16 cases), significant medical conditions reported included Coronary artery disease and Depression (2 each), Angina pectoris, Aortic valve stenosis, Arteriosclerosis coronary artery, Atrial fibrillation, Cardiac failure, Cardiomyopathy, Cardiovascular disorder, Coronary arterial stent insertion, Coronary artery stenosis, Mitral valve incompetence, Myocardial infarction, Palpitations.

Palpitations Duration and Time to Onset

The distribution of the duration values of palpitations (5058 events) is shown in Figure 3 (not reproduced here). About 68% of the events (3433 out of 5058) lasted between 0 and 3 days and about 87% of the events (4414 out of 5058) lasted between 0 and 21 days. The mean is 16.3 days and the median is 1 day with a range between 0 and 544 days.

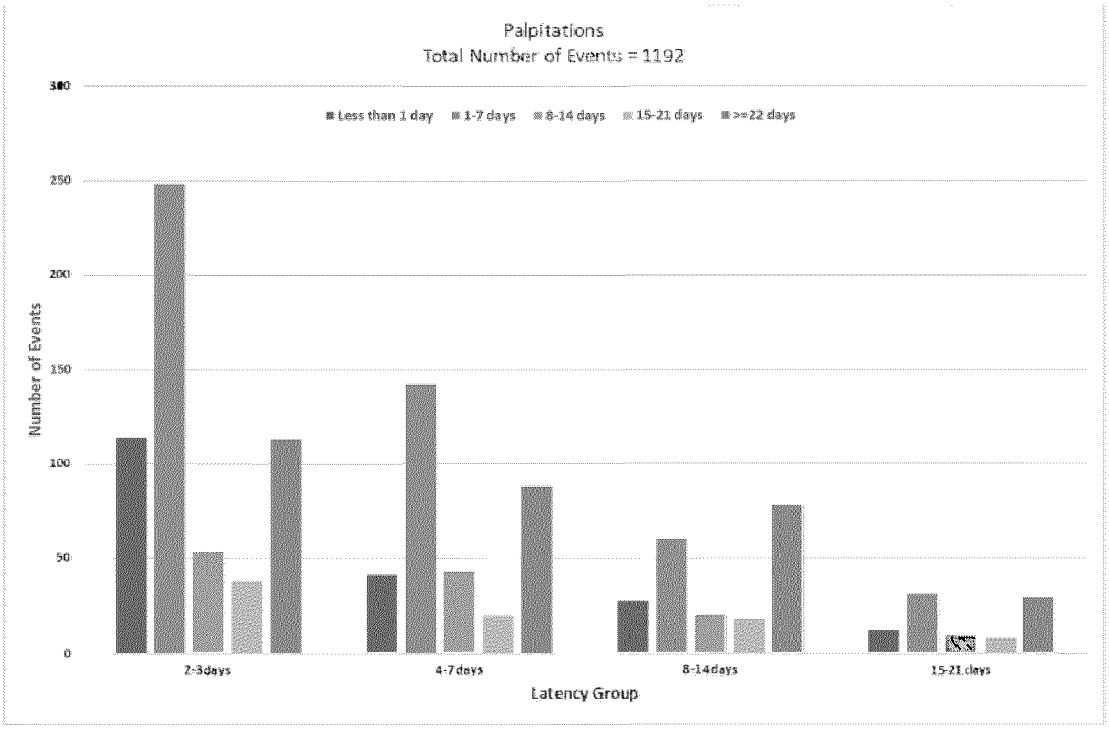
To focus on palpitations less likely to be stress-related reaction, further analysis concentrated on the 1187 cases (1192 Palpitations events) with TTO between 2 and 21 days after vaccination, for which duration can be evaluated.

The most common TTO from vaccination for the 1187 cases was within 2-3 days of vaccination followed by 4-7 days. The 1192 events of the palpitations were grouped into the following duration ranges:

- Less than 1 day (194),
- 1 to 7 days (481),
- 8 to 14 days (125),
- 15 to 21 days (84), and
- ≥22 days (308).

Figure 4 shows duration of palpitations by the TTO subgroups. Whether palpitations occurred within 2-3 days or 4-7 days of vaccination, the duration of palpitations is limited to 1-7 days in most subjects.

Figure 4. Duration of Palpitations Events with TTO between 2 and 21 Days



Co-Reported Events

Among the 8181 cases15 with TTO between 2 and 21 days, the top 15 co-reported events for each duration are provided in Table 3 (not reproduced here). The co-reported events are similar across the different duration ranges and mostly reflect local and systemic reactogenicity events.

Similarly, in the subset of 1187 cases with TTO 2-21 days, an event outcome of resolved/resolved with sequelae and a calculated duration, the co-reported events are largely reactogenicity events (consistent with the larger group of subjects [8181 cases]).

Table 4. Palpitations Events (n = 1190) with TTO 2-21 Days and a Duration Value: Co-reported Events by Duration Range

PTs	Duration					
	Less than 1 Day	1-7 Days	8-14 Days	15-21 Days	≥22 Days	All
Dyspnoea	24	69	25	20	76	214
Fatigue	8	73	24	14	55	174
Headache	14	102	20	5	30	171
Dizziness	23	41	13	11	48	136
Chest pain	14	58	17	7	31	127
Arrhythmia	7	26	10	17	66	126
Nausea	12	71	17	5	19	124
Tachycardia	12	29	11	13	49	114
Pyrexia	11	88	4	2	8	113
Malaise	11	50	7	8	20	96
Chest discomfort	10	35	13	14	22	94
Chills	17	61	4	1	3	86
Myalgia	3	51	9	3	18	84
Vaccination site pain	3	57	3		4	67
Paraesthesia	7	15	3	6	24	55

Overall, most post-authorization reports of palpitations were non-serious and not medically confirmed. Palpitations was reported to occur over a wide range of days following vaccination, but most of the cases were within 1 week of vaccination and lasted a week or less. Palpitations was rarely the only AE reported in a case and some of the commonly co-reported events are events that may precipitate dyspnoea (e.g., fatigue, chest pain, heartrate increased, arrhythmia). In the cases providing medical history, conditions were described that are likely to have palpitations reported as a symptom (e.g., arrhythmias) and in fact many individuals reported palpitations in their medical histories.

MAH's conclusion

Overall, the analysis of CT data for the event of palpitations does not support a causal association with vaccination based on the very low numbers reported during the placebo controlled portion of the study and the failure for the vaccine group to differ from the placebo group. In the PM data, most reports of palpitations are described as occurring within 1 week of vaccination and lasting <1 week. There is not a dominant trend in the PM cases from which to better characterize the event apart from the observation that many of the co-reported events and/or medical histories provided may precipitate palpitations. Furthermore, a mechanism by which the vaccine could cause palpitations is not evident.

Rapporteur assessment comment:

Concerning palpitations, retrieved were 2 clinical trial cases and 35,021 post-marketing cases.

Clinical trial data

The 2 clinical trial cases were both considered unrelated to Comirnaty.

Post-marketing

Duration of palpitations was available for 5,058 (14.4%) of the total 35,021 events, and analysis concentrated on the 1,187 cases least likely to be vaccination related stress responses (1,192 palpitations events [3.4%]) with TTO between 2 and 21 days after vaccination. If palpitations occurred within 2-3

days or 4-7 days of vaccination (most commonly experienced TTO), the duration of palpitations was limited to 1-7 days in most cases (n=675 [56.9%]).

There were 308 (25.8%) of the 1,192 events reporting a duration of ≥22 days of which a detailed evaluation was not provided by the MAH. This could be accepted because 308 events are a relative low number of palpitations reports compared to the background incidence and high Comirnaty exposure and therefore considered not unexpected and coincidence reports.

The MAH stated that a mechanism by which the vaccine could cause palpitations is not evident.

Based on the data provided, no new important information could be identified concerning palpitations. There is not sufficient evidence to conclude a causal association between palpitations and Comirnaty exposure.

Tachycardia and/or Heart rate increased

Search criteria - PTs: Tachycardia, Heart rate increased.

The search retrieved 40,825 cases (3 CT cases and 40,822 PM cases); upon review, 2 PM cases involving babies were excluded from further consideration because they reflected indirect exposure (transplacental/trans-mammary) to the vaccine.

Clinical Trial Data

- Number of relevant cases: 3 (BNT162b2 [2], Blinded therapy [1]).
- Subjects' gender: female (1), male (2).
- Subjects' age in years: n=3, range: 18-67, mean: 50.7, median: 67.0.
- Country/region of incidence: US (3).
- Medical history (n=3): the reported relevant medical16 conditions included Hypertension, Orthostatic hypotension, Tachycardia (1 each).
- COVID-19 Medical history: None.
- Co-suspects: Fexofenadine hydrochloride.
- Number of relevant events: Tachycardia (3), of which 2 were assessed by investigator as unrelated to BNT162b2 and Blinded therapy (1 each) and 1 was assessed as related to BNT162b2.
- Tachycardia time to onset: n=3, mean: 47.7 days, median: 20 days.
- Tachycardia duration: n=3, mean: 0.67 days, median: 1 day.
- Tachycardia outcome: resolved (3).

Tachycardia in these 3 clinical trials cases occurred at least 21-days post vaccination and duration had a range of 2-7 days. The information is not supportive of tachycardia/heart rate increased being caused by the vaccine or the act of vaccination.

Post-Authorisation Data

- Number of cases: 40,820 (BNT162b2 original [40,632], BNT162b2 original + Omi BA.1 [79], BNT162b2 original + Omi BA.4/BA.5 [116]) (2.3% of 1,766,357 cases of the total PM dataset).
- MC cases (14,686), NMC cases (26,134).
- Subjects' gender: female (29,784), male (10,226) and unknown (810).
- Subjects' age in years: n=38,734, range: 0.17-103, mean: 42.8, median: 41.0.

- Country/region of incidence (≥2%): Germany (11,577), UK (4536), US (3213), France (3096), Italy (2975), Mexico (2438), Australia (1675), Japan (1341), Netherlands (939), Sweden (850); the remaining 8180 cases were distributed among 72 countries.
- Medical history (n=15,928): the most frequently (≥200) reported relevant medical conditions included Hypertension (2016), Hypothyroidism (704), Atrial fibrillation (322), Tachycardia (296), Arrhythmia (216), and Tobacco user (211).
- COVID-19 Medical history (n=2244): COVID-19 (1469), Suspected COVID-19 (711), Post-acute COVID-19 syndrome (65), SARS-CoV-2 test positive (26), Coronavirus infection (17), COVID-19 pneumonia (15), Exposure to SARS-CoV-2 (12), Asymptomatic COVID-19 and SARS-CoV-2 antibody test positive (8 each), Occupational exposure to SARS-CoV-2 (2), Coronavirus test positive and COVID-19 treatment (1 each).
- Co-suspects (n=446); the most frequently (≥5) co-suspects included elasomeran (106), influenza vaccine (27), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (25), COVID-19 vaccine (17), adalimumab (15), macrogol (10), apixaban, influenza vaccine inact SPLIT 4V and ocrelizumab (7 each), hepatitis A vaccine and levothyroxine sodium (6 each), Janssen COVID-19 vaccine, epinephrine, ibuprofen, influenza vaccine inact SAG 4V, metoprolol succinate, and paracetamol (5 each).
- Number of relevant events: 41,935. Tachycardia (28,639), Heart rate increased (13,299). In 2242 cases, Tachycardia or Heart rate increased was the only event reported; there were 1264 cases reporting both events.
- Relevant event seriousness: serious (12,992) and non-serious (28,954).
- Co-reported relevant PTs: the most frequently (≥5%) co-reported relevant PTs included Fatigue (11,298), Headache (10,967), Dyspnoea (9397), Dizziness (9078), Palpitations (7471), Pyrexia (7270), Nausea (6186), Chest pain (5458), Myalgia (5316), Chills (5183), Malaise (4759), Asthenia (4540), Vaccination site pain (3897), Arthralgia (3519), Hypertension (3431), Paraesthesia (3290), Chest discomfort (3102), Pain (3081), Blood pressure increased (2933), Pain in extremity (2782), Arrhythmia (2401), Lymphadenopathy (2054).
- Tachycardia/Heart rate increased time to onset: n=31,829, range: <24 hours to 501 days, mean: 6.1, median: 1 day.
    - <24 hours: 14,459 events (20 of which had a fatal outcome);
    - 1 day: 6790 events (18 of which had a fatal outcome);
    - 2-3 days: 3594 events (15 of which had a fatal outcome);
    - 4-7 days: 2612 events (11 of which had a fatal outcome);
    - 8-14 days: 1739 events (7 of which had a fatal outcome);
    - 15-21 days: 782 events (5 of which had a fatal outcome);
    - ≥22 days: 1853 events (7 of which had a fatal outcome).
- Tachycardia/Heart rate increased duration: n=7592, range: <24 hours to 492 days, mean: 160 days, median: 1 day.
    - <24 hours: 2781 events;
    - 1-7 days: 3274 events;
    - 8-14 days: 367 events;
    - 15-21 days: 220 events;
    - ≥22 days: 950 events.
- Tachycardia/Heart rate increased outcome: fatal (113), resolved/resolving (19,326), resolved with sequelae (1123), not resolved (11,011), and unknown (10,439).

Fatal cases: among the 112 cases (reporting 113 fatal events) the most frequently (≥5 cases) reported causes of death included Tachycardia (75), Dyspnoea (26), Pyrexia (27), Heart rate increased (26),

Oxygen saturation decreased (21), Hypotension (14), Cardiac arrest (13), Loss of consciousness and Pulmonary embolism (11 each) Malaise (10), Asthenia, Death and fatigue (9 each), Diarrhoea, Pneumonia and Tachypnoea (8 each), Chest pain, Depressed level of consciousness, General physical health deterioration and Vomiting (7 each), Palpitations, Respiratory failure (6 each), Atrial fibrillation, Cardiac failure, Chills, Confusional state, Drug ineffective, Dyspnoea exertional, Headache, Hyperhidrosis, Oedema peripheral, Respiratory distress, and Shock (5 each).

Medical history was provided in 77 out of 112 fatal cases. Significant cardiac medical conditions (including mainly cardiac arrhythmias, coronary artery disorders, and heart failures) were reported in 38 cases and significant vascular disorders in 28 cases; the most frequently (≥3) reported single medical conditions included Hypertension (25), Atrial fibrillation and Cardiac failure (12 each), Hypothyroidism (5), Arrhythmia and Ex-tobacco user (3).

Tachycardia/Heart rate increased Duration and Time to Onset

The distribution of the duration values of Tachycardia/Heart rate increased (7592 events) is shown in Figure 5 (not reproduced here). More than 70% of the events (5386 out of 7592) lasted between 0 and 3 days and about 87% of the events (6642 out of 7592) lasted between 0 and 21 days.

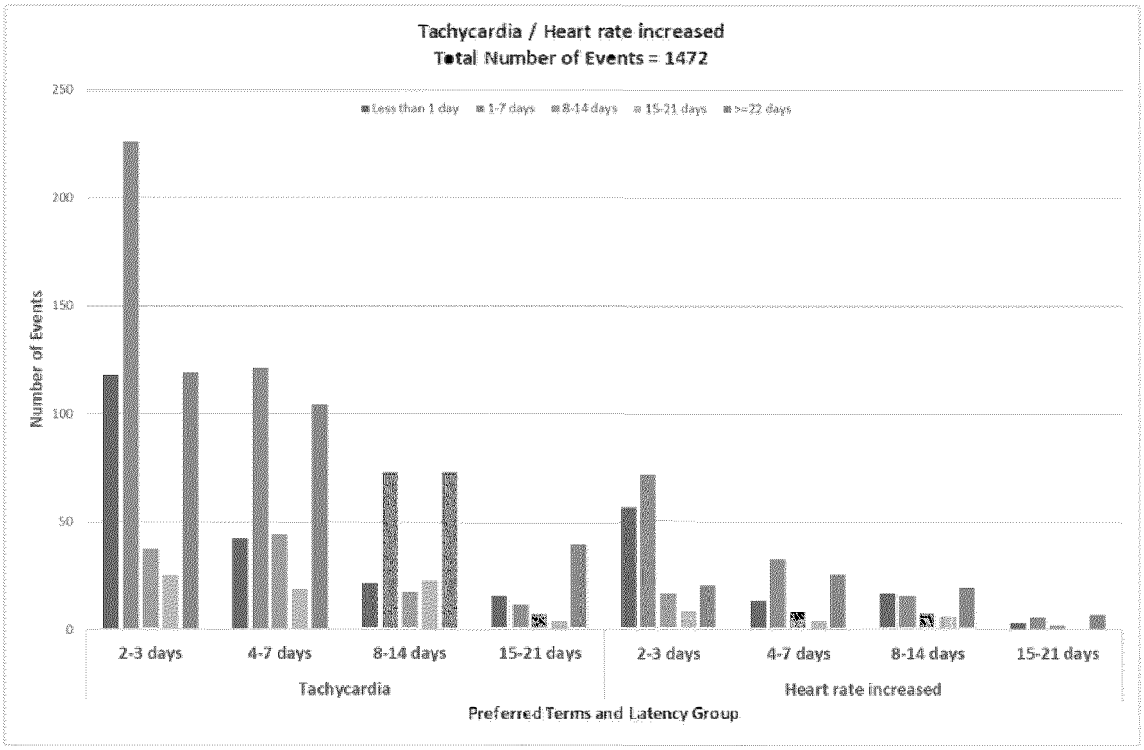
To focus on tachycardia/heart rate increased less likely to be stress-related, the additional analysis concentrated on the 1444 cases (1470 Tachycardia/Heart rate increased events) with TTO between 2 and 21 days after vaccination, for which duration can be evaluated.

The most common TTO from vaccination for the 1444 cases was within 2-3 days of vaccination followed by 4-7 days. The 1470 events of the tachycardia/heart rate increased were grouped into the following duration ranges:

- Less than 1 day (284),
- 1 to 7 days (555),
- 8 to 14 days (138),
- 15 to 21 days (89), and
- ≥22 days (406).

Figure 6 shows duration of tachycardia/heart rate increased by the TTO subgroups. When tachycardia/heart rate increased occurred within 2-3 days of vaccination, the duration of these events is limited to 1-7 days in most subjects. Whether tachycardia/heart rate increased occurred within 4-14 days of vaccination, the duration of these events is limited to 1-7 days or it is greater than 22 days in a similar proportion.

Figure 6. Duration of Tachycardia/Heart rate increased Events with TTO between 2 and 21 Days



Co-Reported Events

Among the 8536 tachycardia/heart rate increase cases with TTO between 2 and 21 days, the top 15 co-reported events for each duration are provided in the table 5 (not reproduced here). The safety profile of the co-reported events is similar across the different duration ranges; for 12 co-reported events, a higher number of them occurred when tachycardia/heart rate lasted between 1 and 7 days; palpitations, arrhythmia and paraesthesia were more frequently reported for higher duration values of tachycardia/heart rate increase.

The list of the co-reported events in the subset of 1444 subjects with TTO 2-21 days and a calculable duration is largely overlapping with the one of the larger group of 8536 subjects with TTO 2-21 days (Table 5) and consists of events largely consistent with reactogenicity events.

Table 6. Tachycardia/Heart rate increased Events (n = 1470) with TTO 2-21 Days and a Duration Value: Co-reported Events by Duration Range

PTs	Duration					
	Less than 1 Day	1-7 Days	8-14 Days	15-21 Days	≥22 Days	All
Dyspnoea	30	68	23	23	68	212
Fatigue	17	70	27	10	84	208
Headache	25	99	24	11	41	200
Dizziness	25	72	14	17	64	192
Palpitations	21	45	17	15	61	159
Arrhythmia	15	37	19	11	67	149
Pyrexia	16	89	13	3	10	131
Nausea	15	61	11	5	23	115
Myalgia	4	57	12	3	26	102
Vaccination site pain	5	83	6		3	97
Chest pain	14	37	14	8	22	95
Chills	18	59	4	3	9	93
Hypertension	17	36	8	8	23	92
Malaise	10	36	15	7	17	85
Blood pressure increased	11	25	4	8	22	70

Overall, most post-authorization reports of tachycardia and increased heartrate were nonserious and not medically confirmed; like other non-serious AEs, more woman than men reported the events. The events were reported to occur over a wide range of days following vaccination, but most of the cases were within 1 week of vaccination and lasted <1 week. The events were rarely the only AE reported in a case and some of the commonly co-reported events are events that may precipitate or be associated with tachycardia/increased heartrate (e.g., dyspnoea, various types of pain, arrhythmia). In the cases providing medical history, conditions were described that may include the events as symptoms (e.g., arrhythmias, hypertension) and in fact many individuals reported tachycardia in their medical histories.

MAH's conclusion

Overall, the analysis of CT data for the events tachycardia and increased heart rate do not support a causal association with vaccination based on the very low numbers reported during the placebo-controlled portion of the study and the failure for the vaccine group to differ from the placebo group. In the PM data, most reports of tachycardia and increased heartrate occurring from 2 to 21 days after vaccination last <1 week. There is not a dominant trend in the PM cases from which to better characterize the event apart from the observation that many of the co-reported events and/or medical histories provided may precipitate these events; and many reported medical histories include the event tachycardia. Furthermore, a mechanism by which the vaccine itself could cause the events is not evident.

Rapporteur assessment comment:

Concerning tachycardia and/or heart rate increased, retrieved were 3 clinical trial cases and 40,820 post-marketing cases.

Clinical trial data

The 3 clinical trial cases were considered unrelated to Comirnaty and blinded therapy (1 each) and 1 was assessed as related to Comirnaty.

Post-marketing

Duration of tachycardia and/or heart rate increased was available for 7,592 (18.1%) of the total 41,935 events, and analysis concentrated on the 1,144 cases least likely to be vaccination related stress responses (1,470 tachycardia and/or heart rate events [3.5%]) with TTO between 2 and 21 days after

vaccination. If tachycardia and/or heart rate increased occurred within 4-14 days of vaccination (n=977), the duration of these events is limited to 1-7 days or it is greater than 22 days in a similar proportion.

There were 406 (27.6%) of the 1,470 events reporting a duration of ≥22 days of which a detailed evaluation was not provided by the MAH. This could be accepted because 406 events are a relative low number of tachycardia and/or heart rate increased reports compared to the background incidence and high Comirnaty exposure and therefore considered not unexpected and coincidence reports.

The MAH stated that a mechanism by which the vaccine could cause tachycardia and/or heart rate increased is not evident.

Based on the data provided, no new important information could be identified concerning tachycardia and/or heart rate increased. There is not sufficient evidence to conclude a causal association between tachycardia and/or heart rate increased and Comirnaty exposure.

MAH's overall conclusion

This review of the events dyspnoea, palpitations, tachycardia and increased heart rate shows that the events are frequently reported with other adverse events and in individuals with medical conditions predisposing to such events. The events are reported over a wide range of time following vaccination and have varying durations. There is not a clear mechanism by which the vaccine itself could cause these events outside of a hypersensitivity scenario which would generally occur soon after vaccination. Given the current available information, a causal association with the vaccine is not supported. No changes to the product labelling appear warranted at this time and routine pharmacovigilance will continue.

Rapporteur assessment comment:

MAH's conclusion is endorsed that based on the current available information, a causal association of dyspnoea, palpitations, tachycardia and/or increased heart rate with Comirnaty is not supported. No changes to the product information is warranted and routine pharmacovigilance should be continued.

Issue solved

Response to the PRAC request 11 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *Concerning post orthostatic tachycardia syndrome, the MAH is requested to discuss the publication of "Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8" concerning post orthostatic tachycardia syndrome and Comirnaty exposure and, if applicable, to perform a cumulative review on the association between Comirnaty and post orthostatic tachycardia syndrome. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.*

MAH's response:

The MAH reviewed the publication of "Kwan, AC, Ebinger, JE, Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-CoV-2 Infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8" concerning post orthostatic

tachycardia syndrome and Comirnaty exposure and noticed several major limitations that do not provide strong evidence for an increased risk of POTS after COVID-19 vaccination or infection.

The observed small increased risk of POTS after COVID-19 vaccination (or COVID-19 infection) could be in part explained by the detection bias during the post-vaccination period as the associations between COVID-19 vaccination (or COVID-19 infection) and POTS were significantly weakened and the small effect sizes moved toward null when the detection bias was taken into account (by comparing with commonly diagnosed conditions during postvaccination period as the reference).

It should be noted that given the large sample size, a small difference in effect size in comparative analyses could attain a statistical significance but that may not be clinically significant or meaningful.

Regarding the disease definition, despite there being diagnostic criteria for POTS, there is no single ICD code for it so the authors chose a set of diagnostic criteria.

In summary, this article does not represent a safety signal, therefore there is no need to perform a cumulative review nor a need to update the product information or the EU-RMP.

Rapporteur assessment comment:

The study included a cohort of COVID-19-vaccinated individuals in which 62% was vaccinated with Comirnaty. Among other comparisons (including postural orthostatic tachycardia syndrome [POTS] in vaccinated persons versus SARS-CoV-2 infected persons) the study compared POTS cases 90 days before vaccine exposure with POTS cases after vaccine exposure. The reported post-vaccination odds of new POTS-associated diagnoses was 1.33 (95% CI 1.25–1.41) ($P < 0.001$) and the authors concluded that POTS-related diagnoses appear to be acquired with increased frequency after, compared to before, COVID-19 vaccination, however, no separate analyses were performed for the different included COVID-19 vaccines.

Detection bias is considered present in the study as the authors stated that "we recognize that our analyses of electronic health record data are intrinsically subject to non-differential misclassification that generally tends to bias results toward the null." and regarding case definition of postural orthostatic tachycardia syndrome "we did not formally adjudicate all diagnoses due to the large number of events, and an adjudicated subsample did show that a significant degree of non-POTS diagnoses were captured within our International Classification of Diseases (ICD) codes; however, given that this would likely result in non-differential misclassification biasing toward the null, we think that our relative comparisons remain valid." However, there was no additional substantiated analysis in the article that showed that the performed comparisons remained valid.

Regarding (clinically) meaningful comparative analyses the authors stated that "in the separate populations of vaccinated and infected patients were mutually exclusive; recognizing that these populations may have inherent differences, the comparisons between the populations should be interpreted more cautiously than the comparisons within the populations."

Overall, MAH's conclusion is endorsed that there are study limitations that do not provide strong evidence for an increased risk of POTS after COVID-19 vaccination and that the results of this study regarding POTS does not represent a safety signal. Also, the study did not include an analysis specific for Comirnaty. No new safety information could be identified. The MAH should closely monitor cases reporting postural orthostatic tachycardia syndrome through routine pharmacovigilance.

Issue solved

Subacute thyroiditis

MAH response on a question from the Australian Therapeutic Goods Administration (TGA):

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)."

MAH's response (Appendix 5.6.3; not fully reproduced here)

MAH's summary and conclusion

This cumulative review of subacute thyroiditis follows a previous cumulative review of thyroiditis conducted through 18 December 2021 and included in SBSR#3. The characteristics of the subjects remains similar (mostly adult women), consistent with the known epidemiology of viral-induced subacute thyroiditis. 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.

Overall, there were 53 cases that were unassessable due to a lack of laboratory and/or imaging data supporting the diagnosis of subacute thyroiditis. Cases containing supportive diagnostic lab and/or imaging data were considered to be possibly causal (51) unless a potential alternative cause of subacute thyroiditis other than vaccination was described (e.g., underlying or concomitant thyroid disorder, preceding viral infection or improbable time to onset). If such information was provided, the cases were assessed as unlikely to be causal (56) to vaccine. It is important to note that many cases assessed as " possible" due to the presence of supportive diagnostic data were missing time to onset and/or medical history. It remains the MAH position that individual case assessments of causality cannot be considered an overall conclusion on causality of an event to the vaccine. The overall determination should be based on the totality of accumulated data and its scientific weight. Furthermore, an association of temporality in and of itself does not allow a conclusion of causality.

Rapporteur assessment comment:

The cumulative review of subacute thyroiditis (through 18 Dec 2021) was assessed in the 2nd Comirnaty PSUSA (reporting period 19 Jun 2021 – 18 Dec 2021; EMEA/H/C/PSUSA/00010898/202112). PRAC concluded that no new safety concern was identified and closure of the signal was accepted.

The cumulative review of subacute thyroiditis (through 18 Dec 2022) retrieved 145 serious cases out of 292 cases with no medical history of thyroiditis subacute or other thyroid disorders, of which 51 cases were considered possible related to Comirnaty exposure and there were no cases considered probable or certain related. However, many possible related cases due to the presence of supportive diagnostic data were missing time to onset and/or medical history. Therefore, given the extensive Comirnaty exposure this is not considered unexpected and does not present a new safety concern.

Overall, MAH's conclusion is endorsed that based on the current available information, a causal association of subacute thyroiditis with Comirnaty is not supported. Routine pharmacovigilance should be continued.

2.2.1. Evaluation of closed signals

Rapporteur assessment comment:

General note, the MAH should present in the section 'Evaluation of closed signals':

- all the signals that were closed during the reporting period of the PSUR;
- previously closed signals as requested by PRAC;
- earlier closed signals only when there are deviating trends in severity of AEs, incidence, and/or outcomes.

However, the signals closed early in the reporting period (19 Jun 2022-18 Dec 2022) in this PSUR 'IgA nephropathy' (closed 10 Aug 2022), 'Acquired haemophilia' (closed 20 Jul 2022), 'hearing loss' (closed 20 Jul 2022), were evaluated in the previous 3rd PSUR assessment (EMEA/H/C/PSUSA/00010898/202112) and are not reproduced in this AR.

Response to the PRAC request 10 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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.*

MAH's response: The MAH agrees to include Brighton Collaboration Criteria for sensorineural hearing loss in future reviews of cases reporting hearing loss.

Rapporteur assessment comment:

Noted.

Signals determined to not 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 Epstein-Barr virus (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 18-40 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.

Rapporteur assessment comment:

In clinical trial C4591001 one person reported haemophagocytic lymphohistiocytosis (HLH) which was assessed as not related.

Through 22 Apr 2022, the MAH retrieved 103 cases reporting HLH of which the majority had insufficient information, confounding factors, alternative causes or questionable diagnoses of HLH.

No relevant literature.

O/E ratios were >1 for the age categories 12-17 and 18-40 years, however the lower limits of the 95% CIs were below 1 and analysis was based on a small number of cases.

A causal mechanism is not evident.

MAH's conclusion is endorsed, that a causal association between HLH and Comirnaty was not concluded. No new safety concern could be identified.

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 investigational medicinal product (IMP) for the treatment of dermatomyositis who attributed her 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 6-year-old participant with a 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.

Rapporteur assessment comment:

The signal was triggered by a persons' treatment of dermatomyositis participating a non-vaccine placebo-controlled clinical trial who attributed her dermatitis to Comirnaty.

There were no reports of dermatomyositis or of flares of dermatomyositis in the vaccine placebo-controlled clinical trials.

Retrieved were 20 relevant publications in which 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.

Through 13 Sep 2022, the MAH retrieved 127 reports of which 64 cases had alternative potential causes, 49 cases with insufficient detail for assessment and 14 cases had with no obvious aetiology for the event.

O/E ratios were <1.

A causal mechanism is not evident.

MAH's conclusion is endorsed, that there was not adequate evidence to support a causal association between dermatomyositis and Comirnaty.

Histiocytic necrotizing lymphadenitis (HNL)

Response to the PRAC request from signal Histiocytic necrotizing lymphadenitis (EPITT 19835):

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) COMIRNATY, BioNTech Manufacturing GmbH, should submit within the next PSUR (with a DLP of 18 December 2022) a cumulative review of all cases concerning Comirnaty associated with histiocytic necrotizing lymphadenitis from all sources, including any relevant articles from literature and to discuss probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of Comirnaty. The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

MAH's response (Appendix 5.3.1)

Introduction[1]

Histiocytic necrotizing lymphadenitis (HNL), aka Kikuchi disease aka Kikuchi-Fujimoto disease aka Kikuchi histiocytic necrotizing lymphadenitis is a rare, benign condition of unknown etiology originally described in young women in Japan. It is a syndrome now described to occur in all races and in both males and females although it is slightly more common in females. Affected age is generally younger than 40 years (range 6 to 80 years) and clinical presentation is of lymphadenopathy (LAD), usually cervical. Retrospective reviews of cases in the literature show that other signs and symptoms most commonly co-reported, occur at much lower incidences: fever in 35%, rash (10%), arthritis (7%), fatigue (7%) and hepatosplenomegaly (3%). These are symptoms often associated with viral infection.

The presentation, course and histology of the lymph node (LN) upon biopsy (needed for diagnosis) are interpreted as suggestive of a T cell and histiocyte immune response. Many infectious agents have been proposed to be responsible for this disorder, including Epstein-Barr virus (EBV), human herpesvirus 6 and 8 (HHV), HIV, Parvovirus B19, paramyxoviruses, parainfluenza virus, Yersinia enterocolitica, and Toxoplasma. It has also occurred with other conditions such as Still's disease, systemic lupus erythematosus (SLE) and B cell lymphoma. Rare reports have been associated with SAR-CoV-2 infection.

There is no effective treatment, and it usually resolves in 1-4 months; recurrence is uncommon. Steroids and other immunosuppressants have been used for older and sicker patients. There appears to be a risk of evolution into an autoimmune syndrome such as SLE and some cases (generally in older and sicker patients) have also described concurrent macrophage activation syndrome.

The rarity and unclear etiology of HNL naturally make it a condition for which there will be speculation of a causative role of vaccination, however, these same characteristics also suggest that the condition's etiology is likely multifactorial and therefore a simple explanation may not be possible.

Surveillance

There were no signals of disproportionality for HNL in MAH's safety database during routine signal detection.

There were no clinical trial reports of HNL in the pivotal BNT162b2 vaccine clinical trials conducted by MAH.

Literature

OVID MEDLINE, EMBASE and BIOSIS Previews were searched up to 19 December 2022 for literature articles on HNL (including Kikuchi-Fujimoto) and BNT162b2 administration. All relevant publications described case reports following COVID-19 or COVID-19 vaccination except one preprint article by Rodriguez-Ferreras[2] which described a review of cases of HNL reported in pharmacovigilance databases. In the review, 14 cases of HNL were found in the Spanish AE (FEDRA) and EudraVigilance databases associated with COVID-19 vaccine (11 of 14 reported Comirnaty administration) and 9 cases were found in association with non-COVID-19 vaccines. The authors state the reports of HNL are an "oddly high number" but provide no rationale for this statement (e.g., any measure of disproportionality or even a baseline number of total COVID-19 vaccine AE reports in the databases). Given the unprecedented number of global vaccinations for COVID-19, it is important to contextualize such statements in order to best understand if AE occurrence is out of the ordinary (and potentially related to vaccination) or simply coincident to vaccination.

The remaining relevant articles were (3) case reports of HNL following COVID-19 and (10) following COVID-19 vaccination. The Comirnaty vaccine case reports were sent to case processing to ensure their inclusion in the global safety database; those pending entry in the safety database are described directly below and the remainder are described in the safety database review.

Rapporteur assessment comment:

The MAH showed the cases summaries of 6 pending case reports of which 4 case reports are not considered reports after Comirnaty exposure (1 after Spikevax, 1 after Sinopharm, and 2 after unspecified COVID-19 vaccines). The 2 remaining pending case reports are presented below.

Source Author Country	Case Summary	*MAH Comment*
BMJ[7] Ikeda, K et al. Japan	20-year-old woman with no medical history and a 2-week history of fever and 1-week history of painful bilateral cervical LAD; fever began 1 day after dose 1 (D1) of PFE/BNT COVID-19 vaccination. She was treated with a course of antibiotics without resolution. She was negative for SARS-CoV-2, HBV, HCV, HV, EBV, CMV and not tested for HIV or HPV B19. A CT confirmed symmetrical LAD in the neck (1 cm), supraclavicular, axillary and inguinal areas and hepatosplenomegaly; a LN biopsy was consistent with HNL and she was treated with corticosteroids with improvement after a failed course of NSAIDs.	*The patient had more extensive LAD than generally seen with HNL and hepatosplenomegaly which is also less common. While the infectious work-up was not complete, she did improve with corticosteroids. No further information on additional doses of vaccine were available.*

Rapporteur assessment comment:

TTO 1 week after dose 1. HLN was diagnosed after biopsy. Although the infectious work-up was not complete, most of the common known causes of HNL were tested. Therefore, this case with confirmed HNL is considered possible related to Comirnaty exposure.

Human Vaccines & Immunotherapeutics[8] Kashiwada T et al. Japan	27-year-old woman with no medical history had left submandibular swelling the day after D1 of PFE/BNT COVID-19 vaccination; a course of antibiotics produced an improvement in a few days. 22 days later, she received D2, and the following day had fever and axillary swelling which spontaneously improved after 3 days. 68 days from D2, she had a fever (39 C) and discomfort in the axilla. Fever persisted despite a course of antibiotics and on day 123 after D1, she presented to the hospital. A chest CT scan showed multiple enlarged nodes on the left (same side as vaccination) and gallium update in multiple left axillary nodes. US showed hepatosplenomegaly. CMV, EBV, ANA, and tests for *M. tuberculosis* and Bartonella were negative. A surgical biopsy of an axillary node was consistent with HNL. Fever resolved in 10 days without treatment and the patient recovered.	*This patient seemed to have post-vaccinated LAD that resolved and was then followed by HNL. Her infectious work-up does not appear to be complete, however she recovered with no treatment after having had a course of antibiotics which had not improved her symptoms.*

Rapporteur assessment comment:

TTO was 68 days after dose 2. HLN was diagnosed after biopsy. The infectious work-up seemed limited. Due to the relative long TTO after improvement from fever and axillary swelling, this case is considered unlikely related to Comirnaty exposure.

Safety database review

The spontaneous BNT162b2 reports were searched cumulatively through 18 Dec 2022 for reports of HNL. There were 21 cases reported (5 of the 21 were from medical literature). Eleven were in women and 9 in men (1 case did not report sex). Seventeen were serious (4 non-serious), all but 2 were medically confirmed and none had fatal outcomes. Seventeen recovered or were recovering at the time of the report; 3 had not recovered and 1 did not provide an outcome. Patient ages ranged from 10 years to 52 years (mean 22.8; 1 not reported).

Eleven cases were reported to occur following dose 1 (ranging from the day of D1 to 35 days after D1). Fewer cases occurred after dose 2 (6, ranging from 1 day to 3 months after D2) and after dose 3 (1, same day as D3) and dose 4 (1, 37 days after D4). Two cases were reported to occur 9 days after D1 and then recur a few days after D2; both patients received D3 of vaccine without repercussion. Two cases did not specify dose.

Nine cases were reported from Japan, 2 each from France, Singapore and Spain and the remaining cases were reported (1 each) from Australia, Austria, Finland, Italy, Qatar and the UK.

Of the 21 reports,

- 2 cases occurred in patients with a known history of HNL ([redacted] and [redacted]). In these cases, and 9 others, there was no mention of lymph node biopsy, a requirement for the accurate diagnosis of HNL.
- 2 additional cases ([redacted] and [redacted]) provided no information about a work-up to rule out infectious diseases as a potential cause for HNL.
- 2 additional cases ([redacted] and one case counted above as not having a lymph node biopsy ([redacted]) posed a differential diagnosis that included HNL, but the patients ended up being diagnosed with SLE.

Due to the alternative explanations for HNL and the lack of clear diagnosis and infectious work-up, these 15 cases were not considered further.

The remaining 6 cases, concerning 5 patients, are detailed in the table below:

	AER **Age(Y)/Sex** **Country** **Latency/Dose**	**Other PTs** **Seriousness** **Outcome**	**Summary** ***Comment***
1	[redacted] 34/Male [redacted] 17 days/Dose 1	None Non-serious Recovered	In this literature report[9], the patient had a medical history of diabetes mellitus, hypertension and COVID-19 and presented with fever and axillary LAD. His infectious work-up was negative for current COVID-19, TB, fungal infection, EBV, CMV, Toxoplasma, Dengue, HBV and HCV. Labs showed leukopenia and LN biopsy was consistent with HLN. He was treated with NSAIDs and recovered. *No alternative cause obvious in this case however temporality does not confirm causality*

Rapporteur assessment comment:

TTO was 17 days after dose 1. HLN was diagnosed after biopsy. The authors of the case report stated that extensive clinical workup was performed to exclude infectious and autoimmune causes, and histology also confirmed the absence of lymphoproliferative disorders. No further information regarding other received doses. Therefore, this case is considered probable related to Comirnaty exposure.

2	[redacted] 30/Female [redacted] 9 days/Dose 1	Lymphadenopathy, Vaccination site lymphadenopathy Serious Recovered	In this spontaneous report from a physician, via EMA, the patient (with "no history of interest") presented with axillary LAD 9 days after Dose 1 (Jan 2021) (same side as vaccination) and had an US interpreted as reactive LAD. She had D2 of vaccine 21 days after D1 and about 2.5 weeks later had another US that showed LAD in both axillae, again thought to be reactive. There was no report of fever. A little less than 2 months after D2, a f/u US showed axillary, cervical, infra and supraclavicular LAD and 3 days later a core biopsy was performed. *See the next case (AER [redacted]) details*
3	[redacted]* 30/Female [redacted] >2 months/Dose 2	Lymphadenopathy, Condition aggravated, Ovarian cyst Serious Recovered	(*Continued from AER* [redacted] Infectious work up was negative for COVID-19, EBV, CMV, Bartonella, Brucella, Parvovirus 19, Coxiella, HSV, Influenza A and B, RSV and Toxoplasma. Labs were negative for interferon gamma release, ANCA, ANA and thyroid abnormalities. LN biopsy was consistent with HNL. She did not receive treatment and recovered. D3 of Comirnaty was administered approximately 1.5 years after the primary series and there were no clinical repercussions. *No alternative cause obvious in this case however temporality does not confirm causality*

Rapporteur assessment comment:

TTO was 2.5 weeks after D2. The one sided lymphadenopathy after dose 1 became two-sided after dose 2 and 2 months later HLN was diagnosed after biopsy. After dose 3 (1,5 year later) there were no complaints. Extensive clinical work-up was done excluding other causes. Therefore, this case is considered possible related to Comirnaty exposure.

4	[redacted] 18/Female [redacted] 35 days/Dose 1	None Non-serious Recovered	In this literature report,[9] PMH was not reported. The patient had fever and axillary LAD. Her infectious work-up was negative for COVID-19, TB, Fungal infection, HIV, EBV, CMV, Toxoplasma, Dengue, HBV and HCV. Labs showed leukopenia and negative ANA and ds-DNA; CT showed enlarged left axillary, supraclavicular and subpectoral nodes up to 2 cm. LN biopsy was c/w HNL. She was treated with NSAIDs and recovered. *No alternative cause obvious in this case however temporality does not confirm causality*

Rapporteur assessment comment:

TTO was 35 days after dose 1. The authors of the case report stated that extensive clinical workup was performed to exclude infectious and autoimmune causes, and histology also confirmed the absence of lymphoproliferative disorders. HLN was diagnosed after biopsy. No further information regarding other received doses. Despite the medical history was not reported (the patient was reported to be 'previously well'), this case is considered probable related to Comirnaty exposure.

5	[redacted] 18/Male [redacted] 10 days/Dose 1	None Serious Recovering	In this literature report,[10] the patient had a history of minimal change renal disease since 2015 with 2 relapses requiring treatment with prednisolone, cyclosporin, and rituximab over the years up until 2 years prior when he went into remission. His symptoms included fever, tender LAD in the cervical and axillary regions, decreased appetite and nausea. Infectious work-up was negative for COVID-19, HBV, HCV, HIV, CMV and EBV. Labs showed low platelets, elevated transaminases and ANA negative. LN biopsy was c/w HNL. He was initially treated with a course of antibiotics, they with paracetamol and NSAIDs for his fever; the patient was recovering at the time of report. *No alternative cause obvious in this case however temporality does not confirm causality*

Rapporteur assessment comment:

TTO was 10 days after first dose. Extensive clinical workup was performed to exclude other causes. HLN was diagnosed after biopsy. No further information regarding other received doses. Therefore, this case is considered probable related to Comirnaty exposure.

6	[redacted] 38/Female [redacted] 3 weeks/Dose 2	Haemophagocytic lymphohistiocytosis (HLH) Serious Recovered	In this literature report[11], a 38-year-old previously healthy woman had D1 2 months after giving birth to a healthy baby. 3 weeks after D2 she presented with fever, chills, fatigue, a diffuse erythematous papular rash and tender left axillary LAD confirmed by CT scan. Symptoms did not respond to a course of antibiotics. She had leukopenia and anemia and an extensive negative infectious workup which included negative tests for SARS, EBV, CMV, HCV, HBV, HIV, Toxoplasma, Rubeovirus, Brucella, Leptospirosis, Bartonella, Chlamydia, Morbillivirus, Mycoplasma, Yersinia, TB, Parvo-19, CMV, JC and Herpes 6. ANA, anti-DNA and rheumatoid factor were negative. A bone marrow biopsy showed hemophagocytosis and a diagnosis of HLH was confirmed based on the fulfilment of six out of eight criteria according to the HLH-2004 diagnostic criteria. An excisional lymph node revealed histiocytes necrotizing lymphadenitis with numerous CD 68+ histiocytes. She was started on corticosteroids and was recovering at the time of the report. *Although HNH is a self-limiting and benign condition, it has previously been rarely reported in conjunction with HLH, a potentially severe hyperinflammatory condition due to uncontrolled histiocytes, macrophages and T-cell activation. The authors hypothesize that COVID-19 vaccination caused axillary LAD followed by a systemic inflammatory reaction that evolved into HLH.*

Rapporteur assessment comment:

TTO was 3 weeks after dose 2. HLN was diagnosed after biopsy. No further information regarding other received doses. Extensive clinical workup was performed to exclude other causes. Therefore, this case is considered probable related to Comirnaty exposure.

MAH's conclusion

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

Rapporteur assessment comment:

Clinical trial data

There were no reports of histiocytic necrotizing lymphadenitis (HNL) in clinical trials.

Literature

Through 19 Dec 2022, 10 case reports were retrieved. Four were send to MAH's safety database and are included in the post-marketing cases. Six case reports were pending of which in 4 case reports the HNL was not after Comirnaty exposure. Of the remaining 2 case reports, 1 case report is considered possible related to Comirnaty exposure and 1 case report unlikely related.

Mechanism of action

No discussion of probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of Comirnaty was provided.

HNL is a rare disease although it has been most frequently reported from Asia (https://www.uptodate.com/contents/kikuchi-disease), has non-specific manifestations, its etiology and pathogenesis are unclear and there are no clear diagnostic criteria, diagnosis can be made only after histologic examination of lymph node biopsy. How the vaccine may lead the development of HNL disease is unknown, however it might induce it because viral or other antigens in the vaccine could lead to aberrant immune response in vaccine recipients resulting into the development of HNL.

Post-marketing

Through 18 Dec 2022, 21 cases reporting HNL were retrieved. Nine originated from Japan and 2 from Singapore. 15 of the 21 cases were not considered further due to the alternative explanations for HNL and the lack of clear diagnosis and infectious work-up. Of the remaining 6 cases (5 persons), 4 cases were considered probable related to Comirnaty exposure and 1 case possible related.

In total, there were 4 post-marketing cases considered probable related to Comirnaty exposure and 2 cases possible related and the mechanism of action is unknown. Given the extensive exposure of Comirnaty this is not considered a convincing piece of evidence to demonstrate a causal relationship and does not present a new safety concern. Overall, MAH's conclusion is endorsed that based on the current provided information, a causal association of HNL with Comirnaty is not supported. Routine pharmacovigilance should be continued.

Issue solved

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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. of the PSUR (not fully reproduced here) for the details of this updated information. MAH's summary and conclusion of the review of additional cases reporting vulval ulceration: Nine new cases from the post-marketing data and two new literature cases have been identified since 16 August 2022. Non-sexually acquired genital ulceration (NAGU) has a poorly understood pathophysiology and is a diagnosis of exclusion, making ascertainment of the diagnosis challenging. In five of the newly reported cases sufficient clinical detail is lacking to establish a diagnosis of genital ulceration occurring without an associated infection, whether sexually acquired (e.g., herpes simplex virus [HSV]) or non-sexually acquired (e.g., Epstein Barr virus [EBV]). In two better described cases a causal association is unlikely, one occurring concurrently with COVID-19 infection and the other with further episodes occurring without a temporal association to BNT162b2 exposure. One well described literature case in the post-marketing dataset and a further literature case identified after the DLP are considered possibly related to BNT162b2. However, in the context of the incredibly large numbers of doses administered to women and adolescent females this does not provide a sufficient strength of association, particularly in the context of a poorly understood clinical entity such as NAGU. There has been no literature published in the interval period, other than case reports, to add to the knowledge base. Incidence rates generated by PRAC for the UK and Spain were used by the MAH to calculate an O/E ratio for the post-marketing data. However, these rates cannot be put into context as there are no published background rates for NAGU specifically. Capturing the diagnosis of NAGU accurately in real world data medical diagnostic codes is also difficult. These caveats mean that the O/E analysis is limited by uncertainty in the background rate and should be interpreted cautiously. Overall, this update contains data consistent with the previous signal evaluation and 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 and specific updates will be included in future PSURs if significant new information is obtained.

Rapporteur assessment comment:

Please refer to the separate signal procedure vulval ulceration (EPITT 19840; EMEA/H/C/005735/SDA/056) in which PRAC concluded that there was not sufficient evidence to conclude a causal association between vulval ulcerations and Comirnaty exposure. The signal vulval ulceration was closed.

As requested the MAH provided a review of additional cases reporting vulval ulceration from 16 Aug 2022 through 18 Dec 2022 in the current 4th PSUR:

Clinical trial data

No new cases retrieved.

Post-marketing data

From 16 Aug 2022 through 18 Dec 2022, 9 new cases reporting vulval ulceration were retrieved. Two ([redacted] and [redacted]) of the 9 cases were considered possible related to Comirnaty exposure (one case after Comirnaty Original and one case after Comirnaty Original/Omicron BA.4-5).

Literature

No new relevant literature articles were identified.

Additional 2 new case reports were retrieved after the DLP of which one case [redacted]) was considered possible related to Comirnaty exposure.

Observed versus expected analysis

Based on the lower background rates from the UK and the estimated number of exposure person-years through 15 December 2022, O/E ratios were well below one for both risk windows of 21- and 42-days with the exception of females 12-17 years using the low background rate from the UK in the 21-day risk window: O/E ratio 1.37 (95% CI 0.98;1.88), although not statistically significant. However, using the higher background incidence rates from Spain, all O/E ratios were well below 1, including for females 12-17 years, suggesting that the number of observed cases may not be higher than the expected cases.

Overall, since the previous signal procedure (EMEA/H/C/005735/SDA/056) that retrieved 3 cases considered probable related and 31 cases considered possible related, there were only 3 new cases considered possible related to Comirnaty exposure. Therefore, the conclusion of the previous signal procedure is not altered that at the moment there is not sufficient evidence to conclude a causal association between vulval ulcerations and Comirnaty exposure. The MAH should closely monitor any new cases, patterns, or trends of reporting vulval ulceration through routine pharmacovigilance.

Issue solved

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

	MAH 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 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.

Rapporteur assessment comment:

Please refer to the separate variation procedure (EMEA/H/C/005735/II/0152) regarding adding dizziness as an ADR with frequency Uncommon to the product information of Comirnaty (SmPC section 4.8 and PL).

Amenorrhoea

Reference is made to the PRAC PRAC EPITT No. 19784 (Amenorrhoea) Assessment Report including the following request - *The MAH of Comirnaty is asked to provide an updated analysis of amenorrhoea in the next PSUR with DLP 18/12/2022. In the analysis, the MAH should provide responses to the following list of questions*:

Q1 *- The MAH should discuss the possibility to further investigate amenorrhoea events post-vaccination in ongoing or planned studies (e.g., PASS planned in the RMP or clinical trials)*

MAH's response

The MAH will be assessing amenorrhea events post-vaccination in the ongoing PASS C4591021. Preliminary results will be included in interim report 3, planned for 31 March 2023.

Rapporteur assessment comment:

The MAH stated that amenorrhoea will be assessed in the ongoing PASS C4591021. Please refer to the ongoing procedure EMEA/H/C/005735/MEA/017.6 regarding preliminary results in the third interim report. No new safety information could be identified concerning (secondary) amenorrhoea in these preliminary results of PASS C4591021.

***Q2** - The MAH should discuss ways in which more information can be obtained from epidemiologic studies or clinical trials on the topic of menstrual disorders, including amenorrhoea. The MAH should outline which possibilities have been considered.*

MAH's response

Clinical Trials

Pfizer/BioNTech understand the reasoning behind this request, and it has been considered. To implement a clinical trial to investigate this issue would be challenging and the study design required would not be feasible (due to a number of factors including challenges in finding a large enough study population of females of childbearing age who have not received their primary series, the difficulty accurately evaluating menstrual disturbances [e.g., quantification of menses, quantification of what is a normal menses for the individual participant], follow up time that would be needed, determination of whether investigations would be required and which ones). However, Pfizer/BioNTech propose that additional information could be collected from clinical trial participants reporting AEs of menstrual disturbances. We are currently in the process of developing an additional form within the CRF that could be completed by the site, and would collect required information including, previous menstrual history, use of hormonal contraception, etc. This would be implemented for any study within the C459 clinical development program including females of childbearing age with enrolment beginning in Q1 2023.

Rapporteur assessment comment:

It is agreed with the MAH that a clinical trial to investigate amenorrhoea would be challenging and the study design required would not be feasible. MAH's alternative proposal to add an additional information form (to collect previous menstrual history, use of hormonal contraception, etc) for clinical trial participants reporting AEs of menstrual disturbances (in trials with enrolment beginning in Q1 2023), is endorsed.

Epidemiologic Studies

While clinically defined secondary amenorrhea is likely to be well captured in electronic health data, patients with more subtle changes or delays in menstrual cycles are unlikely to seek medical attention. Instead, menstrual tracking app data, completed by the patients themselves, may provide improved sensitivity to identify more subtle menstrual cycle delays across a large number of patients.

To better understand what data are available to study menstrual cycle disorders, the MAH conducted a preliminary feasibility assessment of available data sources in the EU and US. Included in this feasibility assessment was a review of data sources from the literature, informational interviews with 3 academic researchers in the field, and a review of 9 data sources (2 menstrual tracking software applications ['apps'] with EU data; 1 menstrual tracking app with US-only data; 4 US EMRs or claims data sources; and 2 US research cohorts). Key data elements assessed included region of data (EU or US prioritized), adequate capture of menstrual cycle disorders (including secondary amenorrhea and heavy menstrual bleeding [HMB]), adequate capture of COVID-19 vaccination (including manufacturer), adequate capture of underlying medical conditions and other potential confounders that may impact menstrual cycle disorders, and a large sample size representative of the general population.

This preliminary feasibility assessment identified several key strengths of menstrual tracking app data, particularly prospective data collection, capture of a wide range of menstrual cycle-related variables (e.g., period dates, menstrual flow volume, menstrual-related pain), and large sample sizes of users from (depending on the app) the EU, the US, and other regions. Identified limitations of menstrual tracking app data include missing information (e.g., it is possible that patients who appear to have amenorrhea

simply forgot to record a menstrual cycle), self-reported COVID-19 vaccination resulting in potential missing information or incorrect dates, and a lack of detailed covariate and other medical history-related variables.

The conclusion from this preliminary feasibility assessment was that linkage of menstrual tracking app data to an EMR data source may help to overcome some of the limitations of using menstrual tracking data alone. For example, linkage of the two data sources may allow for improved identification of subtle delays in the menstrual cycle, ability to validate true cases of secondary amenorrhea, ability to identify administratively-recorded COVID-19 vaccination information, and the collection of comprehensive gynecologic history. It was concluded that a comprehensive data source assessment is required to determine the feasibility of such a linkage in the EU and/or the US. To this end, the MAH proposed to conduct a formal feasibility assessment of available data sources to evaluate a potential association between the Pfizer-BioNTech COVID-19 vaccine and menstrual cycle changes (including HMB and amenorrhea) using linked menstrual tracking app data and EMR records in the EU and/or the US.

In October 2022, the MAH communicated to the PRAC that the MAH has identified a vendor to conduct this comprehensive feasibility assessment in the EU and the US. The MAH confirmed that this feasibility assessment will involve the comprehensive identification of candidate data sources in the EU and the US via a targeted literature search; detailed evaluations of menstrual tracking app and healthcare data sources (via in-depth interviews with the data custodians); evaluation of feasibility findings; and development of a study proposal. Given complexities in studying this outcome using non-traditional real-world data sources, the MAH has proposed to complete this feasibility assessment and provide a study concept proposal to the EMA by 30 April 2023.

Rapporteur assessment comment:
The MAH stated to complete a feasibility assessment that involve the comprehensive identification of candidate (real-world) data sources in the EU and the US; detailed evaluations of menstrual tracking app and healthcare data sources; evaluation of feasibility findings; and development of a study proposal by 30 April 2023. When MAH's study proposal is submitted in the near future to the EMA, assessment will be performed accordingly.

Q3 *- The MAH should provide information on the number of women of childbearing potential participating in the clinical trials including time to follow-up (patient year of exposure). The MAH should discuss whether the trial was designed to identify amenorrhoea (defined as having lasted more than 3 months in those with a regular menstrual cycle) taking into consideration the age of the participants and the duration of the follow-up.*

MAH's response

Based upon the previously used definition of childbearing age (17-45 years) as per the Response to PRAC (Signal Assessment Report, April 2022 and Response to the PAM-SDA- 053 Heavy Menstrual Bleeding Queries Received on 27 May 2022 Regarding the Pfizer- BioNTech COVID-19 Vaccine, August 2022), and reviewing the 2 largest placebo-controlled studies including participants within this age group (C4591001 and C4591031 SSA), the exposure of female participants of childbearing age to 30 µg of BNT162b2 vs Placebo for each study is 1610 PY vs 1720 PY for C4591001 and 270 PY vs 210 PY for C4591031 Sub-study A respectively. Although the source of these data is the Response to the PAM-SDA-053 Heavy Menstrual Bleeding Queries Received on 27 May 2022, it is still accurate as enrolment had completed.

Rapporteur assessment comment:

The exposure of female participants of childbearing age to 30µg of BNT162b2 vs placebo is 1610 PY vs 1720 PY for placebo-controlled study C4591001 and 270 PY vs 210 PY for placebo-controlled study C4591031 (sub-study A).

Please refer to Q2 above regarding the discussion trials were designed to identify amenorrhoea.

Q4 *- The MAH should review all serious cases for the PT "amenorrhoea" and discuss in detail all events of an absent menstruation if this condition persists for at least 3 months or, if less than three months, the outcome is reported as "not resolved" or "unknown". The analysis should differentiate between both groups of reports.*

MAH's response

Please refer to Appendix 5.3.2.1 Amenorrhoea Signal Evaluation.

Rapporteur assessment comment:

Please refer to the assessment of Appendix 5.3.2.1 below.

Q5 *- The MAH is reminded that ICSR that are lacking information on previous menstrual cycle, medical history of risks factors should not be routinely excluded, rather the MAH should provide justification on how cases with possible confounders (e.g., concomitant medication and/or medical history) have been classified.*

MAH's response

Please refer to Appendix 5.3.2.1 Amenorrhoea Signal Evaluation.

Rapporteur assessment comment:

Please refer to the assessment of Appendix 5.3.2.1 below.

Q6 *- The MAH should analyse in addition to serious medically confirmed case, also nonserious and/or non-medically confirmed cases, incl. aggregate analysis of all reports (e.g., age, time-to-onset of first symptoms, presence of confounding factors, impact of potential media attention with report before and after the publicity).*

MAH's response

Please refer to Appendix 5.3.2.1 Amenorrhoea Signal Evaluation.

Rapporteur assessment comment:

Please refer to the assessment of Appendix 5.3.2.1 below.

Q7 *- The MAH should discuss all positive re-challenge cases (regardless of seriousness and medical confirmation). The MAH is required to consider the case narrative information for proper identification of positive re-challenge cases, in addition to the structured E2B data field on positive re-challenge (G.k.9.i.4 "Did Reaction Recur on Re-administration?").*

MAH's response

Please refer to Appendix 5.3.2.1 Amenorrhoea Signal Evaluation.

Rapporteur assessment comment:

Please refer to the assessment of Appendix 5.3.2.1 below.

Q8 - *The MAH should present a critical analysis of all relevant new literature data with a focus on methodology, conclusions, strengths, and limitations.*

The analysis and discussion should be structured according to the instructions in question 4, including the case review with WHO-UMC causality assessment; a justification of causality category should be given for each case. The MAH should state how the seriousness of the cases related to amenorrhoea is assigned.

MAH's response

Please refer to Appendix 5.3.2.1 Amenorrhoea Signal Evaluation.

Rapporteur assessment comment:
Please refer to the assessment of Appendix 5.3.2.1 below.

The MAH should prioritize all ICSR relating to this signal when handling the backlog of cases and report on the backlog at time of DLP.

MAH's response

The MAH has implemented since May 2021 a procedure for the review and prioritisation, on a weekly basis, of non-serious cases that are pending completion in the global safety database and that have been identified as being of interest for the purpose of continuous assessment of the safety profile of the COVID-19 vaccine.

Rapporteur assessment comment:
Noted.

Amenorrhoea - updated cumulative review (Appendix 5.3.2.1)

Methodology

MAH's safety database was searched for all BNT162b2 vaccine (including Bivalent BNT162b2) cases received through 18 December 2022 using the MedDRA version 25.1 search criteria: PT: Amenorrhea.

Results

Overview

A total of 15408 cases (including 40457 events) were identified from the database using the search criteria mentioned above through 18 December 2022.

Most of the cases 15234 (98.8%) were spontaneous reports, 23 (0.1%) were clinical study reports and 151 (1.0%) were solicited reports. A total of 13131 cases (85.2%) were nonserious cases and the remaining 2277 (14.8%) were serious cases. Most of the cases, 14044 (91.1 %), were non-medically confirmed and the remaining 1364 (8.9%) cases were medically confirmed. A total of 332 cases were serious medically confirmed cases (2.15 %). There was also one fatal case (AER# [redacted] unspecified cause of death but unrelated to amenorrhoea). The case distribution by age is in Table 2.

Table 2. Case Distribution by Age

	Age Range	Number of Cases	Percentage (%)
	Less than or equal to 17 years	715	4.6
	18-30 years	5478	35.6
	31-50 years	7996	51.9
Mean= 33.6	51-64 years	379	2.5
Median= 33.0	65-74 years or greater than 75 years	2	0.0
N=14545	Unknown	838	5.4

Most of the cases were reported from Netherlands (3766, 24.4%), followed by Germany (3567, 23.2%) and France (2686, 17.4%).

When reported, the clinical outcome of the selected PT 'Amenorrhea' was reported as not resolved in 10349 cases (67.2%), resolved/resolving/resolved with sequelae in 3017 (19.6%) cases and unknown in 2041 cases (13.2%).

In 4271 cases (27.7 %), the events were reported after the first dose of the vaccination, in 5194 cases (33.7%) after the second dose and in 1274 cases (8.3%) amenorrhea was reported after the third dose and in 23 (0.2%) after the fourth dose. In 5029 cases (32.6%) dose was unspecified.

The latency of the event was unknown in 4005 cases. In the other cases, the time to onset ranged between the same vaccination day up to more than 3 months after vaccination, as detailed in Table 5.

Table 5. Time To Onset of Amenorrhea (Relative to Vaccine Dose)

Time to onset	Number of cases
Same day	3022
1-3 days	1547
4-7 days	1169
8-14 days	1436
15-21 days	1248
22-30 days	1126
1-3 months	1503
> 3 months	343
Unknown	4005

The event duration was unknown in 1411 cases. When reported, it ranged between <1 month up to >1 year, as detailed in Table 6.

Table 6. Amenorrhoea Event Duration

Duration	Number of cases
< 1 month	353
1-3 months	525
3-6 months	322
6-12 months	78
> 1 year	13
Unknown	1411

Out of the 15408 cases, there were 5215 cases that were considered confounded. Reasons that events were considered confounded included report of a medical history of known risk factors such as hypothalamic or pituitary disorders or other endocrines gland disorders, other chronic diseases that may lead to amenorrhea, confounding concomitant medications, co-reported AEs representing a potential alternative etiology for the amenorrhea. Details follow:

- Medical history of hypothalamic or pituitary disorders (stress/depression, eating disorder, hyperprolactinemia, autoimmune diseases, tumors), other endocrines gland disorders (thyroid diseases, polycystic ovary syndrome), chronic diseases that can cause amenorrhea (Inflammatory Bowel Disease/Coeliac disease), contraception (hormonal or intrauterine devices), previous menstrual disorder/premature menopause/menopause/uterine disorders: 1211 cases.

- Co-suspect drugs (e.g., levonorgestrel, tamoxifen, desogestrel, sertraline, venlafaxine, methotrexate) that can cause menstrual disorders: 31 cases.
- Concomitant use of antidepressant, antipsychotics (duloxetine, sertraline, venlafaxine) or hormonal contraception (levonorgestrel) or hormones or hormone-like molecules (estrogen, progesterone, diethylstilbestrol): 956 cases.
- Co-reported AEs (COVID-19 infection, polycystic ovaries, cancer and others) that confound assessment of the role of vaccine on amenorrhea (possible primary ovarian insufficiency, hypothalamic or pituitary disease): 542 cases.
- Cases in age populations (< 15 years old and > 45 years old women) in which changes in menstrual flow and in the length of the cycle can physiologically occur: 2222 cases.

The remaining 10193 cases were comprised of 1106 serious cases (148 medically confirmed) and 9087 non serious cases (619 medically confirmed).

Rapporteur assessment comment:

Retrieved from MAH's safety database, through 18 Dec 2022, were 15,408 cases (13,131 cases [85.2%] non-serious cases and 2,277 [14.8%] serious cases) reporting amenorrhea after Comirnaty exposure.

Medically confirmed were 1,364 (8.9%) cases and non-medically confirmed were 14,044 (91.1%) cases. Serious medically confirmed were 332 cases (2.15%).

There were 5,215 (33.8%) cases considered confounded which included report of a medical history of known risk factors (hypothalamic or pituitary disorders or other endocrines gland disorders), other chronic diseases that may lead to amenorrhea, confounding concomitant medications, co-reported AEs representing a potential alternative etiology for the amenorrhea.

Serious cases

There were 2277 serious cases (10038 events) retrieved from the post marketing database using the selected search criteria. All serious cases were considered, per the PRAC request, including serious cases that were noted in the section above to contain potential confounders.

Among these 2277 cases, amenorrhoea was reported as a serious event in 1786 cases according to the following criteria. The remaining serious cases had another event, not amenorrhoea, reported as serious.

- 1470 were categorized as medically significant events.
- 85 led to hospitalization (13 of these were included within the 1470 medically significant events).
- 20 were reported as life-threatening (6 of these were included within the 1470 medically significant events and 4 within the hospitalized group).

Among them, 278 cases reported unspecified criteria for seriousness.

Many of the cases categorized as serious due to hospitalization or life threatening did not provide additional descriptive information and the seriousness criteria was driven by co-reported adverse events that required medical intervention and/or hospitalization. Cases that reported only the unique PT of amenorrhea and reported hospitalization did not mention the reason for the hospitalization.

A total of 795 cases (34.9%) were received from France, followed by 464 cases (20.4%) received from United Kingdom, 147 cases (6.5%) from Germany, 133 cases (5.8%) from Spain and 101 cases (4.4%) from Italy.

The mean age reported in these 2277 serious cases was 34.7 years (median=34 years), with most of the women (1230 cases, 54%) being 31-50 years old.

The most frequent co-reported PTs in the SOC 'Reproductive system and breast disorder' in the 2277 serious cases, excluding amenorrhea, are listed in Table 7.

Table 7. Most frequently co-reported PTs in the SOC 'Reproductive system and breast disorder' (2277 Serious reports)

Preferred Term	Number of Cases	Percentage
Menstruation irregular	285	12.5
Heavy menstrual bleeding	270	11.9
Dysmenorrhoea	199	8.7
Menstrual disorder	179	7.9
Menstruation delayed	176	7.7
Intermenstrual bleeding	84	3.7
Oligomenorrhoea	78	3.4
Polymenorrhoea	47	2.1
Hypomenorrhoea	39	1.7
Premenstrual syndrome	39	1.7

Out of the total 2277 cases, there were 38 cases of pregnancy. A total of 1171 cases were considered confounded by pre-existing medical history, concomitant medications or co-suspect drugs, co-reported AEs suggestive of an alternative etiology for amenorrhea and age group (case reported in <15 years old and >45 years old). Most cases (1976, 86.8%) did not provide information regarding duration of amenorrhea. There were 220 serious cases in which amenorrhoea lasted for ≥3 months and 81 cases reporting amenorrhoea lasting for <3 months.

Rapporteur assessment comment:

Of the total retrieved 15,408 amenorrhea cases, there were 2,277 (14.8%) serious cases of which:

- 1,171 (51.4%) cases were considered confounded by pre-existing medical history, concomitant medications or co-suspect drugs, co-reported AEs suggestive of an alternative etiology for amenorrhea and age group (case reported in <15 years old and >45 years old).
- 1,976 (86.8%) cases did not provide information regarding duration of amenorrhea.
- 220 (9.7%) cases reporting amenorrhea lasted for ≥3 months.
- 81 (3.6%) cases reporting amenorrhea lasting for <3 months.

Serious cases with amenorrhea lasting for ≥3 months

There were 220 cases that reported amenorrhea lasting for ≥ 3 months. The distribution by age is in Table 8. In 8 cases, the reported age was < 15 years with outcome 'resolved' in 6 out of the 8 cases. In 53 cases, amenorrhoea was reported in women of >45 years old (pre-menopause phase) with outcome of resolved/resolving in almost all cases. In 6 cases, age was unknown. In the remaining 153 cases, age ranged between 16 and 44 years with the distribution pattern as shown in Table 8.

Table 8. Age Distribution in Cases of Amenorrhoea for >3 months

Age	Number of cases
≤ 15 years	8
16-20 years	12
21-25 years	40
26-30 years	37
31-35 years	19
36-40 years	25
41-44 years	20
> 45 years	53
Unknown	6

When reported, the latency was reported as detailed in Table 9.

Table 9. Time to onset of cases reporting amenorrhoea for >3 months

Time To Onset	Number of cases
Same day	45
1-3 days	15
4-7 days	11
8-14 days	14
15-21 days	19
22-30 days	10
1-3 months	40
> 3 months	6

Out of the 220 serious cases reporting amenorrhoea lasting ≥3 months, 126 cases were considered confounded by pre-existing medical history of risk factors or concomitant medications known to be potential causes of amenorrhea. The remaining 94 cases were categorized based on WHO/UMC causality assessment as follows:

- 75 cases: unassessable due to paucity of reported information (lack of clear latency dates, medical history and concomitant medications).
- 9 cases: unlikely (due to implausible time to onset, event existing prior to vaccination, co-reported events such as ovarian oedema that can explain the amenorrhoea or patient on oral contraceptive therapy).
- 10 cases: possible (contained information that did not describe potential alternative explanations for amenorrhea). Refer to table 10 for case details.

Details and WHO-UMC assessment of all serious cases (2277 cases) are included in Appendix 1 (not reproduced here).

Details of 'possible' serious cases (n=10) based on WHO-UMC causality assessment are included in Table 10:

Table 10. Serious Cases of reporting Amenorrhoea Lasting ≥ 3 Months and Assessed as 'possible' based on WHO-UMC Causality Assessment Categories (n=10)

AER # Age/Sex Country Event Outcome AE Duration Medically Confirmed Y/N	PTs Relevant Medical History Concomitant Medications	Summary MAH Comment
[redacted] 30/F [redacted] Resolved 129 Days N	Amenorrhoea Not Reported Not Reported	A 30-year-old female patient received dose 1 of COMIRNATY (Lot number: EW4109) on 26Apr2021. The patient's medical history and concomitant medications were not reported. The patient experienced amenorrhea on 26Apr2021. It was reported that she received the vaccine whilst on her period and that this was a shorter than usual period. She then did not have period until 02Sep2021 - 18 weeks later. Prior to this interruption she reported periods that were quite regular. On an unspecified date, the patient underwent lab tests and procedures which included blood follicle stimulating hormone increased, blood luteinizing hormone, blood prolactin, full blood count, thyroid function test, all with unremarkable results. The event was resolved on 02Sep2021. *MAH comment: subject reported 18 weeks lack of menses (having had always a regular cycle). Hormonal examinations were normal. Outcome resolved.*
[redacted] 36/F [redacted] Unknown 3 months N	Amenorrhoea Abstains from alcohol / Appendicectomy / Bronchogenic cyst / Drug hypersensitivity / Non-tobacco user Lorazepam	A 36-year-old female patient received dose 1 of COMIRNATY (Lot number: FO 6840) on 13Aug2021 and dose 2 on 10Sep2021. Relevant medical history included abstinence from alcohol, appendicectomy, bronchogenic cyst, drug hypersensitivity, non-tobacco user. The patient's concomitant medications included lorazepam. Past drug history included: penicillin for Streptococcal infection, reaction: urticaria. On 21Aug2021, the patient experienced amenorrhoea (medically significant). She had regular cycles every 25, 26 days prior to vaccination. A medical examination and consultation with several gynaecologists were performed, and pregnancy and other pathology were ruled out. The event 'amenorrhoea' was reported with a stop date of 22Nov2021. *MAH comment: patient with regular cycles reported amenorrhea 8 days after dose 1 (lasted 3 months). Examination and consultation with several gynaecologists were performed, and other pathology was ruled out.*
[redacted] 30/F [redacted] Resolved 184 Days N	Amenorrhoea Idiopathic hypersomnia, COVID-19 Pitolisant hydrochloride	A 30-year-old female patient received dose 1 of COMIRNATY (Lot number: FA5831) on 26May2021. Relevant medical history included idiopathic hypersomnia and COVID-19. Concomitant medications included pitolisant hydrochloride (WAKIX). On 26May2021, the patient experienced amenorrhoea. Following the vaccination, the patient experienced amenorrhea for 7 months, which led to a medical consultation. A blood test (urine and blood B-HCG (Beta human chorionic gonadotropin)) and an imaging test (ultrasound) were carried out, but no cause was identified, and pregnancy was ruled out. The patient recovered from the reported event. *MAH comment: amenorrhoea reported on the same vaccination day and lasted for about 7 months (after examinations, no other cause was identified, and pregnancy was ruled out).*

[redacted] 34/F [redacted] Not resolved 3.5 months N	Amenorrhoea, Heavy menstrual bleeding, Hypomenorrhoea Oral contraception (stop date=Apr2020), heavy menstrual bleeding None	A 34-year-old female patient received dose 2 of COMIRNATY (Lot number: FM4289) on 21Jun2021 and dose 1 (Batch/lot number: FM4289) on 13May2021 and experienced amenorrhoea. The patient's relevant medical history included oral contraception (stop date=Apr2020) and heavy menstrual bleeding. There were no concomitant medications. On an unspecified date in Jun2021, the patient experienced amenorrhoea described as lack of menses for about 3-4 months; in Oct2021, she had hypomenorrhoea and on 03Jan2022 she experienced heavy menstrual bleeding described as period that started almost hemorrhagic and lasted about 7 days (compared to 4-5 days before). Unspecified therapeutic measures were taken as a result of amenorrhoea, heavy menstrual bleeding, hypomenorrhoea. The patient did not recover from the event 'heavy menstrual bleeding' while the outcome of the event 'hypomenorrhoea' was reported as resolving. *MAH comment: case reporting absence of menstruation for 3-4 months with outcome of recovery and followed by HMB with no additional information.*
[redacted] 24/F [redacted] Resolved 5 Months N	Amenorrhoea, Vaccination site pain, Dysmenorrhoea Asthma / Dysmenorrhoea / Mite allergy Not Reported	A 24-year-old female patient received booster dose of COMIRNATY on 23Dec2021. The patient's relevant medical history included asthma, mite allergy and dysmenorrhea. The patient's concomitant medications were not reported. On 23Dec2021, the patient experienced vaccination site pain (recovered). On 17Jan2022, she had amenorrhoea described as total absence of menses until May2022 and on Jul2022 she experienced dysmenorrhea. The patient recovered from the event 'amenorrhoea' and 'vaccination site pain', while the outcome of the event 'dysmenorrhoea' was unknown. *MAH comment: Subject reported amenorrhea lasting 5 months and 25 days after the booster dose.*
[redacted] 22/F [redacted] Resolved 3 Months N	Menstruation irregular, Amenorrhoea, Dysmenorrhoea, Hypomenorrhoea, Heavy menstrual bleeding, Pain COVID-19 Not Reported	A 22-year-old female patient received dose 1 of COMIRNATY on 16Aug2021. The patient's relevant medical history included COVID-19. The patient's concomitant medications were not reported. On an unspecified date in Aug2021, she experienced amenorrhoea, described as lack of periods for 3 months, hypomenorrhoea (resolved). On an unspecified date in Oct2021, she had heavy menstrual bleeding, dysmenorrhoea and in Nov2021, she had menstruation irregular and pain. The patient recovered from events "amenorrhoea', 'hypomenorrhoea', 'heavy menstrual bleeding'. The outcome of the events 'menstruation irregular" and 'dysmenorrhea' was reported as not resolved, while the outcome of the event 'pain' was unknown. *MAH comment: Subject reported amenorrhea lasting 3 months followed by HMB. No additional information is reported.*

[redacted] 22/F [redacted] Resolved 3 Months N	Fibroadenoma of breast, Loss of libido, Asthma, Menstruation irregular, Dysmenorrhoea, Migraine, Amenorrhoea, Hormone level abnormal, Cyst, Non-consummation Asthma Not Reported	A 22-year-old female patient received dose 3 of COMIRNATY on 05Jan2022. The patient's relevant medical history included asthma. The patient's concomitant medications were not reported. On 15Jan2022, she experienced amenorrhoea, asthma (not resolved), dysmenorrhoea (not resolved), fibroadenoma of breast (not resolved), loss of libido (not resolved), migraine (not resolved). On an unspecified date in Apr2022, she experienced menstruation irregular (not resolved), hormone level abnormal (not resolved), cyst (not resolved), non-consummation (not resolved). Breast biopsy was performed (unspecified results). *MAH comment: patient reporting amenorrhoea about 10 days after vaccination and lasting 3 months, in the context of menstrual irregularities lasting about 4 months after vaccination.*
[redacted] 27/F [redacted] Resolved 6 Months	Dysmenorrhoea, Heavy menstrual bleeding, Uterine haemorrhage, Uterine pain, Night sweats, Amenorrhoea, Fatigue, Menstruation delayed COVID-19 (start date:2020) Not Reported	A 34-year-old female patient received dose 1 of COMIRNATY on 16Sep2021. The patient's relevant medical history included COVID-19 in 2020. The patient's concomitant medications were not reported. On 17Sep2021, she experienced dysmenorrhoea (medically significant), heavy menstrual bleeding (medically significant) and uterine haemorrhage (medically significant), all resolved on 25Sep2021. On 17Sep2021, she also had uterine pain with an unknown event outcome. On25Sep2021, she had amenorrhoea that resolved in Mar2022. She also complained of night sweats (non-serious) with onset Feb2022, that was resolving at the time of the report and fatigue with an unknown outcome. *MAH comment: case reporting amenorrhoea 9 days after vaccination that recovered about 6 months after, in the context of other menstrual irregularities reported (dysmenorrhoea, HMB) that occurred after vaccination.*
[redacted] 27/F [redacted] Resolved 7 Months N	Amenorrhoea, Dysmenorrhoea, Headache, Nausea, Fatigue COVID-19 Not Reported	A 27-year-old female patient received dose 2 of COMIRNATY on 18Aug2021 and dose 1 on an unspecified date. The patient's relevant medical history included COVID-19 on 12Jul2022. The patient's concomitant medications were not reported. On 30Nov2021, she experienced amenorrhoea, dysmenorrhea, fatigue, headache, nausea. The patient recovered from the event amenorrhoea, fatigue, nausea and headache on 23Jul2022 and on an unspecified date from the event dysmenorrhea. *MAH comment: patient reporting amenorrhea for more than 7 months. No additional relevant information was provided.*
[redacted] 21/F [redacted] Resolved 3 Months N	Amenorrhoea, Dysmenorrhoea, Menstruation irregular Asthma, COVID-19 Not Reported	A 21-year-old female patient received dose 2 of COMIRNATY on 16Feb2022 and dose 1 on an unspecified date. The patient's relevant medical history included: asthma and COVID-19. Concomitant medications were not reported. On an unspecified date in Feb2022, she experienced amenorrhoea for about 3 months, dysmenorrhea and menstruation irregular. The patient recovered from the event amenorrhoea on an unspecified date and did not recover from the event 'dysmenorrhoea'. The outcome of the event 'menstruation irregular' was unknown. *MAH comment: the subject reports lack of menses for 3 months with an outcome of recovery. No mention on previous regularity of the cycle is reported.*

Rapporteur assessment comment:

As requested, the MAH reviewed all serious cases for the PT "amenorrhoea" and discussed in detail all events of an absent menstruation persisting for ≥3 months.

Of the 220 serious cases that reported amenorrhea lasting for ≥3 months:

- 10 cases were considered possible related to Comirnaty exposure.
- 9 cases were unlikely related (due to implausible time to onset, event existing prior to vaccination, co-reported events such as ovarian oedema that can explain the amenorrhoea or patient on oral contraceptive therapy).
- 75 cases were considered unassessable due to paucity of reported information (lack of clear latency dates, medical history and concomitant medications).
- 126 cases were considered confounded by pre-existing medical history of risk factors or concomitant medications.

Of the total retrieved 15,408 amenorrhea cases, 10 (0.06%) serious cases reporting amenorrhea lasting for ≥3 months were considered possible related to Comirnaty. These 10 serious amenorrhea cases are considered a relative low number of reports compared to the background incidence (from signal procedure EMEA/H/C/005735/SDA/052 - EPITT 19784: 3,300 per 110,000 PY) and high Comirnaty exposure (84,994,706 females aged 15-45 years who received at least one dose of Comirnaty in the US or EEA countries through February 15, 2022) and therefore considered not unexpected and coincidence reports.

No new safety information could be identified within the 220 serious cases reporting amenorrhea lasting for ≥3 months.

Serious cases with amenorrhea lasting for <3 months

There were 81 cases reporting amenorrhea lasting for <3 months. Of out them, 73 cases reported an outcome of 'resolved/resolving' and 8 cases had outcome 'unknown' or 'not resolved'. The details of the cases with unknown or not resolved outcomes, all with WHO/UMC assessment: unlikely, are shown in Table 11 (not reproduced here).

Rapporteur assessment comment:

As requested, the MAH reviewed all serious cases for the PT "amenorrhoea" and discussed in detail all events of an absent menstruation if this condition persists for <3 months with an outcome 'not resolved' or 'unknown'.

Of the total retrieved 15,408 amenorrhea cases, 8 (0.05%) serious cases reporting amenorrhea lasting for <3 months with outcome 'unknown' or 'not resolved' were all considered unlikely related to Comirnaty exposure.

No new safety information could be identified within the 81 cases reporting amenorrhea lasting for <3 months.

Non-serious cases

There were 13,131 non serious cases (30419 events), of which 13,106 were reported with BNT162B2 as suspect vaccine, 22 cases reported with Bivalent BNT162B2 OMI BA.1 and 3 cases reported with Bivalent BNT162B2 OMI BA.4-5. Most of these cases (3693, 28.1%) were received from Netherlands, followed by 3420 cases (26 %) received from Germany, 1891 cases (14.4%) from France, 942 cases (7.2%) from Sweden and 577 cases (4.4%) from Denmark. The mean age was 33.4 years (median=32 years), with most of the women (6766, 51.5%) being 31-50 years old.

The most frequently co-reported PTs in the SOC 'Reproductive system and breast disorder' with amenorrhea in the non-serious cases are in Table 12 (not reproduced here).

Out of the total 13,131 cases, there were 17 cases of pregnancy. A total of 4039 cases were considered confounded by pre-existing medical history, concomitant medications or co-suspect drugs, co-reported AEs suggestive of an alternative potential etiology for amenorrhea (e.g pregnancy) and age group (<15 years old and >45 years old). The remaining 9075 cases included 619 medically confirmed cases and 8456 non-medically confirmed cases. Case details of the 619 medically confirmed non serious cases are included in Appendix 2 (not reproduced here).

The majority (12141, 93%) of cases did not provide duration information. There were 1734 non serious cases (15 medically confirmed cases) in which amenorrhoea lasted for ≥3 months. Details of the 15 medically confirmed cases, all with WHO/UMC assessment: unassessable, are in Table 13 (not reproduced here).

Out of the 8546 non-medically confirmed non-serious cases, there were 8532 cases deemed unassessable due to paucity of available information as described below (many cases were missing more than one of these details):

- 617 cases where the age was unknown
- 8035 cases where concomitant medications were not reported
- 6698 cases where the medical history was not reported
- 7862 cases where the AE duration was not reported

The remaining 14 cases reporting information on AE duration, concomitant medications and medical history are described in Table 14 (not reproduced here). There were 9 cases assessed as 'possible' and 5 cases assessed as 'unlikely'.

Rapporteur assessment comment:

As requested, the MAH analysed in addition to serious medically confirmed cases, also the non-serious amenorrhea cases and/or non-medically confirmed cases.

Of the total retrieved 15,408 amenorrhea cases, 15 (0.1%) non-serious medically confirmed cases reporting amenorrhea lasting for ≥3 months were considered unassessable.

Of the total retrieved 15,408 amenorrhea cases, there were 14 (0.1%) non-serious non-medically confirmed cases (those cases who reported AE duration, concomitant medications and medical history). Nine of these 14 cases were considered possible related to Comirnaty exposure and 5 cases were considered unlikely related.

No new safety information could be identified within the 15 non-serious medically confirmed cases reporting amenorrhea lasting for ≥3 months, and the 14 non-serious non-medically confirmed cases who reported AE duration, concomitant medications and medical history. The remaining cases, which did not report AE duration, concomitant medications and medical history, are considered insufficiently documented to allow causality assessment.

Literature review

A literature search was conducted for significant new information using Database: <1969 to 2023 Week 04>, Embase <1974 to 2022 December 21>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-

Data-Review & Other Non-Indexed Citations and Daily <1946 to December 21, 2022> for coronavirus vaccine and amenorrhoea and coronavirus vaccine and menstrual alterations.

A summary of the newest relevant articles discussing menstrual cycle alteration is reported in Appendix 3 (not reproduced here).

No published studies were found describing secondary amenorrhoea due to COVID-19 vaccination, using the definition of amenorrhoea as the cessation of previously regular menses for three months or previously irregular menses for six months. A few post-COVID-19 vaccination studies report transient oligomenorrhea, defined as the lack of menstruation for intervals >35 days in adults or >45 days in adolescents, however, researchers often used differing definitions and criteria, this lack of a standard approach limits a comparative assessment of the literature. Some studies[7-11] mention menstruation delay using >38 days but for example do not mention the regular menstrual cycle of the participants.

Rapporteur assessment comment:

Among the presented 12 newest relevant articles there were no studies evaluating secondary amenorrhoea due to COVID-19 vaccination, using the definition of amenorrhoea as the cessation of previously regular menses for three months or previously irregular menses for six months.

Overall, the studies reported that the menstrual cycle change following COVID-19 vaccination appears relative small and temporary.

No new safety information could be identified from the retrieved literature.

There is not a unified position on heavier-than-normal bleeding cycles based on different published studies.[12,13] Published data suggest that the type of vaccine does not affect the chance that an individual will experience a change to menstrual timing[11,12,14] or flow,[12,15] suggesting that the effect is a result of the immune response to vaccination rather than a specific vaccine component. In support of this hypothesis, menstrual changes have previously been reported with hepatitis B,[16] and human papillomavirus (HPV)[17] vaccines.

Rapporteur assessment comment:

Heavy menstrual bleeding is labelled as an ADR in the Comirnaty PI.

A review paper on menstrual alteration after COVID-19 vaccination and infection from Male V[18] states that spontaneous reporting systems (e.g. VAERS) are not designed to detect increased rates of nonserious events that occur commonly. In fact, menstrual cycles are naturally varying also in the absence of vaccination. Overall different studies reported that COVID-19 vaccination is associated with a small increase in menstrual cycle length that resolves rapidly.

The review from Male V[18] cites two studies on the hypothesis that menstrual changes after COVID-19 vaccination are associated with activation of the immune response, but with conflicting results. In one study no association was found between the extent of side effects and changes to cycle length or flow,[12] while the second study found that those who experienced fever or fatigue post vaccination were more likely to experience a heavier-than usual period.[15] The author describes two proposed hypothetical mechanisms by which immune stimulation might cause menstrual changes:

- Innate immune responses could transiently interfere with the hormones that drive the menstrual cycle, or they could affect macrophages and natural killer cells in the lining of the uterus, which control the breakdown and regeneration of this tissue through the cycle. Furthermore, the timing of vaccination within the menstrual cycle affects whether cycle length increases. The menstrual cycle is divided into two phases: the follicular phase, which occurs before ovulation and can be prolonged by hormonal alterations, and the luteal phase, which occurs after ovulation and is more consistent in length. If menstrual changes are mediated by immune effects on the control of ovarian hormones vaccination would be expected to prolong the follicular phase, but this can only occur if vaccines are administered during this phase. Indeed, the Apple Women's Health Study found that cycle-length increases are only associated with vaccination in the follicular phase of the cycle.[13]
- In support of the possibility that COVID-19 vaccination affects immune cells in the uterine lining, the survey of 27,143 menstruating individuals found that increasing age was associated with an increased risk of heavier bleeding.[15] This could suggest that altered tissue repair, which is mediated by immune cells in the uterus and may be less effective in older people, is the mechanism by which COVID-19 vaccination increases menstrual flow. The evidence for the underlying mechanism is therefore mixed and could be consistent with effects mediated by both ovarian hormones (affecting cycle length) and endometrial repair (affecting menstrual flow).

Rapporteur assessment comment:

One study of Male (2022) proposed interesting hypothetical mechanism(s) by which immune stimulation due to COVID-19 vaccination might cause menstrual changes:

Innate immune responses could transiently interfere with the hormones that drive the menstrual cycle, or they could affect macrophages and natural killer cells in the lining of the uterus, which control the breakdown and regeneration of this tissue through the cycle.

However, plausible potential mechanisms for the occurrence of amenorrhoea after Comirnaty exposure are considered unknown at present.

MAH's discussion and conclusion

In all, 15,408 cases reporting Amenorrhoea were reported to the safety database in the context of over 3.5 billion Pfizer/BioNTech Covid-19 vaccines doses distributed and >1.8 million AE reports received. Most cases are non-serious and non-medically confirmed. Among the 2277 serious cases, 220 described lack of menstrual bleeding lasting ≥ 3 months (consistent with a clinical diagnosis of amenorrhoea). However, most reports described shorter periods of an absence of menstrual flow, for example, menstruation delayed by days or weeks, or not occurring when expected. Many of these cases had co-reports of other menstrual abnormalities such as dysmenorrhea and heavy menstrual bleeding. While true amenorrhoea is not often reported, the cases were more commonly consistent with menstrual irregularities, including the absence of expected menstrual blood flow. Unfortunately, most cases do not provide information such as date of last menstrual period or the phase of their menstrual cycle during vaccinations which would provide stronger data from which to determine a possible role of the vaccine. Almost 40% of the cases reported the event to occur on the same vaccination day up to 15 days after vaccination. The spontaneous reports do not contribute new significant information compared to those previously reviewed (up to 14 February 2022) for the initial response to PRAC.

The medical literature describes studies that are largely reliant on self-reporting which, while meaningful, lead to inherent difficulties in interpretation, particularly with estimations of menstrual flow. To add to the number of variables potentially affecting one's interpretation of the collected data, a recent published meta-analysis of over 21,000 women by Chao[19] provides more data-driven support regarding the effect of the disruptive COVID-19 pandemic experience itself on menstrual cycles. Chao found a statistically significant association between experiencing COVID lockdowns and menstrual cycle irregularities in women of reproductive age; neither COVID-19 nor vaccination against the virus were considered in the review.

Considering the totality of data, including the clinical trial data, the spontaneous reports and the medical literature, the support for a causal association between vaccination with COMIRNATY and amenorrhoea is lacking. As noted, the MAH is looking into methods to obtain data to better characterize menstrual changes coincident with COVID-19 vaccination and plans to collect more specific and targeted data in clinical trials when a menstrual adverse event is reported. This topic will also continue to be monitored with routine pharmacovigilance. Based on current knowledge, the benefit risk profile of the vaccine remains favorable.

Rapporteur assessment comment:

Clinical trials/ Epidemiologic studies

There was no update presented of cases reporting amenorrhea in clinical trials. However, the MAH stated to complete a feasibility assessment that involve the comprehensive identification of candidate (real-world) data sources in the EU and the US; detailed evaluations of menstrual tracking app and healthcare data sources; evaluation of feasibility findings; and development of a study proposal by 30 April 2023 (not yet submitted to EMA). When MAH's study proposal is submitted in the near future to the EMA, assessment will be performed accordingly.

Furthermore, the MAH stated that they are looking into methods to obtain data to better characterize menstrual changes coincident with COVID-19 vaccination and plans to collect more specific and targeted data in clinical trials when a menstrual adverse event is reported, which is supported.

Post-marketing

Retrieved from MAH's safety database, through 18 Dec 2022, were 15,408 cases (13,131 cases [85.2%] non-serious cases and 2,277 [14.8%] serious cases) reporting amenorrhea after Comirnaty exposure. Of the total retrieved 15,408 amenorrhea cases, there were:

- 10 (0.06%) serious cases reporting amenorrhea lasting for ⩾3 months, considered possible related to Comirnaty exposure.

- 8 (0.05%) cases reporting amenorrhea lasting for <3 months with outcome 'unknown' or 'not resolved', considered unlikely related to Comirnaty exposure.

- 15 (0.1%) non-serious medically confirmed cases reporting amenorrhea lasting for ⩾3 months, considered unassessable.

- 9 (0.05%) non-serious non-medically confirmed cases (those cases who reported AE duration, concomitant medications and medical history), considered possible related to Comirnaty exposure.

No positive re-challenge amenorrhea cases were reported.

The total of 19 possible related amenorrhea cases are considered a relative low number of reports compared to the estimated background incidence (from signal procedure EMEA/H/C/005735/SDA/052 -

EPITT 19784: 3,300 per 110,000 PY) and the high estimated Comirnaty exposure (84,994,706 females aged 15-45 years who received at least one dose of Comirnaty in the US or EEA countries through February 15, 2022) and therefore considered not unexpected and coincidence reports.

Literature

Among the presented 12 newest relevant articles there were no studies evaluating secondary amenorrhoea due to COVID-19 vaccination, using the definition of amenorrhoea as the cessation of previously regular menses for three months or previously irregular menses for six months.

Mechanism

Plausible potential mechanisms for the occurrence of amenorrhoea after Comirnaty exposure are considered unknown at present.

PASS

Amenorrhea will be assessed by the MAH in the ongoing PASS C4591021. Please refer to the ongoing procedure EMEA/H/C/005735/MEA/017.6 regarding preliminary results in the third interim report.

Overall, MAH's conclusion is endorsed that a causal association between vaccination with Comirnaty and amenorrhoea is lacking. No new safety information could be identified from the updated review of amenorrhea as requested from the (closed) signal procedure EMEA/H/C/005735/SDA/052 - EPITT 19784. The MAH should continue to be monitor cases reporting amenorrhea after Comirnaty exposure with routine pharmacovigilance and in PASS C4591021.

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2.2.2. 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.

Rapporteur assessment comment:

Regarding pemphigus and pemphigoid, please refer to the separate signal procedure (EMEA/H/C/005735/SDA/061 - EPITT 19859). After DLP of this PSUR, PRAC (April 2023) concluded that currently there is insufficient evidence to establish a causal association between Comirnaty and pemphigus and/or pemphigoid. The signal is closed and the MAH is requested to present and discuss new data (after 15 Nov 2022) on pemphigus/ pemphigoid after exposure to Comirnaty in the next PSUR and should include new cases reporting pemphigus/ pemphigoid (clinical trials and post-marketing), new relevant literature, and O/E analysis.

2.3. Evaluation of risks and new information

2.3.1. Evaluation of important identified risks

Myocarditis and Pericarditis

Interval period 4th PSUR– myocarditis/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, the subjects developed both myocarditis and pericarditis):

Myocarditis

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

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.
- 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: fatal (46), resolved/resolving (482), resolved with sequelae (65), not resolved (314), unknown (424).

Pericarditis

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

O/E analysis

Consistent with the analyses in the most recent PSUR, for myocarditis in the EEA, all O/E ratios were above 1 across age groups, genders, and doses, except for males and females <5 years, using the low background rate. This was also true for most age groups other than the youngest and oldest in both genders using the mid and high background rates.

For myocarditis in the US, O/E ratios were above 1 for all stratifications 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 using the mid background rate, as well as for males 12-17 years and overall all doses using the high background rate. 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.

Rapporteur assessment comment:

Please refer regarding the course and outcome (including fatal cases) of myocarditis and pericarditis, the assessment of MAH's response on PRAC and CHMP requests here below.

Response to the CHMP request associated with procedure EMEA/H/C/005735/II/0139:

To ascertain whether the SmPC text in 4.4 and 4.8 currently covers these severe cases adequately, with the next PSUR, the MAH is 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 post-marketing 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).

Response to the PRAC ad-hoc request:

Since the initial labelling of myocarditis and pericarditis, further data have emerged on the course and outcome of myocarditis and pericarditis after Comirnaty vaccination. Therefore there is a need to determine whether the current SmPC section 4.4 wording on myocarditis and pericarditis remains appropriate, especially the sentence 'Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general'.

Consequently, the MAH is requested to provide a review of both course (e.g. severity, duration, treatment, length of hospital stay, complications) and outcome (e.g. recovered without sequelae, recovered with sequela, e.g. heart failure etc., fatal outcome) of myocarditis and/or pericarditis.

The review should include any available relevant data from (observational) studies and published literature as well as case reports. Case reviews including causality assessment should be reserved for cases with serious outcome and fatal cases. Summary of this case review, should be stratified into relevant age groups.

The course and outcome of myocarditis and pericarditis after Comirnaty vaccination should be placed in the context of course and outcome of myocarditis and pericarditis with alternative causality (e.g. post-viral cases etc.).

The MAH should discuss whether the current PI wording remains appropriate or whether an update of the PI is warranted, in which case a PI update proposal should be provided.

Response to the PRAC request 3 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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, subsequent dosing, outcome and possible risk factors (such as age of the participant) of the myocarditis/pericarditis cases following Comirnaty exposure.*

MAH's response

Background Information on Myocarditis Clinical Characteristics, Prognosis and Outcomes, Including Mortality

(Not reproduced here)

Post-vaccine Myocarditis – Clinical Characteristics, Prognosis, and Outcomes

Population-based Studies

Of the large population studies published to date, follow-up data after COVID-19 vaccine were generally limited to several months. Across all studies, the vast majority of individuals who developed myocarditis after vaccination did not experience further AEs within the follow-up period and appeared to have either improving symptoms or complete recovery. While rare instances of life-threatening myocarditis after COVID-19 vaccine have been reported, these events are rare and atypical for this subtype of myocarditis.[30]

The latest publication by investigators of the **NORDIC Cohort Study** assessed clinical outcomes of new onset myocarditis up to 90 days post hospital discharge.[31] In this population-based cohort study using nationwide register data from 4 Nordic countries (Denmark, Finland, Norway, and Sweden), from 01 Jan 2018 to the latest date of follow-up in 2022, authors included 7292 individuals aged ≥12 years who had an incident diagnosis of myocarditis as a main or secondary diagnosis, in a population of 23 million individuals, of whom, 530 (7.3%) had myocarditis associated with mRNA COVID-19 vaccination, 109 (1.5%) had myocarditis associated with COVID-19, and 6653 (91.2%) had myocarditis not related to COVID-19 or vaccination (i.e., 'conventional myocarditis' as used by authors). The main outcome measures were heart failure, or death from any cause within 90 days of admission to hospital for new onset myocarditis, and hospital readmission within 90 days of discharge to hospital for new onset myocarditis.

- Death was rare during the 90 days of follow-up, with 6 (1.1%), 6 (5.5%), and 156 (2.3%) patients dying of any cause within 90 days of admission to hospital in the vaccination, COVID-19, and conventional myocarditis groups, respectively. The relative risk of death over 90 days of follow-up was 0.48 (0.21 to 1.09) for patients with myocarditis associated with vaccination and 2.35 (1.06 to 5.19) for patients with myocarditis associated with COVID-19 disease, compared with conventional myocarditis used as reference (Figure 1; not reproduced here).
- Patients with myocarditis after vaccination had a significantly decreased risk of heart failure at 90 days after admission to hospital for myocarditis (relative risk 0.56, 95% CI: 0.37 to 0.85, P=0.006) compared with those with conventional myocarditis
- Among men and when the analysis was restricted to patients admitted on or after 01 Jan 2020, authors found a significantly lower risk of heart failure or death for patients with myocarditis after SARS-CoV-2 mRNA vaccination compared with the 2 other types of myocarditis (P=0.005 and P=0.002, compared with conventional myocarditis, respectively, and both P<0.001 compared with COVID-19 type myocarditis, respectively.
- For risk of re-admission, there were no significant differences in younger patients and in women for the 3 myocarditis groups, but a significantly reduced risk of re-admission was found for post-vaccination myocarditis in men and those admitted on or after 01 Jan 2020 compared with the conventional myocarditis group (P=0.03 and P=0.03, respectively) (Figure 2).

▪ **Figure 2. → Relative Risk of Incident Heart Failure or Death, As A Combined Outcome, Within 90 Days of Follow-Up Since Admission for New Onset Myocarditis, by Subgroup¶**

Table S5. Relative risk of incident heart failure or death, as a combined outcome, within 90 days of follow-up since admission for new-onset myocarditis, by subgroup.

Myocarditis type by subgroup	Heart failure diagnosis or death within 90 days of admission	Total number of individuals	Relative risk of heart failure diagnosis or death within 90 days since admission
12–39 year olds			
Vaccine myocarditis	8	340	0.61 (0.30–1.24)
COVID-19 myocarditis	5	48	2.71 (1.16–6.31)
Conventional myocarditis	128	3,327	1 (ref.)
≥ 40 year olds			
Vaccine myocarditis	19	190	0.68 (0.44–1.05)
COVID-19 myocarditis	13	61	1.45 (0.89–2.37)
Conventional myocarditis	488	3,326	1 (ref.)
Men			
Vaccine myocarditis	16	413	0.49 (0.30–0.81)
COVID-19 myocarditis	12	76	2.01 (1.19–3.41)
Conventional myocarditis	378	4,815	1 (ref.)
Women			
Vaccine myocarditis	11	117	0.73 (0.41–1.29)
COVID-19 myocarditis	6	33	1.40 (0.67–2.92)
Conventional myocarditis	238	1,838	1 (ref.)
Admitted on January 1, 2020 or later			
Vaccine myocarditis	27	530	0.54 (0.37–0.80)
COVID-19 myocarditis	18	109	1.77 (1.14–2.73)
Conventional myocarditis	265	2,833	1 (ref.)

The authors concluded that compared with conventional and COVID-19 myocarditis, myocarditis after vaccination with SARS-CoV-2 mRNA vaccines was associated with better clinical outcomes within 90 days of admission to hospital.

The **earlier study from the Nordic Registry** (Karlstad et al, 2022)[32] that evaluated 28-day mortality similarly found a lower mortality after vaccination with BNT162b2 compared with myocarditis without vaccination: for all age groups, the 28-day mortality of the unvaccinated cases with myocarditis was 0.8% (95% CI: 0.3%-2.0%) and 0.2% (95% CI: 0.0%-0.4%) after the Dose 2 of BNT162b2; there were no deaths among BNT162b2 myocarditis cases for males of any age and for patients of any gender younger than 40 years.

In the **French EPI-PHARE study**[33] investigators conducted a paired case-control study of all cases of hospitalisation for myocarditis or pericarditis which occurred between 12 May 2021 and 31 Oct 2021 among all persons 12 to 50 years of age in France, corresponding to 46 million doses of mRNA vaccines, with 21 million of them received at least one dose of BNT162b2. Authors matched the 1,612 cases of myocarditis and 1,613 cases of pericarditis in vaccinated with 16,120 and 16,130 cases in controls respectively. The study revealed that:

- The frequency of admission in intensive care unit (ICU), mechanical ventilation or death was lower for post-vaccination cases than for unexposed cases.
- The lengths of hospital stay were not significantly different in post-vaccination cases of myocarditis (median 4 days) and pericarditis (median 2 days) than in unexposed myocarditis cases.
- Drugs treatments within 30 days after hospital discharge were similar between post-vaccination myocarditis and unexposed cases. Regardless of the vaccination status, the therapeutic classes

most frequently used during the follow-up of myocarditis cases included beta blocking agents (63% of patients), analgesics (52%) and agents acting on the renin–angiotensin system (46%). The corresponding treatments of pericarditis cases were analgesics (83%), colchicine (69%) and beta blocking agents (14%).

Patone et al[34] analysed **England data** in a self-controlled case series study that included 42,842,345 people aged 13 years or older receiving at least 1 dose of vaccine, 21,242,629 received 3 doses, and 5,934,153 had SARS-CoV-2 infection before or after vaccination. Authors found that the risk of hospital admission or death from myocarditis is greater after SARS-CoV-2 infection than COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine.

Lai et al[35] conducted a retrospective cohort study in **Hong Kong** to compare prognosis of myocarditis developing after mRNA COVID-19 vaccination with viral myocarditis over 180 days of follow-up. All-cause mortality, heart failure, dilated cardiomyopathy (DCM), heart transplant, and post-discharge health-care utilisation were examined. A total of 866 patients were included for analysis, 104 (12.0%) were patients with myocarditis following mRNA vaccination, and 762 (88.0%) were viral infection related myocarditis. There were more male patients than female patients in both the post–mRNA vaccination and viral infection related myocarditis groups except for older adults. Authors observed:

- Very low incidence rates (<1 per 10,000 person-days) of mortality, heart failure, and DCM following myocarditis after mRNA vaccination, in contrast with incidence rates of 7, 8, and 2 per 10,000 person-days, respectively, among the viral infection related myocarditis patients.
- Zero incidences of heart transplant surgery were recorded for both groups.
- Over the follow-up period, 1 death (1.0%) of 104 patients with post-vaccination myocarditis and 84 deaths (11.0%) of 762 patients with viral infection related myocarditis were identified. Adjusted analysis showed that the post-vaccination myocarditis group had a 92% lower mortality risk (adjusted HR: 0.08; 95% CI: 0.01-0.57).

Several studies of myocarditis occurrences in **Israel** have been published to date and converge to a mild clinical course, prompt resolution and low mortality.

- In the Witberg et al[36] study of 2.5 million vaccinated members of a large health-care organisation in Israel, 54 met the criteria for myocarditis. Of them, a total of 76% of cases of myocarditis were described as mild and 22% as intermediate; 1 case was associated with cardiogenic shock. After a median follow-up of 83 days after the onset of myocarditis, 1 patient had been readmitted to the hospital, and 1 had died of an unknown cause after discharge. Of 14 patients who had left ventricular/left ventricle (LV) dysfunction on echocardiography during admission, 10 still had such dysfunction at the time of hospital discharge. Of these patients, 5 underwent subsequent testing that revealed normal heart function.
- Mevorach et al report an updated analysis of 5.1 million individuals fully immunised with 2 doses of BNT162b2 in Israel, among 304 persons with symptoms of myocarditis, 21 had received an alternative diagnosis. Of the remaining 283 cases, 142 occurred after receipt of the BNT162b2 vaccine; of these cases, 136 diagnoses were definitive or probable. In the 136 cases of definite or probable myocarditis, the clinical presentation in 129 (95%) was generally mild, with resolution of

myocarditis in most cases, as judged by clinical symptoms and inflammatory markers and troponin elevation, electrocardiographic and echocardiographic normalisation, and a relatively short length of hospital stay. However, 1 person with fulminant myocarditis died. The ejection fraction (EF) was normal or mildly reduced in most persons and severely reduced in 4 persons. MRI that was performed in 48 persons showed findings that were consistent with myocarditis on the basis of at least 1 positive T2-based sequence and 1 positive T1-based sequence (including T2-weighted images, T1 and T2 parametric mapping, and late gadolinium enhancement (LGE)). Follow-up data regarding the status of cases after hospital discharge and consistent measures of cardiac function were not available.[37]

In the US, the largest study was published by Oster et al[38] and included more than 192 million persons receiving 354 million mRNA vaccines. Using data from VAERS and adjudicated with CDC criteria, there were 1991 reports of myocarditis and 1626 of these reports met the case definition of myocarditis. Of those with myocarditis, the median age was 21 years (IQR, 16-31 years) and the median time to symptom onset was 2 days (IQR, 1-3 days). There were 826 cases of myocarditis among those younger than 30 years of age who had detailed clinical information available; of these cases, 792 of 809 (98%) had elevated troponin levels, 569 of 794 (72%) had abnormal electrocardiogram (ECG) results, and 223 of 312 (72%) had abnormal cardiovascular magnetic resonance (CMR) imaging results. Approximately 96% of persons (784/813) were hospitalised and 87% (577/661) of these had resolution of presenting symptoms by hospital discharge. The most common treatment was non-steroidal anti-inflammatory drugs (589/676; 87%). Authors conducted a qualitative comparison with myocarditis of other causes (termed as 'classical myocarditis') and noted that cases of myocarditis reported after COVID-19 vaccination were typically diagnosed within days of vaccination, whereas cases of typical viral myocarditis can often have indolent courses with symptoms sometimes present for weeks to months after a trigger if the cause is ever identified. The major presenting symptoms appeared to resolve faster in cases of myocarditis after COVID-19 vaccination than in typical viral cases of myocarditis. Even though almost all individuals with cases of myocarditis were hospitalised and clinically monitored, they typically experienced symptomatic recovery after receiving only pain management. In contrast, typical viral cases of myocarditis can have a more variable clinical course- e.g., up to 6% of typical viral myocarditis cases in adolescents require a heart transplant or result in mortality. The initial evaluation and treatment of COVID-19 vaccine-associated myocarditis cases were similar to that of typical myocarditis cases. Initial evaluation usually included measurement of troponin level, electrocardiography, and echocardiography. Supportive care was a mainstay of treatment, with specific cardiac or intensive care therapies as indicated by the patient's clinical status.

Rapporteur assessment comment:

The MAH described 9 population based studies (Denmark, Finland, Norway, Sweden, France, UK, China (Hong Kong), Israel, US) evaluating:

- persons with myocarditis after mRNA vaccination compared to persons with myocarditis without vaccination and/or myocarditis associated with COVID-19 (3 studies[31,32,33]); concluding that myocarditis after vaccination with mRNA vaccines was associated with better clinical outcomes within 90 days of admission to hospital and outcome death was rare (1.1% in the latest Nordic study) and was significantly lower than both conventional myocarditis or myocarditis associated with COVID-19 (relative risks 0.48 (0.21 to 1.09) and 2.35 (1.06 to 5.19) respectively).
- persons with myocarditis after COVID-19 vaccination compared to persons with myocarditis after SARS-CoV-2 infection (1 study[34]); this study concluded that the risk of hospital admission or death

from myocarditis is greater after SARS-CoV-2 infection than COVID-19 vaccination and remains modest after sequential doses including a booster dose of Comirnaty vaccine.

- persons with myocarditis after mRNA vaccination compared to persons with viral myocarditis (2 studies[35,38]); concluding low incidence rates (<1 per 10,000 person-days) of mortality, heart failure, and dilated cardiomyopathy following myocarditis after mRNA vaccination and that the post-vaccination myocarditis group had a 92% lower mortality risk (adjusted HR: 0.08; 95% CI: 0.01-0.57). Also, the major presenting symptoms appeared to resolve faster in cases of myocarditis after vaccination than in viral cases of myocarditis and they experienced symptomatic recovery after receiving only pain management. In contrast, viral cases of myocarditis can have a more variable clinical course e.g., up to 6% of typical viral myocarditis cases in adolescents require a heart transplant or result in mortality.
- persons with myocarditis after mRNA vaccination (3 studies[30, 36,37]); concluding that the clinical presentation in most cases was generally mild and the vast majority of individuals who developed myocarditis after vaccination did not experience further AEs within the follow-up period and appeared to have either improving symptoms or complete recovery. While rare instances of life-threatening myocarditis after COVID-19 vaccine have been reported, these events are rare and atypical for this subtype of myocarditis.

Overall, the results of these 9 studies suggest for myocarditis associated with SARS-CoV-2 mRNA vaccination that the course was generally milder with less severe outcome than for other types of myocarditis (associated with COVID-19 or other virus).

Comparative studies that included CMR imaging

Keshavarz et al[39] report a review of cardiac imaging findings of post-vaccine myocarditis in the literature comprising of 532 cases (462, 86.8% men and 70, 13.2% women, age range 12 to 80) with the following distribution: Pfizer/BioNTech: 367 (69%), Moderna: 137 (25.8%), AstraZeneca: 12 (2.3%), Janssen/Johnson & Johnson: 6 (1.1%), COVAXIN: 1 (0.1%), and unknown mRNA vaccine: 9 (1.7%). Most patients were discharged from the hospital uneventfully. There were 3 reported deaths (one after Moderna vaccine, and 2 after Johnson and Johnson) and one re-admission following the post-COVID-19 vaccination myocarditis event.

- The principal diagnostic imaging method reported in all 532 cases was CMR imaging, with abnormal findings in 361 (67.8%) cases. Abnormal findings included myocardial oedema 188 (35.3%), patchy or global myocardial signal hyperintensity in T1-weighted 142 (26.7%) and T2-weighted images 150 (28.2%), and pericardial, epicardial, and subepicardial LGE (overall 234, 44%). LGE of cardiac MRI was observed mainly on the epicardial/subepicardial segments (318 of 350 locations of enhancement, 90.8%) with the involvement of the inferior and inferolateral walls. Moreover, septal involvement was scanty.
- Echocardiography was reported in 73% (388 of 532) of cases with normal findings in 228 cases. Abnormal echocardiographic findings in 41.2% (160 of 388) of cases included pericardial effusion 5.1% (20 of 388), focal and general hypokinesia 12.1% (47 of 388), reduction in mono or biventricular ejection fraction (EF) 21.9% (85 of 388), and others were not reported. The left ventricle ejection fraction (LVEF) was reported in 197 cases of which 32% (63 of 197) were less than 50% and 68% (134 of 197) cases were greater than 50%.

Fronza et al[40] report a retrospective cohort study comparing the post-vaccination myocardial injury with other causes of myocarditis. Of the 92 included patients, 21 (23%) had myocarditis following COVID-19 vaccination (mean age, 31 years ± 14 [SD]; 17 men; mRNA–1273 in 12 [57%] and BNT162b2 in nine [43%]). Ten of 92 (11%) patients had myocarditis following COVID-19 illness (mean age, 51 years ± 14; 3 men) and 61 of 92 (66%) patients had other myocarditis (mean age, 44 years ± 18; 36 men).

- In the vaccine myocarditis group (n=21), chest pain occurred in all patients and started at a median of 3 days (IQR, 1–7 days) after vaccination, lasting 1-6 days. Fourteen (67%) of the 21 patients were admitted to the hospital, with a median length of stay of 3 days (IQR, 2–5 days). No patients were admitted to the ICU. Of the 21 patients, 10 (48%) were treated with colchicine, 7 (33%) with aspirin, 4 (20%) with ibuprofen, and one (5%) with steroids. Troponin levels were elevated in all patients admitted to the hospital (>26 pg/mL) and substantially decreased by the time of discharge (median, 2723 pg/mL [IQR, 1500-5772 pg/mL] vs 49 pg/mL [IQR, 0-205 pg/mL]; P = .001).
- MRI findings in the 21 patients with vaccine-associated myocarditis included LGE in 17 patients (81%) and LV dysfunction in 6 (29%).
- Compared with patients with other causes of myocarditis, patients with vaccine-associated myocarditis had a significantly higher LVEF and right ventricular ejection fraction (RVEF); less impaired global longitudinal strain, global circumferential strain (GCS), and global radial strain; lower native T1; and less extensive LGE; even after controlling for age, sex, and time from symptom onset to MRI.
- Compared with patients with COVID-19 illness, patients with vaccine-associated myocarditis had a higher LVEF, less regional wall motion abnormalities, and lower native T1.
- In all 3 patient groups, the most frequent pattern of LGE was subepicardial and the most frequent myocardial segment involved was the basal inferolateral wall. However, patients with COVID-19 illness and other myocarditis had a higher prevalence of abnormalities involving the basal to mid anterior and inferior septum, while patients with vaccine-associated myocarditis rarely had abnormalities involving the anterior wall or septum.
- There were no significant differences in blood biomarkers or electrocardiographic parameters between groups.
- At short-term follow-up (median, 22 days [IQR, 7-48 days]), all patients with vaccine-associated myocarditis were asymptomatic with no AEs. Of the 6 patients with impaired LVEF at MRI, 4 underwent subsequent transthoracic echocardiography or follow-up MRI, which demonstrated normal LVEFs in all. No patient with vaccine-associated myocarditis had an adverse cardiac event over the short-term follow-up.

Authors concluded that the severity of MRI abnormalities was milder, in general, compared with that of patients with other causes of myocarditis, even after controlling for age, sex, and time from symptom onset to imaging and these milder MRI abnormalities in patients with vaccine-associated myocarditis compared with other causes raises the possibility that this group may have a lower future AE rate.

Patel et al[41] also compared the phenotypic clinical characteristics and cardiovascular MRI findings in 14 patients with mRNA COVID-19 vaccine-associated myocarditis to those in 14 patients with acute myocarditis from other causes. The study found that:

- Patients in the case group had higher LVEF compared with the control group (59% vs 54%, P = .02), as well as higher LV GCS (−14.8% vs −12.7%, P=.045) and higher LV global radial strain (22.8% vs 18.8%, P=.048).
- Septal LGE and midmyocardial LGE involvement were more common in the control group than in the case group.
- The control group also had more LGE by volume and mass (median LGE volume percentage, 9.4% vs 5.7%; P=.11 and median LGE mass, 12.9 g vs 6.6 g; P=.08).

Authors concluded that patients with COVID-19 vaccination–associated acute myocarditis have higher LVEF, higher LV global circumferential and radial strain, and less involvement of LGE in the septal segments with less involvement of midmyocardial pattern of LGE, compared with patients with acute myocarditis from other causes, and thus, a favourable prognosis may be expected.

Evertz et al[42] conducted a comparative study of post-vaccine myocarditis with matched controls with non-vaccination myocarditis. In post-vaccination group (n=10), all patients received mRNA vaccinations; with 6 of them vaccinated with Spikevax by Moderna and 4 patients with COMIRNATY by BioNTech. All patients (n=20, 10 in each group) were hospitalised and underwent a standardised clinical examination, as well as an echocardiography and a CMR. Both, clinical and imaging findings and, in particular, functional and volumetric CMR assessments, as well as detailed tissue characterisation using LGE and T1 + T2-weighted sequences, were compared between both groups. The median age of the overall cohort was 26 years (group 1: 25.5; group 2: 27.5; p=0.57). All patients described chest pain as the leading reason for their initial presentation.

- CMR volumetric and functional parameters did not differ significantly between both groups. This was in concordance with a similar clinical presentation, ECG changes, and assimilable echocardiographic findings in patients of both groups.
- In all cases, the lateral LV wall showed LGE without significant differences in terms of the localisation or in-depth tissue characterisation (LGE enlargement: group 1: 5.4%; group 2: 6.5%; p=0.14; T2 global/maximum value: group 1: 38.9/52 ms; group 2: 37.8/54.5 ms; p=0.79 and p=0.80). In all patients, LGE was present within the subepicardial layers without statistical differences regarding its relative enlargement within the myocardium (group 1: LGE 5.4%; group 2: LGE 6.5%; p=0.143). Myocarditis affected the lateral segment in all cases, with partial involvement of the inferior segments in some of the patients (group 1: 40%; group 2: 20%; p=0.329).
- In both groups, myocarditis-related symptoms, such as chest pain, were improved (n=2; 10%) or even resolved (n=18; 90%) at the time of discharge. The mean time of the hospital stay was 5 (3.8-6.3) days in group 1 when compared to 6 (4.8-7.0) days in group 2 (p=0.653). Patients of both groups required non-steroidal anti-inflammatory drugs (group 1: 50%; group 2: 60%; p=0.653) in equal partitions.

Authors concluded COVID-19 mRNA vaccine-associated myocarditis does not show specific CMR patterns during the very acute stage in the most affected patient group of young male patients. The observed imaging markers were closely related to regular viral myocarditis, and no markers implying adverse outcomes were identified in this relatively little number of patients

Jain et al[43] conducted a retrospective multi-center study across 16 US hospitals of 63 patients <21 years with a diagnosis of vaccine induced myocarditis compared with a cohort with MIS-C. Authors evaluated clinical presentation, short-term abstract prognosis, and myocardial tissue changes as noted on CMR or

cardiac MRI. The 63 patients with vaccine induced myocarditis had a mean age of 15.6 years and 92% were male. All had received a mRNA vaccine and, except for one, presented after the Dose 2. Four patients had significant dysrhythmia; 14% had mild LV dysfunction on echocardiography, which resolved on discharge; 88% met the diagnostic CMR Lake Louise criteria for myocarditis. LGE on CMR was more prevalent in comparison with MIS-C. None of the patients required inotropic, mechanical, or circulatory support. There were no deaths. Follow-up data obtained in 86% of patients at a mean of 35 days revealed resolution of symptoms, arrhythmias, and ventricular dysfunction. Compared with MIS-C cases, patients with post-vaccine myocarditis had statistically significant higher troponin (8.78 vs 0.67 ng/mL), higher LVEF (60.9 vs 45.1%) lower CRP (37 vs 151 mg/L), lower duration of intensive care (2.5 vs 6.6 days), higher proportion of patients with LGE (88 vs 20%) and myocardial oedema (83.9 vs 28.6%). Authors concluded that the initial clinical course and short-term outcomes for post-vaccine myocarditis are good and reassuring, and the clinical presentation of post-vaccine myocarditis is distinct from MIS-C and appears to be less severe.

Patel et al[44] conducted a retrospective cohort study to evaluate patients aged <21 years with classic myocarditis, MIS-C myocarditis, and COVID-19 vaccine-related myocarditis. Of 201 total participants, 43 patients had classic myocarditis, 149 had MIS-C myocarditis, and 9 had vaccine-related myocarditis. At presentation, EF was lowest for those with classic myocarditis, with EF <55% present in 58% of patients. Nearly all patients with MIS-C myocarditis (n=139, 93%) and all patients with vaccine-related myocarditis (n=9, 100%) had normal LVEF at the time of discharge compared with 70% (n=30) of the classic myocarditis group (P<0.001). At 3 months after discharge, of the 21 children discharged with depressed EF, none of the 10 children with MIS-C myocarditis had residual dysfunction compared with 3 of the 11 (27%) patients in the classic myocarditis group.

Rapporteur assessment comment:

The MAH described 6 studies that included cardiovascular magnetic resonance imaging:

- review of cardiac imaging findings of post-COVID-19 vaccination myocarditis (1 study[39,]); this study concluded that post-COVID-19 vaccination myocarditis was most commonly reported in symptomatic men after the second or third dose, with cardiovascular magnetic resonance imaging findings including late gadolinium enhancement in 90.8% of inferior and inferolateral epicardial/subepicardial segments.
- comparing persons with myocarditis after COVID-19 vaccination to persons with other causes of myocarditis (3 studies[40, 41, 42]); concluding that the severity of cardiovascular MRI abnormalities was milder, in general, compared to persons with other causes of myocarditis. Therefore, a favourable prognosis may be expected.
- comparing vaccine induced myocarditis compared with MIS-C (1 study[43]); this study concluded that the clinical course and short-term outcomes (up to 35 days) for post-vaccine myocarditis are good, and the clinical presentation of post-vaccine myocarditis appears to be less severe compared to MIS-C.
- comparing classic myocarditis, MIS-C myocarditis, and COVID-19 vaccine-related myocarditis (1 study[44]); the study concluded that patients with COVID-19 vaccine-related myocarditis had a normal ventricular function recovery at discharge from the hospital.

Overall, the results of these 6 studies suggest for myocarditis associated with SARS-CoV-2 mRNA vaccination good clinical outcomes and milder abnormalities seen on cardiac MRI than for other types of myocarditis (associated with COVID-19 or other virus, MIS-C).

Studies on Long Term Outcomes That Included CMR Imaging

Comparative Studies

Vago et al[45] analysed the clinical, immunological, and CMR features of 16 myocarditis cases after COVID-19 immunisation in the acute phase and during follow-up (3-6 months) and compared with matched historical myocarditis cases unrelated to COVID-19. The study included 16 CMR-confirmed cases of myocarditis following SARS-CoV-2 immunisation, with chest pain presenting a mean of 4 ± 2 days after vaccination. All patients were young (5 were <18 years, mean age 22 ± 7 years, between 13 and 36 years) male patients and generally presented after their Dose 2 of COVID-19 immunisation (13, 81%). Most of them received mRNA vaccines (75%), while 25% presented with myocarditis after receiving a vector vaccine. ECG alterations were documented in 7 patients (ST elevation in 6, negative T wave in 1). The initial troponin level was elevated in all study participants. During the acute phase, there were no heart failure symptoms, syncope, or documented sustained bradyarrhythmias or tachyarrhythmias. CMR performed on average 4 days after the onset of symptoms showed in the majority of cases a localised pattern of myocarditis, mainly affecting the lateral wall of the LV with signs of subepi-midmyocardial oedema and necrosis. The LVEF was in the normal range for most cases, except for 2 patients whose LVEF was mildly decreased (46 and 47%); these 2 patients had no previous history of acute myocarditis. There was no definitive pericardial involvement in any patients.

- During follow-up, one patient experienced a recurrent episode of acute myocarditis (3 months after the vaccine), preceded by gastrointestinal infection. Other patients did not report symptom recurrence.
- The LVEF marginally increased upon follow-up, and LV end-diastolic volume index slightly decreased, both remaining in the normal range. Elevated T2 values depicting local oedema in the affected area were resolved. The native T1 value and ECV measured in the affected area also decreased; however, ECV remained slightly elevated.
- The LGE area shrank in all participants and disappeared completely in 31% (4/13) of cases. None of the participants had extensive (>20%) LGE during follow-up.
- There was no difference between the trajectory of cardiac volumes, function, mass, oedema and LGE between myocarditis patients' immunisation and age- and sex-matched myocarditis patients unrelated to COVID-19 vaccination or infection.

Dove et al[46] pre-print study reports intermediate CMR findings of COVID-19 vaccine-associated myocarditis (n=8) and compared to 'conventional myocarditis' (n=20) and MIS-C (n=61). In vaccine-associated myocarditis, follow-up CMRs performed at median 107 days (IQR 97, 177) showed normal ventricular systolic function, T1, and T2 values; 3/7 patients had LGE. At follow-up:

- For COVID-19 vaccine-associated myocarditis, intermediate follow-up CMR demonstrated resolution of inflammation, myocardial oedema, and ventricular dysfunction.
- The vaccine group had a lower percentage of LVEF<55% compared to classical myocarditis and MIS-C (0.0 vs 30.0 vs 6.6%, respectively, p=0.018).
- While improvement in the burden of LGE was seen, some patients had persistent LGE (42.9 vs 75.0 vs 3.3%, respectively, p<0.001). Pairwise comparisons showed fewer myocardial segments with LGE in the vaccine group versus classical myocarditis (4/119 vs 42/340, p=0.004) and more segments with LGE than MIS-C (4/119 vs 2/1020, p=0.0014).

Authors concluded that patients with vaccine-associated myocarditis had no evidence of active inflammation or ventricular dysfunction on intermediate CMR although a minority had persistent LGE. Intermediate findings in vaccine myocarditis may be favourable compared to classical myocarditis though LGE is more common compared to MIS-C.

Rapporteur assessment comment:

The MAH described 2 long-term (up to 12 months) comparative studies that included cardiovascular magnetic resonance imaging:

- comparing persons with myocarditis after COVID-19 vaccination with historical myocarditis cases unrelated to COVID-19 (1 study[45]); this study concluded that myocarditis occurred after both mRNA and vector anti-SARS-CoV-2 vaccination, with no apparent difference regarding cardiovascular MR metrics between myocarditis cases potentially associated with COVID-19 vaccination and myocarditis unrelated to COVID-19 vaccination.
- comparing persons with COVID-19 vaccine associated myocarditis with classic myocarditis and MIS-C (1 study[46]); this study concluded that patients with vaccine-associated myocarditis had no evidence of active inflammation or ventricular dysfunction on intermediate cardiovascular magnetic resonance although a minority had persistent late gadolinium enhancement. Intermediate findings in vaccine myocarditis may be favourable compared to classical myocarditis though late gadolinium enhancement is more common compared to MIS-C.

Overall, the results of these 2 long-term studies suggest for myocarditis associated with SARS-CoV-2 mRNA vaccination no differences on cardiac MRI and more favourable findings than for other types of myocarditis (unrelated to COVID-19, MIS-C).

Non-comparative Studies

Krakalik et al[47] aimed to assess clinical outcomes and quality-of-life at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults. Authors collected data for 519 (patients for whom a myocarditis report has been submitted to VAERS and conducted two-component survey, one component to patients (or parents or guardians) and one component to health-care providers, to assess patient outcomes at least 90 days since myocarditis onset: 126 patients via patient survey only, 162 patients via health-care provider survey only, and 231 patients via both surveys. Median patient age was 17 years (IQR 15-22); 457 (88%) patients were male and 61 (12%) were female.

- Most (81%) patients for whom a follow-up health-care provider survey was completed were considered recovered from myocarditis, and most self-reported overall good health on the quality-of-life questionnaire. Re-admissions to hospital were uncommon, and no deaths were identified during the follow-up period. At the last health-care provider follow-up, 104 (26%) of 393 patients were prescribed daily medication related to myocarditis.
- Of 249 individuals who completed the quality-of-life portion of the patient survey, 4 (2%) reported problems with self-care, 13 (5%) with mobility, 49 (20%) with performing usual activities, 74 (30%) with pain, and 114 (46%) with depression.
- Mean weighted quality-of-life measure (0·91 [SD 0·13]) was similar to a pre-pandemic US population value (0·92 [0·13]) and significantly higher than an early pandemic US population value (0·75 [0·28]; p<0·0001).

- 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), ECGs (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients).
- Among 357 patients with available data, only 6 (2%) patients had a subsequent hospital admission; in 3 of these patients, hospital admission was the result of iatrogenic adverse reactions to intravenous immunoglobulin therapy. Only 3 (<1%) of the 357 patients were hospitalised for cardiac causes: one due to reduction in LVEF, one due to chest pain and elevated troponin, and one due to pericarditis.
- 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 LGE 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).

Authors concluded that from a clinical standpoint, study results suggest that myocarditis after mRNA COVID-19 vaccination could have a more favourable prognosis than myocarditis after viral infection, based on data available from the pre-COVID-19 period.

Alhussein et al[48] reports the baseline and 90-day CMR assessment in 20 patients with mRNA vaccine myocarditis in Canada. The median age was 23.1 years (range 18-39 years), and 17 (85%) were male. Eighteen patients (90%) were hospitalised during their acute illness and were discharged without in-patient cardiac complications (median length of hospital stay 3 days [IQR 2-3 days]). All but 1 patient was treated with colchicine, combined with non-steroidal anti-inflammatory drugs in 75%. Five patients, all having an LVEF <55%, were prescribed angiotensin-converting enzyme inhibitors (ACEis), 4 a beta-blocker in addition, and 1 spironolactone in addition. No patient was prescribed steroids. All patients reported >50% symptom improvement within 48 hours of the first colchicine dose. At baseline, all patients showed subepicardial-pattern LGE involving the inferolateral and/or lateral wall segments. Convalescent evaluations were performed at a median (IQR) 3.7 (3.3-6.2) months.

- The LVEF showed a mean 3% absolute improvement, accompanied by a 7% reduction in LV end-diastolic volume and 5% reduction in LV mass (all P<0.015). Of 5 patients demonstrating LVEF ≤ 50% at baseline, all recovered to above this threshold in convalescence.
- Global LGE burden was reduced by 66% (P < 0.001). Absolute reductions in global T2, native T1, and ECV of 2.1 ms, 58 ms, and 2.9%, respectively, were documented (all P ≤ 0.001). A total of 18 (90%) patients showed persistence of abnormal LGE although mean burden was < 5% of LV mass in 85% of cases.
- No patient experienced major clinical outcomes.

Authors concluded that COVID-19 mRNA vaccine-associated myocarditis showed rapid improvements in CMR-based markers of oedema, contractile function, and global LGE burden beyond 3 months of recovery in this young patient cohort.

Shiyovich et al[49] report on a follow-up CMR performed at a median of 65 days in 15 patients with post-vaccine myocarditis in Israel. All patients were males, median age of 32 years (interquartile range =

22.5-40), and presented with chest pain (87%) and had an abnormal ECG (79%). The severity of the disease was mild in 67% and intermediate in 33%. The median ejection fraction (EF), as evaluated by echocardiography upon presentation, was 55% (IQR = 50–58.5). CMR was performed at a median of 65 days (range 3-130 days) following diagnosis.

- All patients survived and one patient was readmitted during the study period.
- At follow-up, median EF was 58% (range 51-74%) global- and regional wall motion abnormalities were present in 1 and 3 patients, respectively. Native T1 was available in 13/15 patients (2/3 in 3 T and 11/12 in the 1.5 T), with increased values among 6/13.
- LGE was found among 13/15 patients with a median of 2% (range 0-15%) with inferolateral wall being the most common location (8/13). The patterns of the LGE were: mid-wall in 6 patients; epicardial in 5 patients; and mid-wall and epicardial in 2 patients.

Authors concluded that among patients who were diagnosed with post-vaccination clinical myocarditis, CMR imaging findings are mild and consistent with 'classical myocarditis'. The short-term clinical course and outcomes were favourable.

Schauer et al[50] published the analysis of 16 patients with post-vaccine (BNT162b2) myocarditis who underwent follow-up cardiac MRI at 3-8 months after their initial CMR study (median 3.7 months, range 2.8-8.1 months). This group had a median age of 15 years (range, 12-17 years), were mostly male (n = 15, 94%), White, and non-Hispanic (n=14, 88%).

- Follow-up cardiac MRI LVEF (57.7 ± 2.8%) was significantly improved from initial (54.5 ± 5.5%, P<.05), and none of the patients had regional wall motion abnormalities.
- LVEF by echocardiogram was normal for all patients at the time of follow-up.
- Eleven patients (68.8%) had persistent LGE, although there was a significant decrease in the quantifiable LGE (8.16 ± 5.74%) from the initial study (13.77±8.53%, P<.05).
- Cardiac oedema resolved in all but 1 patient. Global longitudinal strain (%) remained abnormal in most patients (75%, mean −16.4 ± 2.1%) at follow-up without significant change from the initial study (−16.0 ± 1.7, P=.6).
- Eight patients (5 of whom had persistent LGE) underwent 24-hour cardiac rhythm monitoring, all of which were normal.
- Six patients, all with persistent LGE, underwent exercise tests, all of which were normal.
- Four patients complained of intermittent chest pain at follow-up with no identifiable abnormality on evaluation; no therapy or intervention was required. No patient received heart failure medication.

Hadley et al[51] report on 10 patients (9 male, median age 15 years) with vaccine-associated myocarditis who underwent follow-up CMR at a median of 92 days (range 76-119) after hospital discharge.

- Since hospital discharge, the majority of patients have been asymptomatic. Two patients subsequently presented to the emergency room with chest pain in the setting of acute COVID-19 infection; in both cases, cardiac evaluation with laboratory data and ECG was unremarkable and neither patient required hospital admission. One patient continues to endorse fatigue, and the

other endorses chest pain thought to be musculoskeletal in origin. Two patients continue to have non-specific ST-T segment changes on follow-up ECG; all other ECG and echocardiograms were normal at most recent follow-up.

- All patients had normal ventricular systolic function on follow-up CMR. Two patients (20%) had abnormal LV global T1 at presentation, which normalised on follow-up.
- LGE improved on all repeat CMR at 3-month follow-up. Most patients (80%) still had a small amount of LGE, the clinical significance of which is yet to be determined.
- Extracellular volume decreased between acute presentation and follow-up in 6/10 patients; it remained elevated at follow-up in 1 patient and borderline in 3 patients.

Similar findings of recovery of clinical parameters and persistent, yet not increasing, LGE on follow-up imaging have been reported in smaller case series[52-57] and case reports[58].

Rapporteur assessment comment:

The MAH described 5 long-term follow-up (up to 8 months) non comparative studies that included cardiovascular magnetic resonance imaging evaluating:

- clinical outcomes and quality-of-life of myocarditis after mRNA COVID-19 vaccination (1 study[47]); the study concluded that most individuals in the cohort were considered recovered by health-care providers, and quality of life measures at least 90 days since myocarditis onset were comparable to those in pre-pandemic and early pandemic general populations of a similar age.
- Follow-up CMR assessment in persons with mRNA vaccine myocarditis (4 studies[48, 49, 50, 51]); concluding that mRNA vaccine-associated myocarditis showed rapid improvements in cardiovascular magnetic resonance based markers of oedema, contractile function, and global gadolinium enhancement burden beyond 3 months of recovery. Cardiovascular magnetic resonance imaging findings were mild and consistent with 'classical myocarditis'. The short-term clinical course and outcomes were favourable. Although all patients showed rapid clinical improvement, many had persistent cardiac magnetic resonance imaging findings at follow-up.

Similar findings of recovery of clinical parameters and persistent (not increasing) global gadolinium enhancement on follow-up imaging was reported by another (smaller) 7 studies[52-58].

Overall, the results of these 5 long-term non comparative studies suggest for myocarditis associated with SARS-CoV-2 mRNA vaccination favourable clinical course and outcomes.

Systematic Reviews, Expert Opinions

In the largest review published to date, Pillay et al[59] included a total of 46 studies to assess incidence rates and risk factors for myocarditis and pericarditis after use of mRNA vaccination against COVID-19, clinical presentation, short-term and longer-term outcomes of cases (≥4 weeks), and proposed mechanisms. With respect to case characteristics and short-term clinical course, authors found that most (≥84%) patients with myocarditis were admitted to hospital with few admitted to ICU (five of 49 patients with data); the average length of hospital stay was 2 to 4 days. Non-steroidal anti-inflammatory drugs were most often used as treatment for myocarditis; other interventions included bisoprolol, ramipril, colchicine, famotidine, steroids (for myocarditis), and intravenous immune globulin (for myopericarditis).

For pericarditis, hospital admission rates varied (35% and 73% reported in 2 series with a total of 59 cases); one series (n = 37) reported 3% admitted to ICU and one day for median length of stay. One series (n = 37) reported no fatalities, and a larger study of unconfirmed cases (n = 4250) reported 15 deaths (0.4%). For long term outcomes, authors acknowledged the limited data available at the time they conducted the analysis and concluded that long term follow-up of patients with myocarditis is needed to better understand the natural history including disease recurrence.

Rapporteur assessment comment:

The results of this study reviewing 46 studies showed at short-term (<4 weeks) that patients with myocarditis after COVID-19 mRNA vaccination had an average length of hospital stay of 2 to 4 days and that non-steroidal anti-inflammatory drugs were most often used as treatment for myocarditis. For long term outcomes (≥4 weeks) there was limited data available which is needed to better understand the clinical course of myocarditis after COVID-19 mRNA vaccination.

In the DSRU (Lane et al)[60] systematic review of spontaneously reported data from the UK, Europe and the USA and of the scientific literature authors analysed 18,204 myocarditis and pericarditis events submitted to the UK, USA and EU/EEA regulators by mid-March 2022. In review of fatalities, authors found 4 fatalities in the UK (0.25% of all spontaneous reports), 62 in the USA (1.3% of all reports) and 56 in the EU/EEA (0.6% of all reports). Where age of fatal cases was reported (EudraVigilance and VAERS databases only), 85.83% (n=103) of fatal cases overall were aged 18 years or older. Five cases (4.17%) were aged under 18 years; all were myocarditis events (6.41% of all fatal myocarditis events reported). All fatal cases of pericarditis reported to EudraVigilance and VAERS were aged 18 years or older. In literature, 0.22% (n=30) myocarditis or pericarditis events had a fatal outcome (range 0.41%–45.85%).

Rapporteur assessment comment:

This study reported a total of 122 (0.7%) fatalities out of 18,204 spontaneously reported myocarditis and pericarditis events after mRNA COVID-19 vaccines in the UK, US and EU. In literature, myocarditis or pericarditis events with fatal outcome seem to range from 0.4%–45.9%.

Matar et al[61] conducted a systematic review and meta-analysis to evaluate the clinical characteristics of patients (>18 years) with myocarditis following COVID-19 vaccination. Seventy-five unique studies (patient n=188, 89.4% male, mean age 18–67 years) were included. Eighty-six patients had Moderna vaccines while one hundred and 2 patients had Pfizer-BioNTech vaccines. The most common presenting symptoms were chest pain (34.5%), fever (17.1%), myalgia (12.4%), and chills (12.1%). The most common radiologic findings were ST-related changes on an ECG (58.7%) and hypokinesia on CMR imaging or echocardiography (50.7%). LVEF was measured in 167 patients at the time of admission with either echocardiogram or CMR imaging, of which 40 (23.7%) patients had LVEF <50%. Laboratory findings included elevated Troponin I levels (81.7%) and elevated CRP (71.5%). The length of hospital stay was an average of 3.598 days. Seven patients were admitted to the ICU. The most common treatment modality was non-steroid anti-inflammatory drugs (36.6%) followed by colchicine (28.5%). Only one patient required supplemental oxygen therapy. Additionally, none of the patients required mechanical circulatory support. One patient died due to cardiogenic shock.

Rapporteur assessment comment:

This review of 75 studies (188 patients) showed that patients with myocarditis after COVID-19 mRNA vaccination had an average length of hospital stay of 3.6 days and that non-steroidal anti-inflammatory drugs were most often used as treatment for myocarditis followed by colchicine.

Yasuhara et al[62] conducted a systematic review and meta-analysis of 23 studies, including 854 patients aged 12 to 20 years with vaccine-associated myopericarditis (mean age, 15.9 [95% CI: 15.5-16.2] years). Most patients (84.4% [95% CI: 80.5%-88.3%] of patients) had preserved LV function. Of the 15.6% (95% CI: 11.7%-19.5%) of patients with LV systolic dysfunction (LVEF <55%), most (14.1% [95% CI: 10.2%-18.1%]) were mild (ie, LVEF 45%-54%), and only 1.3% (95% CI: 0%-2.6%) of patients had severe LV systolic dysfunction (ie, LVEF<35%). CMR imaging revealed LGE in 87.2% (95% CI: 79.8%-94.7%) of patients. Although 92.6% (95% CI: 87.8%-97.3%) of patients were hospitalised and 23.2% (95% CI: 11.7%-34.7%) of patients required ICU admission, inotropes were used in only 1.3% (95% CI: 0%-2.7%) of patients, no patients died or required mechanical support, and the hospital length of stay was 2.8 (95% CI: 2.1-3.5) days.

Rapporteur assessment comment:

This review of 23 studies (854 patients aged 12 to 20 years with vaccine-associated myopericarditis) reported that 92.6% (95% CI: 87.8%-97.3%) of the patients were hospitalised and 23.2% (95% CI: 11.7%-34.7%) of the patients required intensive care unit admission, no patients died or required mechanical support, and the mean hospital length of stay was 2.8 (95% CI: 2.1-3.5) days.

In the systematic review by Woo et al[63] of 74 patients with myocarditis, clinical manifestations, diagnostic findings, and outcomes were analysed. Most patients were male (94.6%), and the median age (range) was 17.6 (14–70) years. Patients who received the BNT162b2 (n=58, 78.4%) vaccine presented fewer systemic symptoms and LV dysfunction than mRNA-1273 recipients. Although patients under 20 years experienced more fever and myalgia, they had better EF and less prominent myocardial inflammation in MRI than older patients. The clinical course of all patients was favourable without mortality, and one-third of patients resolved with conservative care alone. Risk factor analyses revealed that patients with gastrointestinal symptoms required intensive care (OR: 20.3, 95% CI: 1.90-217, p=0.013). However, patients with gastrointestinal symptoms received more intensive care, and a significant proportion of patients recovered with conservative management.

Rapporteur assessment comment:

This study reviewing 74 patients with myocarditis after COVID-19 mRNA vaccination showed that the clinical course of all patients with a median age 17.6 years (range 14-70 year) was favourable without fatal outcome.

The MAH concludes, by all reports, that the expert consensus is that COVID-19 vaccine-associated myocarditis has a milder presentation, a higher recovery rate, and lower mortality compared with myocarditis of other causes.[30, 64-67]

Rapporteur assessment comment:

MAH's conclusion is endorsed that the expert consensus suggest that COVID-19 vaccine-associated myocarditis has a milder presentation, a higher recovery rate, and lower mortality compared with myocarditis of other causes.

Data from MAH Non-interventional and Low-interventional PASS

This is a summary of available information on post-vaccination myocarditis and pericarditis collected in Pfizer's post-marketing non-interventional and low-interventional studies. The MAH is conducting 7 non-interventional and 1 low-interventional PASS that include myocarditis and/or pericarditis study endpoints, including 3 primary data collection studies and 5 secondary data collection studies (Table 1; not reproduced here). Five of the studies will include follow-up of the cases, e.g., with CMR imaging, to evaluate the clinical course/sequalae of disease.

Of these 8 studies, data on myocarditis/pericarditis are available for 6 studies (the other 2 studies, C4591011 and C4591038, are still planned and do not have interim analyses at this time). While 5 of the studies have identified myocarditis and/or pericarditis cases, these outcomes were rare and rates in the study populations were low. Data on the clinical course/sequalae of the disease are not yet available. Please see below for a summary of preliminary results (not reproduced here) for myocarditis/pericarditis available to date by study.

Rapporteur assessment comment:

Data on myocarditis/pericarditis were available for 5 of the 8 Comirnaty PASSs that include myocarditis/pericarditis endpoints: myocarditis/pericarditis outcomes were rare, rates in the study populations were low and data on the clinical course/sequalae of myocarditis/pericarditis are not yet available.

Post-marketing Data

Post-marketing Exposure

From the receipt of the first temporary authorisation for emergency supply on 01 Dec 2020 through 18 Dec 2022, approximately 4,369,782,515 doses of BNT162b2 were shipped from BioNTech and Pfizer worldwide.

Post-authorisation data for Myocarditis and Pericarditis

Myocarditis and pericarditis are considered important identified risks for BNT162 vaccine (including variants) and included and described accordingly in the vaccine RMP and aggregate safety reports. Cumulatively, there were 22,221 cases of myocarditis and pericarditis: 13,619 cases reported myocarditis and 10,725 cases reported pericarditis (in 2123 of these 22,221 cases, the subjects developed both myocarditis and pericarditis). As described in the PSUR, whereas the most commonly reported outcome being 'recovered' is reassuring, it is notable that a large proportion of the cases (approx. 30%) did not report an event outcome. In view of the known limitations of the post-marketing data, the limited follow-up the vaccine cases receive (reference to PSUR 3 – Appendix 6A; not reproduced here), a meaningful assessment of the myocarditis clinical course and outcomes is precluded and its value is significantly undermined by the availability of larger and better structured data from pharmacoepidemiologic and populational studies as provided above.

Rapporteur assessment comment:

Cumulatively, there were 13,619 cases reporting myocarditis and 10,725 cases reporting pericarditis. In 2,123 of these cases, both myocarditis and pericarditis was reported.

Post-marketing reports have been assessed in subsequent (M)SSRs and PSUSAs.

Safety Database Review of Fatal Myocarditis/Pericarditis Events

Methodology

MAH's global safety database contains cases of AEs reported spontaneously to MAH, cases reported by the Health Authorities, cases published in the medical literature, cases from MAH-sponsored marketing programmes, non-interventional studies, and cases of serious adverse events (SAEs) reported from clinical studies regardless of causality.

A cumulative search for all BNT162 cases reporting MedDRA PTs included in Non-infectious myocarditis/pericarditis narrow scope and reporting a relevant event clinical outcome as fatal until 31 Jan 2023 was performed.

Results

The safety database search retrieved a total of 267 cases reporting a myocarditis/pericarditis fatal outcome (Table 2; partially reproduced here).

Table 2. → Cases Reporting Myocarditis/Pericarditis Fatal Outcome

Patient Characteristics (267 cases)		Number of Cases	Percent %
Gender	Female	80	30.0
	Male	177	66.3
	No data	10	3.7
Age Min 6 years Max 96 years Mean = 55.9 Median = 59.0 Standard Deviation = 22.37	6 months - 5 years	0	0
	5-11 years	3	1.1
	12-15 years	7	2.6
	16-17 years	2	0.7
	18-24 years	14	5.2
	25-29 years	17	6.4
	30-39 years	19	7.1
	≥ 40 years	183	68.5
	- of which, ≥65 years	103	38.6
	- of which, ≥85 years	20	7.5
	Unknown	22	8.2
Dose Number	Dose 1	64	24.0
	Dose 2	100	37.5
	Dose 3	62	23.2
	Dose 4	10	3.7
	Dose 5	1	0.4
	Unknown	36	13.5

The majority (177 [66.3%]) were reported in males and concerned patients of older age (median age 59 years); there was no case reported in patients younger than 5 years. Two thirds of the cases were medically confirmed (186 [69.7%]) and more than half of the cases (146 [54.7%]) had a medical history present. Most of the cases were reported from Japan and Germany (61 [22.8%] and 54 [20.2%] respectively) and were reported between the third quarter of 2021 and first quarter of 2022.

In a total of 146 cases, a medical history was present, most frequently coded to MedDRA SOCs Vascular disorders (50), Cardiac disorders (44), and Metabolism and nutrition disorders (40); the most frequently reported medical history PTs (>5 cases) were: hypertension (43), diabetes mellitus, obesity (12 each),

type 2 diabetes mellitus (10), cardiac failure, chronic obstructive pulmonary disease (9 each), atrial fibrillation (8), arteriosclerosis coronary artery, cardiac disorder, COVID-19 (7 each), dyslipidemia (6).

Cases Reported in Patients Aged <40 Years

Cumulatively, there were 62 cases that reported a myocarditis/pericarditis event with fatal outcome in patients aged less than 40 years; no fatal cases were reported in patients younger than 5 years of age.

Most of the cases were medically confirmed (45 [72.6%]) or reported a medical history present (32 [51.6%]).

A total of 58 cases concerned fatal myocarditis events and 4 concerned fatal pericarditis events.

Most frequently reported medical histories coded to MedDRA SOCs Respiratory, Thoracic and Mediastinal disorders (8), Congenital, familial and genetic disorders (6), Metabolism and nutrition disorders, Social circumstances (5 each); the most frequently reported medical history PTs were obesity (4) and asthma (2). All the other medical histories were reported 2 times or less. Case and patient characteristics are provided in Table 3.

Table 3. Cases Reported Myocarditis/Pericarditis Event With Fatal Outcome in Patients Aged Less Than 40 Years

Patient Characteristics (Patient age <40 years)		Number of Cases	Percent % (N=62)
Gender	Female	12	19.4
	Male	49	79.0
	No data	1	1.6
Dose Number	Dose 1	14	22.6
	Dose 2	30	48.4
	Dose 3	9	14.5
	Dose 4	1	1.6
	Unknown	8	12.9
Most frequently reported PTs (≥10% of cases) - any event outcome -	Myocarditis	58	93.5
	Pyrexia	15	24.2
	Cardiac arrest	12	19.3
	Chest pain	9	14.5
	Interchange of vaccine products	9	14.5
	Arrhythmia	7	11.3
	Cardio-respiratory arrest	7	11.3
	Dyspnoea	7	11.3
Most frequently reported PTs (>5 cases) - only those events with the outcome reported as fatal	Myocarditis	58	93.5
	Cardiac arrest	9	14.5
	Interchange of vaccine products	8	12.9
	Arrhythmia	7	11.3
	Cardio-respiratory arrest	6	9.7
	Chest pain	6	9.7
	Pulmonary oedema	6	9.7
Patient history	Present	32	51.6
	Unknown	30	48.4
Medically confirmed	Yes	45	72.6
	No	17	27.4
Top 5 countries of reporting	Japan	11	17.7
	Germany	9	14.5
	US	7	11.3
	Israel	5	8.1
	Canada, Portugal, Taiwan, United Kingdom	3 (each)	4.8

Upon detailed review of the cases, in 8 (12.9%) cases the myocarditis or pericarditis event was ruled out, either in histology or excluded due to presence of myocardial infarction. In 18 (29%) cases there was limited information precluding a meaningful assessment of the role of the vaccine in inducing myocarditis and its fatal outcome. In another 27 (43.5%) cases, an alternative explanation, either as a predisposing medical history, a concurrent condition (e.g. infection), or a very long latency since the vaccine

administration to the event occurrence, thus making the role of the vaccine in inducing the fatal myocarditis unlikely.

In the 9 (14.5%) remaining cases (case numbers [redacted], the role of the vaccine in the development of myocarditis could not be ruled out. Six of the 9 remaining cases concerned patients aged between 26 and 34 years, and 8 of 9 were male patients. A detailed case by case review of all the 62 cases reporting fatal myocarditis or pericarditis events in patients younger than 40 years of age is provided in Appendix 2 (see below in comment box).

Rapporteur assessment comment:

Please refer regarding the assessment of the 62 fatal myocarditis/pericarditis cases to the PRAC Rapporteur's comments in:

Appendix2%20Myocarditis.docx

In persons 6 months – <5 years, there were no fatal myocarditis/pericarditis cases.

In persons aged 5-11 years, there were 3 myocarditis cases of which in 1 case (BC level 1) fatal outcome is considered possible related to Comirnaty and 2 cases (BC level 1;3) are considered unassessable or fatal outcome is unlikely related to Comirnaty.

In persons aged 12-15 years, there were 7 myocarditis cases (BC level 1;3;4;5) which are considered unassessable or fatal outcome is unlikely related to Comirnaty.

In persons aged 16-17 years, there were 2 myocarditis cases (BC level 1) which are considered unassessable or fatal outcome is unlikely related to Comirnaty.

In persons aged 18-24 years, there were 13 myocarditis cases of which in 2 cases (both BC level 1) fatal outcome is considered possible related to Comirnaty and 11 cases (BC level 1;2;4;5) are considered unassessable, unclassified or fatal outcome is unlikely related to Comirnaty. There was 1 pericarditis case (BC level 5) which is considered unassessable.

In persons aged 25-29 years, there were 16 myocarditis cases of which in 5 cases (four BC level 1 and one BC level 2) fatal outcome is considered possible related to Comirnaty and 11 cases (BC level 1;4;5) are considered unassessable, unclassified or fatal outcome is unlikely related to Comirnaty. There was 1 pericarditis case (BC level 2) in which fatal outcome is considered unlikely related to Comirnaty.

In persons aged 30-39 years, there were 17 myocarditis cases of which in 2 cases (both BC level 1) fatal outcome is considered possible related to Comirnaty and 15 cases (BC level 1;2;4;5) are considered unassessable or fatal outcome is unlikely related to Comirnaty. There was 1 pericarditis case (BC level 5) and 1 myopericarditis case (BC level 4) which are both considered unassessable.

In total, in persons <40 years, in 10 myocarditis cases (16.1%) of the 62 myocarditis/pericarditis cases fatal outcome is considered possible related to Comirnaty.

Cases Reported in Patients Aged 40 Years or Older, Including Age Unknown

Of the total 267 cases reporting fatal myocarditis or pericarditis events, 205 cases reported a patient aged 40 years or older (including age unknown [22]). Most of the cases were medically confirmed (141 [68.8%]) or reported a medical history present (114 [55.6%]).

A total of 171 cases concerned fatal myocarditis events and 36 concerned fatal pericarditis events (2 cases reported both myocarditis and pericarditis events).

Most frequently reported medical histories coded to MedDRA SOCs Vascular disorders (47), Cardiac disorders (42), and Metabolism and nutrition disorders (35); the most frequently reported medical history PTs were hypertension (41), diabetes mellitus (12), Type 2 diabetes mellitus (10), cardiac failure, chronic obstructive pulmonary disorder (9 each), atrial fibrillation and obesity (8 each). Case and patient characteristics are provided in Table 4 (not reproduced here).

Upon detailed review of the cases, in 36 (17.6%) cases the myocarditis or pericarditis event was ruled out, either in histology or excluded due to presence of myocardial infarction. In 71 (34.6%) cases there was limited information precluding a meaningful assessment of the role of the vaccine in inducing myocarditis and its fatal outcome.

In another 88 (42.9%) cases, there was an alternative explanation, either as a predisposing medical history, pre-existing cardiac injury, a concurrent condition (e.g., infection), or a very long latency since the vaccine administration to the event occurrence, thus making the role of the vaccine in inducing the fatal myocarditis unlikely. These cases concerned older patients (median age 72 years; with 13 cases reported in patients ≥85 years of age), with more relevant cardiovascular and metabolic medical histories and higher proportion of non-cardiac co-reported events.

In the 10 (4.9%) remaining cases, the role of the vaccine could not be ruled out. Eight of the 10 cases were reported from Japan, and 6 were patients of male gender. Three patients were aged 46 years or less, and 4 patients were aged 65 years or more.

In 4 of these cases, the event and outcome occurred during or following medical care. In 2 cases ([redacted][JP], [redacted] [JP]), patients were admitted to hospital due to non-specific symptoms and experienced the events during hospitalisation.

1. In the first case ([redacted][JP], literature case), the 61-year-old female patient with no remarkable history experienced non-specific symptoms (fever, malaise) 3 days after receipt of the first dose and was admitted to the hospital; the only notable finding was an elevated CK at admission. On the third day in the hospital, patient developed abrupt elevation of CK and CK MB and experienced cardiogenic shock with pulseless electrical activity. The patient received resuscitation and advanced life support measures, but cardiac function did not recover and patient died after 10 days. The EMB performed before death showed no evidence of myocarditis; therefore, cardiopulmonary arrest due to arrhythmic mitral valve prolapse was considered a possible differential diagnosis. However, the autopsy revealed extensive necrosis, with severe inflammatory cell infiltration and oedema. The inflammatory infiltrates adjacent to the damaged cardiomyocytes were predominantly lymphocytes, macrophages, neutrophiles (eosinophils rare, giant cells absent). CBN was absent. There was slight fibrosis predominantly in the perivascular area, which might suggest presence of certain cardiac risk factor. The lesions had focal, geographical, and transmural distribution, in part, and affected throughout the myocardial layer; lesions in the conduction system were present, yet infiltrates were milder. Mild fibrosis and slight infiltration of lymphocytes and macrophages were observed in the epicardium, confirming the diagnosis of pericarditis. The authors commented that the presence of the fibrosis indicated that the patient had an arrhythmogenic substrate and was more susceptible to fatal arrhythmias, and

the negative biopsy before death may have been either due to sampling error, or due to an arrhythmic event due to mitral valve prolapse.

2. The second patient ([redacted][JP]) had a similar course of development of ventricular arrhythmia during hospitalisation which resulted in death, but there was no histology reported to better assess the extent and localisation of the myocardial injury and the relationship with the fatal ventricular arrhythmia.
3. In another case ([redacted][JP]) the 87-year-old patient called emergency services the day of the vaccination due to dyspnoea and loss of consciousness, and experienced cardiac arrest during ambulance transport and was resuscitated and stabilised, including by placing an external pacemaker and endotracheal intubation. However, the next day the patient experienced circulatory failure that resulted in death. Myocarditis was diagnosed based on blood tests and was considered fulminant; there was no cardiac histology reported, but autopsy revealed intestinal dilatation and bilateral lung congestion.
4. In the fourth case ([redacted][JP]) the 80-year-old patient was referred to hospital for non-specific symptoms occurring post-vaccination, a cardiac disorder was suspected based on ECG, but patient decided to leave the hospital of her own will. Due to development of cardiogenic shock, the patient was readmitted to hospital in intensive coronary care, but the circulatory failure progressed and patient expired. Myocarditis diagnosis was made based on the echocardiography and ischaemia was excluded by angiography. At the same time, patient also presented gastrointestinal symptoms and increased white blood cells and CRP, however, there is no further information regarding the presence of an infectious process leading to or contributing to the fatal circulatory failure.

In another 2 cases ([redacted] [JP], [redacted][JP]), patients experienced out of hospital cardiac arrest, which was attributed to the development of a fatal arrhythmia due to myocarditis. One of these cases [redacted] [JP]) documents on autopsy that the extent of myocarditis lesions was limited, but the localisation near the AV node was suspected to have triggered the fatal ventricular arrhythmia which, despite resuscitation, led to irreversible brain and multi-organ damage that ultimately resulted in death.

In another case ([redacted][JP]) the 71-year-old patient experienced a cardiac arrest which was attributed to a myocarditis arrhythmic effect on ventricular conduction system. The patient was successfully resuscitated but died 82 days later due to the progression of cardiac failure and occurrence of multi-organ dysfunction.

In the remaining 3 cases ([redacted] [NL], [redacted] [DE], [redacted][JP]), patients with unremarkable medical histories experienced non-specific symptoms prior to the event without seeking medical care, and autopsy documented presence of inflammatory infiltrates in myocardium; myocyte necrosis was not reported as per Dallas criteria, and the extent of the lesions was not provided as to better ascertain the role of the cardiac injury relative to the outcome reported.

Rapporteur assessment comment:

In persons aged ≥40 years, there were 205 cases reporting fatal myocarditis (n=169), fatal pericarditis (n=34), or both fatal myocarditis and pericarditis (n=2) events.

Although a detailed case by case review of the fatal cases in persons ≥40 years is not provided, the MAH stated that in 10 of the 205 fatal myocarditis/pericarditis cases (4.9%), the role of the vaccine could not be ruled out.

MAH's conclusion

Myocarditis and pericarditis are considered important identified risks for BNT162b2 vaccine (including variants) and are included and described accordingly in the EU-RMP and aggregate safety reports. From the receipt of the first temporary authorisation for emergency supply on 01 Dec 2020 through 18 Dec 2022, approximately 4,369,782,515 doses of BNT162b2 (original and bivalent) were shipped from BioNTech and Pfizer worldwide.

The current EU-SmPC section 4.4 wording on myocarditis and pericarditis states that 'Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general'. In response to PRAC, the MAH has conducted a thorough evaluation of clinical course and outcome of myocarditis and/or pericarditis to determine if there is evidence to warrant an update of the label. Furthermore, to address the CHMP request, the MAH has provided a detailed cumulative case-level review of all fatalities reported for myocarditis and pericarditis events.

Overall, data from large populational pharmacoepidemiology studies have shown that the clinical course of post-vaccination myocarditis and pericarditis is mild, responds to standard of care treatments and requires a relatively short duration of hospitalisation (2-4 days). Short-term data on mortality is reassuring, with some studies showing a lower mortality for post-vaccination myocarditis compared with myocarditis of other causes, and other studies findings statistically comparable rates. The clinical course and prognosis of post-vaccination myocarditis are comparable with myocarditis of other causes. There is no data to suggest that myocarditis severity, clinical course or outcomes are worse than for myocarditis of other causes. Notably, the burden of cardiovascular disorders following COVID-19, including myocarditis, is significant, and mortality rates significantly exceed those after vaccination.

The analysis of the Nordic Study Cohort showed that compared with myocarditis associated with COVID-19 and myocarditis not related to COVID-19 or vaccination, myocarditis after COVID-19 vaccination was associated with better clinical outcomes within 90 days of admission to hospital. The earlier study from the Nordic Registry similarly found a lower mortality after vaccination with BNT162b2 compared with myocarditis without vaccination. In the French EPI-PHARE study, the frequency of admission in ICU, mechanical ventilation or death was lower for post-vaccination myocarditis cases than for unvaccinated myocarditis cases. Analyses of over 42 million vaccinations in England found that the risk of hospital admission or death from myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses of BNT162b2 mRNA vaccine. The retrospective cohort study in Hong Kong that compared prognosis of myocarditis developing after mRNA COVID 19 vaccination showed that the post-vaccination myocarditis group had a 92% lower mortality risk than viral myocarditis. Similarly, large studies of myocarditis from US and Israel converge to report a mild clinical course, prompt resolution and low mortality.

In review of the cardiac MRI assessments of acute post-vaccination myocarditis, studies have found severity of MRI abnormalities was milder, in general, compared with that of patients with other causes of myocarditis, even after controlling for age, sex, and time from symptom onset to imaging. Follow-up assessments at 3-6 months showed resolution of symptoms, marked improvement in the cardiac function, and decreasing LGE.

The available literature supports that COVID-19 vaccine-associated myocarditis has a milder presentation, a higher recovery rate, and lower mortality compared with myocarditis of other causes. No relevant data informing on myocarditis clinical course and outcomes has yet emerged from the MAH conducted

non-interventional post-authorisation studies. The study C4591036 titled 'Low-Interventional Cohort Study of Myocarditis/Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age' has recently begun enrolment, and this study will provide important information regarding the clinical course of myocarditis and outcome assessment over a 5-year period of follow-up.

A cumulative review of the post-marketing safety database through 31 Jan 2023 revealed a total of 267 cases with a relevant myocarditis/pericarditis event resulting in a fatal outcome. Most of the cases described patients over 40 years of age; 62 reports were in patients <40 years of age and no cases with a fatal outcome were reported in children 5 years of age or younger. In almost half of the cases (116/267; 43.4%) there were other contributory factors in the occurrence of the myocarditis event and the reported fatal outcome, which support that the fatalities are more likely the result of multiple complex conditions and intrinsic risk factors that contribute to the poor progress and irreversible outcomes. In a third of the cases (86/267; 32.2%) there was insufficient information precluding a meaningful assessment of the clinical circumstances and the role of the vaccine in the development of the event and the fatal outcome. In other 44 cases (16.5%), myocarditis was ruled out by histology or by diagnostic criteria. In the remaining fraction of the fatal cases (19; 7.1%) there were no contributory factors identified and given the temporal relationship, the role of the vaccine could not be excluded. There was no specific trend identified in these 19 cases. In some, the fatal outcome was attributed to the anatomical location of the myocardial injury near the conduction system that resulted in an arrhythmic event and cardiac arrest. In other cases, the myocardial injury was reported to develop into irreversible heart failure. Similar to non-fatal myocarditis cases, patients experienced non-specific symptoms but medical care was not sought in all cases, and in isolated cases, despite the event developing during professional care (i.e., in-hospital), the medical interventions and life support did not result in clinical recovery. Given the vaccine exposure exceeding 4 billion doses distributed worldwide in 2 years, these 19 reports reflect a relatively small number of cases in which the role of the vaccine in the reported fatal myocarditis or pericarditis events could not be excluded.

In summary, accumulated results from large pharmacoepidemiologic studies continue to support that the course of post-vaccination myocarditis is mild, responds to standard of care measures and results in clinical recovery, comparable with myocarditis of other causes. Short-term data on mortality is reassuring, with some studies showing a lower mortality compared with myocarditis of other causes, others findings rates statistically comparable. There is no data to suggest that myocarditis severity, clinical course or outcomes are worse than for myocarditis of other causes. Emerging data on longer-term outcomes at 36 months show that most patients remain symptom free and do not experience recurrences or exacerbations requiring re-admissions to hospital. Notably, the burden of cardiovascular disorders following COVID-19, including myocarditis, is significant, and mortality rates significantly exceed those after vaccination. There is no new information identified that would warrant an update to the Product Information at this time. Monitoring of myocarditis and pericarditis will continue.

Rapporteur assessment comment:

Exposure

Through 18 Dec 2022, approximately 4,369,782,515 doses of Comirnaty (original and bivalent) were shipped worldwide.

Literature

Overall, through Jan 2023, the data from multiple large (EU) population-based cohort studies (12 comparative studies, 3 non-comparative studies and 5 systematic reviews) showed that at short term follow-up (up to 3 months) clinical course (e.g., severity, duration, treatment, length of hospital stay,

complications) and outcomes (e.g. recovered without sequelae, recovered with sequela, fatal outcome) of Comirnaty associated myocarditis/pericarditis compared to myocarditis/pericarditis associated with other causes seems to be milder and less severe, respectively. However, long term follow-up (>3 months) data regarding the course and outcome of Comirnaty associated myocarditis/pericarditis is considered more limited available, 7 studies (including 5 non-comparative studies) suggesting favourable clinical course and outcomes. This however would need to be confirmed by further data.

PASS

From MAH's PASSs stated in the Comirnaty RMP, data on the clinical course/sequalae of myocarditis/pericarditis are not yet available.

Post-marketing

Cumulative, there were 13,619 cases reporting myocarditis and 10,725 cases reporting pericarditis. In 2,123 of these cases, both myocarditis and pericarditis was reported.

Cumulative through Jan 2023, 267 Comirnaty associated myocarditis/pericarditis cases with fatal outcome were reported in persons:

- Aged 6 months-<5 years: no fatal cases.
- Aged 5-11 years: 3 cases of which in 1 case (BC level 1) fatal outcome is considered possible related to Comirnaty.
- Aged 12-15 years: 7 fatal myocarditis cases of which in none of the cases fatal outcome is considered at least possible related to Comirnaty.
- Aged 16-17 years: 2 fatal myocarditis cases of which in none of the cases fatal outcome is considered at least possible related to Comirnaty.
- Aged 18-24 years: 13 myocarditis cases of which in 2 cases (both BC level 1) fatal outcome is considered possible related to Comirnaty. There was 1 pericarditis case in which fatal outcome is not considered at least possible related to Comirnaty.
- Aged 25-29 year: 16 myocarditis cases of which in 5 cases (four BC level 1 and one BC level 2) fatal outcome is considered possible related to Comirnaty. There was 1 pericarditis case in which fatal outcome is not considered at least possible related to Comirnaty.
- Aged 30-39 years: 17 myocarditis cases of which in 2 cases (both BC level 1) fatal outcome is considered possible related to Comirnaty. There was 1 pericarditis and 1 myopericarditis case, in both, fatal outcome is not considered at least possible related to Comirnaty.
- Aged ≥40 year: 169 fatal myocarditis cases of which in 10 cases the role of Comirnaty could not be ruled out. There were 34 fatal pericarditis and 2 myopericarditis fatal cases, all in which Comirnaty could be ruled out.

In total, in persons <40 years, in 10 myocarditis cases (of the 62 myocarditis/pericarditis cases) fatal outcome is considered possible related to Comirnaty. In persons ≥40 years, in 10 (of the 205) fatal myocarditis/pericarditis cases the role of Comirnaty could not be ruled out.

Based on the provided information concerning the clinical course (including intensive care support) and outcomes (including fatal outcome) of Comirnaty associated myocarditis/pericarditis, new important safety information could be identified. Studies have reported that the clinical course and outcome of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months) compared to myocarditis/pericarditis associated with other causes seems to be milder and less severe, respectively. Long term follow-up (>3 months) data regarding the course and outcome of Comirnaty associated myocarditis/pericarditis is limited available at the moment, however, suggests similar favourable course and outcome as reported at short-term. This however would need to be confirmed by further data.

Furthermore, in the product information of Comirnaty concerning myocarditis and pericarditis (e.g., section 4.4 of the SmPC and section 2 of the package leaflet) the requirement of intensive care support and the reported occurrence of fatal outcome in both literature and post-marketing reports are not explicitly stated.

Therefore, it is proposed that the warning concerning myocarditis and pericarditis in section 4.4 of the Comirnaty SmPC and section 2 of the package leaflet should be modified as follows (deleted text: ~~strikethrough~~; new text: **underlined) and in bold**:

SmPC section 4.4 Special warnings and precautions for use

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males **(see section 4.8)**. Available data **indicate** ~~suggest~~ that **most cases are mild and tend to recover within a short time. Some cases require intensive care support and fatal cases have been observed. Data also indicate that** the **short-term (≤3 months)** course **and outcome** of myocarditis and pericarditis following vaccination is ~~not different~~ **milder and less severe than** from myocarditis or pericarditis in general (see section 4.8).

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Package Leaflet section 2

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. **Most cases of myocarditis and pericarditis are mild and individuals tend to recover within a short time. Some cases require intensive care support and fatal cases have been observed.** Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

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2.3.2. Evaluation of important potential risks

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

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.

Interval period 4th PSUR

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.

Post-Authorisation Data

- 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.
- 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):
  - The most frequently (>1) reported causes of death in the 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, Haemod namic instability, Hypoxia, Respiratory distress, and SARS-CoV-2 sepsis (2 each).
  - In all 46 fatal cases, drug ineffective or vaccination failure was reported.
  - Thirty-four of these 46 fatal 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 fatal 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 fatal 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.

No cases reported events occurring after administration of a second booster vaccination.

Rapporteur assessment comment:

During the reporting period, no new important safety concern could be identified regarding VAED/VAERD.

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.

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.

Cumulative summary information through 18 December 2022

Clinical study data

- 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. Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and VAED/VAERD.

Post-marketing data

- Number of cases: 3883.
- Relevant PTs most frequently reported (>2%): Drug ineffective (2203), Vaccination failure (1680), COVID-19 pneumonia (1601), Dyspnoea (1172), 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).

MAH's conclusion: 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. 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.

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.*

MAH's 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:

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

Rapporteur assessment comment:

Based on the available cumulative data (clinical trial and post-marketing), MAH's conclusion is endorsed that no new significant safety information has been identified that substantiates retaining VAED/VAERD as an important potential risk in the PSUR Summary of safety concerns.

Therefore, MAH's proposal to remove VAED/VAERD from the list of safety concerns in both RMP and PSUR, is accepted. The MAH should amend the safety specification in the RMP accordingly at the next regulatory opportunity.

The MAH should continue to monitor VAED/VAERD as part of their pharmacovigilance activities.

Evaluation of other risks (not categorised as important)

Adverse events of special interest (AESIs)

Response to the PRAC request 4 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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.*

MAH's 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.

Rapporteur assessment comment:

Noted.

Response to the PRAC request 5 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *The vaccination stress/anxiety related ADRs are considered well documented and adequately managed in clinical practice, and therefore could be removed from section 'Evaluation of other risks (not categorised as important)' in future PSURs.*

MAH's response: This section has been removed from the text of the PSUR.

Rapporteur assessment comment:

Noted.

Anaphylactic AESIs

Search criteria: *Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock*.

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 procedures. 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.
- Reported relevant PTs: Anaphylactic reaction (321), Anaphylactic shock (128), Anaphylactoid reaction (9), Anaphylactoid shock (1).
- 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.

O/E analysis

Since anaphylaxis has already been identified as a risk of vaccination, the goal of the observed versus expected analysis is risk estimation rather than signal identification. Risk of anaphylaxis is reported per dose administered and compared to rates of anaphylaxis observed for other vaccines rather than rates in an unexposed population.

The current analysis is restricted to the bivalent vaccine and to the US and EEA given the availability of the exposure data in these regions. Previous PSURs provided O/E ratios for the monovalent vaccine, which had steadily declined from 9.47 (95% CI, 8.61, 10.40) first reported in Summary Monthly Safety Report 2 (through 31 January 2021) to 2.404 (95% CI 2.353, 2.455) in the PSUR#3.

The MAH has conducted unadjusted observed versus expected analyses for the 20 cumulative cases of anaphylaxis reported through 18 December 2022 after the bivalent BA.1 or BA.4/5 vaccine in the US/EEA. Anaphylaxis cases were identified using the following PTs: anaphylactic shock, anaphylactic reaction, anaphylactoid shock, and anaphylactoid reaction.

Expected case counts were determined by multiplying the number of doses administered by the expected rate per million doses. An estimated 51,751,231 doses of Pfizer-BioNTech bivalent BA.1 or BA.4/5 COVID-19 vaccine have been administered through 18 December 2022. A background rate of 1.31 anaphylaxis cases per million vaccine doses was assumed.

An O/E ratio of 0.295 (95% CI 0.180, 0.456) was observed for BNT162b2 bivalent vaccines compared to the expected cases of anaphylaxis based on background rates observed in the US. The reason for the lower O/E ratio for the bivalent vaccine compared with the monovalent vaccine is unknown but could reflect decreased reporting, changes in the accuracy of the exposure estimate, or changes in population being vaccinated.

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.

MAH's 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.

Rapporteur assessment comment:

It is noted that the reason for the lower O/E ratio (0.295 [95% CI 0.180, 0.456]) for the bivalent vaccine compared with the monovalent vaccine (O/E ratio 2.404 [95% CI 2.353, 2.455] in the 3rd PSUR) is unknown but could reflect decreased reporting, changes in the accuracy of the exposure estimate, or changes in population being vaccinated.

No new important safety information concerning anaphylaxis could be identified from the data in current PSUR. At the moment, the current risk minimisation measures described in the product information of Comirnaty are considered adequate.

COVID-19 AESIs

Search criteria: *SMQ COVID-19 (Narrow and Broad) OR PTs Ageusia; Anosmia; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease.*

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. None of the events were related to BNT162b2 or blinded therapy.

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.
- Time to event onset: n=49,091, range: <24 hours to 365 days, median: 136 days.
- Duration of relevant events: n=900, range: 24 hours to 421 days, median: 9 days.
- Relevant event outcome: 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).

O/E analysis

O/E analysis was performed for Ageusia/anosmia: all O/E ratios <1.

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.

Long COVID

Search criteria: *PT Post-acute COVID-19 syndrome.*

Clinical trial data

- No cases; no cases were retrieved in the PSUR#3.

Post-authorization 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.
- 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.

MAH's 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.

Rapporteur assessment comment:

During the interval period, an increased number of cases reporting COVID-19 AESIs (57,462 [20.3% of the total PM dataset] compared to 54,335 cases (10.7%) retrieved in the 3rd PSUR is noted. However, no conclusions can be drawn because the percentage of the total post-marketing dataset depends on the other ICSRs of which the more known ADRs are less reported in time and/or within the current circulating more infective SARS-CoV-2 virus variants more vaccinees got COVID-19 and report this.

No new important safety concern could be identified for COVID-19 AESIs.

Immune-mediated/autoimmune AESIs

Search criteria: *SMQ Immune-mediated/autoimmune disorders (Narrow and Broad) OR HLGT (All Path) Autoimmune disorders OR PTs Cytokine storm; Hypersensitivity; Thyroiditis subacute; Thrombocytopenia.*

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. All SAEs were assessed as not related to BNT162b2 or blinded therapy.

Post-authorization data

- Number of cases: 6155 (BNT162b2 [6012], BNT162b2 + BNT162b2 Omi BA.1 [68] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [85]) (2.2% of 282,992 cases of the total PM dataset), compared to 11,726 cases (2.3%) retrieved in the PSUR#3.
- 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).

- Relevant event outcome: 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).

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. All O/E ratios were <1, except for ADEM (narrow definition) the O/E ratio 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.

MAH's 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.

Rapporteur assessment comment:

Please refer regarding subacute thyroiditis to section 2.2 Signal evaluation of this AR.

No new important safety concern could be identified for immune-mediated/autoimmune AESIs.

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.*

Clinical Trial Data

- Number of cases: 0; no cases were retrieved in the PSUR#3.

Post-authorization 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).
- 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).
- 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).

O/E analysis

- O/E analysis was performed for Multisystem inflammatory syndrome: 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.

Table 11. Observed to Expected (O/E) Analysis of Multisystem Inflammatory Syndrome in European Economic Area Countries and in the United States, Cumulative Period

Stratification	Bkgd Rate[a,52]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95% CI	Obs Cases	PY	Exp Cases	O/E Ratio	95% CI
Age											
<5 years	2.77	2	91,575	2.5	0.788	0.095, 2.848	2	123,230	3.4	0.586	0.071, 2.117
5-11 years	2.77	14	1,893,579	52.5	0.267	0.146, 0.448	14	2,797,396	77.5	0.181	0.099, 0.303
12-17 years	2.77	40	3,397,235	94.1	0.425	0.304, 0.579	51	5,203,454	144.1	0.354	0.263, 0.465
18-20 years	1.50	6	2,064,665	31.0	0.194	0.071, 0.422	9	3,237,459	48.6	0.185	0.085, 0.352
21-24 years	0.23	9	2,752,887	6.3	1.421	0.650, 2.698	10	4,316,612	9.9	1.007	0.483, 1.852
25-49 years	0.58	58	20,289,383	117.7	0.493	0.374, 0.637	68	32,156,932	186.5	0.365	0.283, 0.462
50-59 years	1.47	33	10,097,627	148.4	0.222	0.153, 0.312	39	16,387,819	240.9	0.162	0.115, 0.221
60-69 years	3.38	41	9,500,558	321.1	0.128	0.092, 0.173	47	15,799,132	534.0	0.088	0.065, 0.117
70+ years	7.42	133	13,707,708	1,017.1	0.131	0.109, 0.155	165	23,018,623	1,708.0	0.097	0.082, 0.113
Gender											
Males	2.36	177	29,988,444	707.7	0.250	0.215, 0.290	212	48,368,881	1,141.5	0.186	0.162, 0.212
Females	2.36	159	33,806,773	797.8	0.199	0.170, 0.233	193	54,671,775	1,290.3	0.150	0.129, 0.172
Vaccine											
Monovalent (any dose)	2.36	332	60,991,637	1,439.4	0.231	0.207, 0.257	401	97,975,499	2,312.2	0.173	0.157, 0.191
Bivalent BA.1	2.36	2	527,066	12.4	0.161	0.019, 0.581	2	1,001,576	23.6	0.085	0.010, 0.306
Bivalent BA.4/5	2.36	2	2,276,515	53.7	0.037	0.005, 0.134	2	4,063,581	95.9	0.021	0.003, 0.075

a. Background rate per 100,000 person years (PY).[8] Background rates from ACCESS include Kawasaki disease codes

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.

MAH's 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.

Rapporteur assessment comment:

Please refer regarding new cases of MIS-C/ -A to section 2.2 Signal evaluation of this AR.

It is noted that in the O/E analyses for multisystem inflammatory syndrome, the O/E ratios were somewhat elevated for the 21-day risk window (same as in previous 3rd PSUR) (O/E ratio 1.42, 95% CI 0.65;2.70), and for the 42-day risk window (new compared to the previous 3rd PSUR) (O/E ratio 1.01, 95% CI 0.48;1.85) in the 21-24 years age group, although not statistically significant.

No new important safety concern could be identified for multisystem inflammatory syndrome in children/adults.

Myocarditis and Pericarditis AESIs

Rapporteur assessment comment:

Please refer to section 2.3 'Evaluation of important identified risks' of this assessment report.

Neurological AESIs (including demyelination)

Search Criteria: *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*.

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. None of these SAEs were assessed as related to BNT162b2/blinded therapy.

Post-authorization 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.
- 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), Ataia (67), Meningitis (53).
- Relevant event outcome: 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).

O/E analysis

- O/E analysis was performed for Generalized convulsive, Fibromyalgia, Guillain-Barré syndrome, Meningitis, Narcolepsy, Multiple sclerosis and Polyneuropathy. All O/E ratios were <1, except 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]).

Table 9. Monovalent and Bivalent-Stratified Observed to Expected (O/E) Analyses of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

AESI	Bkgd Rate[a]	Monovalent (any dose)				Bivalent BA.1				Bivalent BA.4/5			
		Obs Cases	Exp Cases[b]	O/E Ratio	95% CI[c]	Obs Cases	Exp Cases[d]	O/E Ratio	95% CI	Obs Cases	Exp Cases[e]	O/E Ratio	95% CI
Narcolepsy	1.16[24]	74	707.5	0.105	0.082, 0.131	0	6.1	0.000	-	0	26.4	0.000	-
Pericarditis	18.00[42]	3,362	10,978.5	0.306	0.296, 0.317	4	94.9	0.042	0.011, 0.108	10	409.8	0.024	0.012, 0.045
Polymyalgia rheumatica	95.90[43]	742	58,491.0	0.013	0.012, 0.014	2	505.5	0.004	0.000, 0.014	2	2,183.2	0.001	0.000, 0.003
Polyneuropathy	2.50[23]	1,550	1,524.8	**1.017**	**0.967, 1.068**	5	13.2	0.379	0.123, 0.886	8	56.9	0.141	0.061, 0.277

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.

MAH's 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.

Rapporteur assessment comment:

It is noted that in the O/E analyses for Polyneuropathy, the O/E ratio was somewhat elevated for the 21-day risk window (new compared to the previous 3rd PSUR) (O/E ratio 1.02, 95% CI 0.97;1.07), although not statistically significant. For bivalent vaccines this was not the case, although observed numbers are low.

No new important safety concern could be identified for neurological AESIs.

Pregnancy related AESIs

Rapporteur assessment comment:

Please refer to 'Use in pregnant/lactating women' in section 'Update on special patient populations' in this AR below.

Glomerulonephritis and Nephrotic Syndrome AESIs

Search Criteria: *HLT Glomerulonephritis and nephrotic syndrome*.

Clinical Trial Data

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

Post-authorization 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.
- 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).
- 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).

O/E analysis

O/E analysis was performed for Glomerulonephritis/nephrotic syndrome. All O/E ratios were <1.

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.

MAH's conclusion

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.

Rapporteur assessment comment:

No new important safety concern could be identified for glomerulonephritis and nephrotic syndrome AESIs.

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. None of the SAEs were assessed as related to BNT162b2 or blinded therapy.

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).
- 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).
- Relevant event outcome: 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).

O/E analysis

- O/E analysis was performed for Cerebral venous sinus thrombosis, Ischemic stroke and Hemorrhagic stroke. The CVST analysis (table 12) using the low background rate, 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. Using the mid-range background rate (Table 13, not reproduced here), all stratifications have an O/E ratio less than 1.

Table 12. Observed to Expected (O/E) Analysis of Cerebral Venous Sinous Thrombosis in European Economic Area Countries and in the United States, Cumulative Period, Low Background Rate

Stratification	Low Bkgd rate[a,16]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95%CI[c]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males <5 years	0.45	0	43691.043	0.2	0.000	-	0	58749.912	0.3	0.000	-
Males 5-11 years	0.45	0	893,455	4.0	0.000	-	0	1,318,570	5.9	0.000	-
Males 12-17 years	0.45	4	1,601,261	7.2	0.555	0.151, 1.421	5	2,449,692	11.0	0.454	0.147, 1.058
Males 18-24 years	0.42	11	2,270,238	9.5	**1.154**	**0.576, 2.064**	13	3,555,446	14.9	0.871	0.464, 1.489
Males 25-49 years	0.40	56	9,551,716	38.2	**1.466**	**1.107, 1.903**	75	15,120,116	60.5	**1.240**	**0.975, 1.554**
Males 50-59 years	1.24	29	4,742,810	58.8	0.493	0.330, 0.708	40	7,685,823	95.3	0.420	0.300, 0.572
Males 60-69 years	1.25	21	4,458,018	55.7	0.377	0.233, 0.576	31	7,401,897	92.5	0.335	0.228, 0.476
Males 70+ years	1.51	27	6,427,256	97.1	0.278	0.183, 0.405	39	10,778,587	162.8	0.240	0.170, 0.328
Females <5 years	0.97	0	47,884	0.5	0.000	-	0	64,480	0.6	0.000	-
Females 5-11 years	0.97	0	1,000,124	9.7	0.000	-	0	1,478,826	14.3	0.000	-
Females 12-17 years	0.97	5	1,795,974	17.4	0.287	0.093, 0.670	7	2,753,762	26.7	0.262	0.105, 0.540
Females 18-24 years	0.97[b]	42	2,547,315	24.7	**1.700**	**1.225, 2.298**	47	3,998,625	38.8	**1.212**	**0.890, 1.611**
Females 25-49 years	0.26	133	10,737,666	27.9	**4.764**	**3.989, 5.646**	164	17,036,815	44.3	**3.702**	**3.157, 4.314**
Females 50-59 years	1.55	56	5,354,817	83.0	0.675	0.510, 0.876	69	8,701,996	134.9	0.512	0.398, 0.647
Females 60-69 years	0.75	37	5,042,541	37.8	0.978	0.689, 1.349	42	8,397,235	63.0	0.667	0.481, 0.901
Females 70+ years	1.07	55	7,280,453	77.9	0.706	0.532, 0.919	63	12,240,037	131.0	0.481	0.370, 0.615
Overall, monovalent dose 1	0.76	160	23,679,349	180.0	0.889	**0.757, 1.038**	183	23,679,349	180.0	**1.017**	**0.875, 1.175**
Overall, monovalent dose 2	0.76	259	21,041,667	159.9	**1.620**	**1.428, 1.829**	317	42,062,666	319.7	0.992	0.885, 1.107
Overall, monovalent dose 3+	0.76	54	16,270,622	123.7	0.437	0.328, 0.570	91	32,233,484	245.0	0.371	0.299, 0.456
Overall, bivalent BA.1	0.76	2	527,065	4.0	0.499	0.060, 1.804	2	1,001,576	7.6	0.263	0.032, 0.949
Overall, bivalent BA.4/5	0.76	1	2,276,515	17.3	0.058	0.001, 0.322	2	4,063,581	30.9	0.065	0.008, 0.234

a. Background rate per 100,000 person years (PY). Source: Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, Narrow Algorithm ES SIDIAP PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

b. Background rate from ACCESS 0-19 years used since 20-29 years rate is 0 and O/E would not be able to be calculated.

c. All occurrences of "-" in the table indicate not estimable because of 0 observed cases

Table 13. Observed to Expected (O/E) Analysis of Cerebral Venous Sinous Thrombosis in European Economic Area Countries and in the United States, Cumulative Period, Mid Background Rate

Stratification	Mid Bkgd rate[a,b,16,17]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95%CI[c]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males <5 years	0.45	0	43691.043	0.2	0	-	0	58749.912	0.3	0	-
Males 5-11 years	0.45	0	893,455	4.0	0.000	-	0	1,318,570	5.9	0.000	-
Males 12-17 years	0.45	4	1,601,261	7.2	0.555	0.151, 1.421	5	2,449,692	11.0	0.454	0.147, 1.058
Males 18-24 years	1.10	11	2,270,238	25.0	0.440	0.220, 0.788	13	3,555,446	39.1	0.332	0.177, 0.568
Males 25-49 years	1.50	56	9,551,716	143.3	0.391	0.295, 0.508	75	15,120,116	226.8	0.331	0.260, 0.415
Males 50-59 years	1.71	29	4,742,810	81.1	0.358	0.239, 0.514	40	7,685,823	131.4	0.304	0.217, 0.414
Males 60-69 years	3.97	21	4,458,018	177.0	0.119	0.073, 0.181	31	7,401,897	293.9	0.105	0.072, 0.150
Males 70+ years	6.22	27	6,427,256	399.8	0.068	0.045, 0.098	39	10,778,587	670.4	0.058	0.041, 0.080
Females <5 years	0.97	0	47,884	0.5	0.000	-	0	64,480	0.6	0.000	-
Females 5-11 years	0.97	0	1,000,124	9.7	0.000	-	0	1,478,826	14.3	0.000	-
Females 12-17 years	0.97	5	1,795,974	17.4	0.287	0.093, 0.670	7	2,753,762	26.7	0.262	0.105, 0.540
Females 18-24 years	4.71	42	2,547,315	120.0	0.350	0.252, 0.473	47	3,998,625	188.3	0.250	0.183, 0.332
Females 25-49 years	2.85	133	10,737,666	306.0	0.435	0.364, 0.515	164	17,036,815	485.5	0.338	0.288, 0.394
Females 50-59 years	2.05	56	5,354,817	109.8	0.510	0.385, 0.662	69	8,701,996	178.4	0.387	0.301, 0.490
Females 60-69 years	1.70	37	5,042,541	85.7	0.432	0.304, 0.595	42	8,397,235	142.8	0.294	0.212, 0.398
Females 70+ years	1.35	55	7,280,453	98.3	0.560	0.422, 0.728	63	12,240,037	165.2	0.381	0.293, 0.488
Overall, monovalent dose 1	2.34	160	23,679,349	554.1	0.289	0.246, 0.337	183	23,679,349	554.1	0.330	0.284, 0.382
Overall, monovalent dose 2	2.34	259	21,041,667	492.4	0.526	0.464, 0.594	317	42,062,666	984.3	0.322	0.288, 0.360
Overall, monovalent dose 3+	2.34	54	16,270,622	380.7	0.142	0.107, 0.185	91	32,233,484	754.3	0.121	0.097, 0.148
Overall, bivalent BA.1	2.34	2	527,065	12.3	0.162	0.020, 0.586	2	1,001,576	23.4	0.085	0.010, 0.308
Overall, bivalent BA.4/5	2.34	1	2,276,515	53.3	0.019	0.000, 0.105	2	4,063,581	95.1	0.021	0.003, 0.076

a. Background rate per 100,000 person years (PY)

b. Background rates for age groups <18 years from Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES SIDIAP PCHOSP. Background rates for age groups ≥18 years and overall from Ashrani AA, Crusan DJ, Petterson T, Bailey K, Heit JA. Age- and Sex-Specific Incidence of Cerebral Venous Sinus Thrombosis Associated With Ad26.COV2.S COVID-19 Vaccination. JAMA Intern Med. 2021 Nov 1:e216352.

c. All occurrences of "-" in the table indicate not estimable because of 0 observed cases

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.

MAH's 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.

Rapporteur assessment comment:

It is noted that for cerebral venous sinus thrombosis the O/E analysis results (O/E ratios >1) for the 18-24 and 25-49 year age groups (in both males and females) using the low background rate for both the 21-day and 42-day risk windows are consistent with the previous 3rd PSUR:

Table 11. Observed to Expected (O/E) Analysis of Cerebral Venous Sinous Thrombosis in European Economic Area Countries and in the United States, Cumulative Period, Low Background Rate

	Low	21-Day Risk Window					42-Day Risk Window				
Stratification	Bkgd rate[a,38]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	0.45	0	901,382	4.1	0.000	NE[c]	0	1,306,591	5.9	0.000	NE
Males 12-17 years	0.45	4	1,562,311	7.0	0.569	0.155, 1.457	5	2,409,778	10.8	0.461	0.150, 1.076
Males 18-24 years	0.42	11	2,224,929	9.3	1.177	0.588, 2.106	12	3,514,277	14.8	0.813	0.420, 1.420
Males 25-49 years	0.40	53	9,186,672	36.7	1.442	1.080, 1.887	74	14,565,823	58.3	1.270	0.997, 1.594
Males 50-59 years	1.24	26	4,241,876	52.6	0.494	0.323, 0.724	33	6,796,938	84.3	0.392	0.270, 0.550
Males 60-69 years	1.25	20	3,713,614	46.4	0.431	0.263, 0.665	30	6,042,722	75.5	0.397	0.268, 0.567
Males 70+ years	1.51	26	5,152,276	77.8	0.334	0.218, 0.490	37	8,411,485	127.0	0.291	0.205, 0.402
Females ≤11 years	0.97	1	1,016,452	9.9	0.101	0.003, 0.565	1	1,473,390	14.3	0.070	0.002, 0.390
Females 12-17 years	0.97	6	1,761,755	17.1	0.351	0.129, 0.764	9	2,717,409	26.4	0.341	0.156, 0.648
Females 18-24 years	0.97[b]	35	2,508,963	24.3	1.438	1.002, 2.000	40	3,962,908	38.4	1.041	0.743, 1.417
Females 25-49 years	0.26	122	10,359,439	26.9	4.529	3.761, 5.408	150	16,425,290	42.7	3.512	2.973, 4.122
Females 50-59 years	1.55	50	4,783,392	74.1	0.674	0.501, 0.889	62	7,664,632	118.8	0.522	0.400, 0.669
Females 60-69 years	0.75	35	4,187,692	31.4	1.114	0.776, 1.550	39	6,814,133	51.1	0.763	0.543, 1.043
Females 70+ years	1.07	50	5,810,014	62.2	0.804	0.597, 1.060	58	9,485,291	101.5	0.571	0.434, 0.739
Overall, dose 1	0.76	150	22,917,286	174.2	0.861	0.729, 1.011	173	22,917,286	174.2	0.993	0.851, 1.153
Overall, dose 2	0.76	240	21,280,003	161.7	1.484	1.302, 1.684	302	42,494,750	323.0	0.935	0.833, 1.047
Overall, dose 3	0.76	48	13,213,476	100.4	0.478	0.352, 0.634	74	26,178,631	199.0	0.372	0.292, 0.467

a. Background rate per 100,000 person years (PY). Source: Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, Narrow Algorithm ES SIDIAP PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

b. Background rate from ACCESS 0-19 years used since 20-29 years rate is 0 and O/E would not be able to be calculated.

c. Not estimable (NE) because of 0 observed cases

In the age-stratified and overall analysis, some of the O/E ratios (including 95% CI) were >1 (not in paediatric persons), this was only seen when applying the low background rates. Using the mid-range background rate all O/E ratios were below 1.

The O/E result using the low background rate and the 42-day risk window (O/E ratio 1.017 [95%CI 0.875; 1.175]) for the overall monovalent dose 1 of which the 95% CI included 1 that indicate lack of statistical significance, is new in current 4th PSUR.

O/E ratios for ischemic stroke and hemorrhagic stroke were well below 1.

No new important safety concern could be identified for stroke.

Sudden Death

Rapporteur assessment comment:

Please refer to 'Death' in section 'Evaluation of special situations' of this AR below.

Thromboembolic AESIs

Search criteria: *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. None of these SAEs were assessed as related to BNT162b2.

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).
- 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).
- Relevant event outcome: 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).

O/E analysis

- O/E analysis was performed for Arterial thromboembolism, Deep vein thrombosis, Disseminated intravascular coagulation, Thrombotic thrombocytopenia syndrome and Venous thromboembolism. All O/E ratios were below 1.

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.

MAH's 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.

Rapporteur assessment comment:

No new important safety concern could be identified for thromboembolic AESIs.

AESIs in subjects with Malnutrition; HIV infection

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. None of the events were related to BNT162b2.

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). .

  Patients with pre-existing HIV Infection:

  - 80 (0.02% of 282,992 cases, the total PM dataset).

  Patients with pre-existing tuberculosis:

  - 56 (0.01% of 282,992 cases, the total PM dataset).

  Patients with pre-existing malnutrition:

  - 12 (<0.01% of 282,992 cases, the total PM 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.

MAH's conclusion

No safety signals have emerged based on the review of these cases and on the second booster analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Based on the data presented concerning individuals with pre-existing HIV infection, pre-existing tuberculosis, or pre-existing malnutrition, no new important safety concern could be identified.

For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition; HIV infection should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2

- New data originated from 2 analyses on adults 18-55 years and adults >55 years enrolled in C4591031 Substudy E: In both, 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.
- 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.

Rapporteur assessment comment:

No new important safety concern could be identified based on the data presented regarding reactogenicity on individuals previously exposed or not to SARS-COV-2.

For future PSURs in the section 'Evaluation of other risks (not categorised as important)', the reactogenicity on individuals previously exposed or not to SARS-COV-2 should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Systemic adverse reactions

Search criteria: *PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia*.

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. Not assessed as related to BNT162b2 by the investigator and Sponsor.

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).
- Relevant PTs: Headache (35,637), Fatigue (31,585), Pyrexia (29,952), Myalgia (23,460), Arthralgia (17,222), Chills (14,598).
- 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.

MAH's 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.

Rapporteur assessment comment:

During the interval period, a decreased number of 79,312 (28.0% of 282,992 cases in the total PM dataset) reporting systemic adverse reactions were retrieved compared to 167,760 (33.0%) retrieved in the previous 3rd PSUR.

Systemic adverse reactions are stated in the ADR table of section 4.8 of the Comirnaty SmPC. No new important safety concern could be identified for systemic adverse reactions.

For future PSURs in the section 'Evaluation of other risks (not categorised as important)', the systemic adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Age-related adverse reactions

Clinical trial data

- Number of cases: 309 (668 in 3rd PSUR).

Post-authorisation data

- Number of cases: 282,992 (507,683in 3rd PSUR).

MAH's 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.

Rapporteur assessment comment:

No new important safety concern could be identified for age-related adverse reactions.

For future PSURs in the section 'Evaluation of other risks (not categorised as important)', the age-related adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Evaluation of special situations

Response to the PRAC request 6 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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.

MAH's 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 in this PSUR.

Rapporteur assessment comment: Noted.

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. None of the fatal events were assessed as related to blinded therapy/BNT162b2.

Post-authorisation data

- Number of cases: 1234 (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.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

O/E Analysis

O/E analysis was performed for events with a fatal outcome. All O/E ratios were <1.

MAH's conclusion

No new risks were identified following review of fatal cases.

Rapporteur assessment comment: No new important safety concern could be identified for cases reporting fatal outcome. For future PSURs in the section 'Evaluation of special situations', Death (cases reporting fatal outcome) should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Lack of therapeutic efficacy

Search Criteria: PTs Drug ineffective, Vaccination failure.

Clinical trial data

- No lack of efficacy cases in the clinical trial dataset for this reporting period or for the reporting period of PSUR#3.

Post-authorization 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.
    - 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).

Confirmed vaccination failure (25,883 cases)

- Cases involving BNT162b2: 25,734 cases.
- Cases involving BNT162b2 + BNT162b2 Omi BA.1: 6 cases.
- Cases involving BNT162b2 + BNT162b2 Omi BA.4/BA.5: 143 cases.

Suspected vaccination failure (763 cases)

Not a vaccination failure case (29,449 cases)

SARS-CoV-2 Variants (6529 cases)

- In 6529 of the 56,095 cases, information on SARS-CoV-2 variants was provided:
- Delta (India) variant (4668 cases)
- Omicron variant (1857 cases)
- Alpha (UK) variant (4 cases)

Literature

- Review of the literature identified significant new information with regards to the use of BNT162b2 and lack of therapeutic efficacy.

MAH's conclusion

No new safety signals have emerged based on a review of these cases.

Rapporteur assessment comment:

During the interval period, an increase of cases reporting lack of efficacy was retrieved by the MAH 56,095 [19.8% of the total PM dataset]) compared to 51,028 [10.1%) in the previous 3rd PSUR. The MAH stated as reasons for this increase (as in the previous 3rd PSUR) that a high number of cases were reported from Austria due to the active solicitation of lack of efficacy cases (including retrospective cases), and that Comirnaty efficacy against current Omicron variants is less than against the previous dominant variants.

In view of the 813,783,710 shipped Comirnaty doses during the current interval period, a total of 25,883 (0.003%) confirmed vaccination failures cases is not considered a safety signal.

No new important safety concern could be identified for lack of therapeutic efficacy.

Update on special populations

Response to the PRAC request 7 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *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.*

MAH's conclusion: 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 the PSUR.

Rapporteur assessment comment:

Noted.

Use in elderly

Clinical trial data

- Number of cases: 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. None were assessed as related to BNT162b2, blinded therapy, or BNT162b2s01 by the investigator and Sponsor.

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.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 in elderly.

MAH's 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.

Rapporteur assessment comment:

No important new information could be identified regarding the use of Comirnaty in the elderly.

For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Use in paediatric population

Paediatric subjects <5 years of age

Clinical trial data

- Number of cases: 62 (blinded therapy [43], BNT162b2 [18] and pre-randomisation [1]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (9.3% of 668 cases, the total CT dataset), compared to 25 cases (3.5%) retrieved in the PSUR #2. All events were assessed as unrelated to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 606 (BNT162b2 [592], BNT162b2 + BNT162b2 Omi BA.1 [1] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [24]) (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: n=992, range: from <24 hours to 196 days, median: <1 day.
- Duration of relevant events: n=66, range: from <24 hours to 24 days, median: 3 days.
- Event outcome: fatal (7), resolved/resolving (232), not resolved (78), resolved with sequelae (7), unknown (1131).
- Fatal cases (3):
    - Age: 7 months (1), 2 years (2).
    - MC case (1), NMC cases (2).
    - Gender: males (2), unknown (1).
    - Country: US (2), Taiwan, Province of China (1).
    - 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 (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) 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.
        - Of note, 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.

Rapporteur assessment comment:

During the reporting period, the Comirnaty Original indication was extended to children 6 months - 4 years old (Tris/Sucrose formulation, 3 micrograms per dose; procedure EMEA/H/C/005735/X/0138).

During the interval period, post-marketing 606 cases were retrieved of which 3 cases reported fatal outcome. Two of 3 fatal cases were made invalid after DLP and the other fatal case had limited information.

No important new information could be identified regarding the use of Comirnaty in children <5 years of age.

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. All events were assessed as unrelated to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 4983 (BNT162b2 [4798], BNT162b2 + BNT162b2 Omi BA.1 [12] and BNT162b2 + BNT162b2 Omi BA.4/BA.5 [295])(1.8% of 282,992 cases, the total PM dataset), compared to 9605 cases (1.9%) retrieved in the PSUR#3.
- 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).
- Relevant event outcome: resolved/resolving (3803), resolved with sequelae (21), not resolved (554), fatal (39), unknown (6192).
- Fatal cases (18)
    - Age: 5 years (2), 6 years (2), 7 years (3), 8 years (3), 9 years (1), 10 years (3), 11 years (2), unknown (2).
    - MC cases (12), NMC cases (6).
    - Gender: females (11), males (5), unknown (2).
    - Country: Philippines (11), Japan, US (2 each), Brazil, Malaysia, and Taiwan, Province of China (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.

Rapporteur assessment comment:

Please refer to section 2.3.1. 'Evaluation of important identified risks' regarding 3 fatal cases aged 5-11 years reporting myocarditis (cumulative through Jan 2023) of which in 1 fatal case (BC level 1 myocarditis) is considered possible related to Comirnaty.

During the interval period, there were 12 medically confirmed fatal cases in persons aged 5-11 years compared to 17 medically confirmed fatal cases in the previous reporting period of the 3rd PSUR, and 1 medically confirmed fatal case in the 2nd PSUR.

No important new information could be identified regarding the use of Comirnaty in children 5-11 years of age.

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. All events were assessed as unrelated to BNT162b2 or blinded therapy.

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.
- 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).
- Relevant event outcome: fatal (73), resolved/resolving (6266), not resolved (2979), resolved with sequelae (176), unknown (9599).
- Fatal cases (28):

- Age: 12 years (3), 13 years (1), 14 years (5), 15 years (3), 16 years (8), 17 years (7), unknown (1).
- 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: 16 years; gender: female; 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: 14 years; gender: female; 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: 16 years; gender: female; 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: 14 years; gender: male; 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.

Rapporteur assessment comment:

Please refer to section 2.3.1. 'Evaluation of important identified risks' regarding 9 fatal cases aged 12-17 years reporting myocarditis (cumulative through Jan 2023) of which in none of these fatal cases is considered related to Comirnaty exposure.

During the interval period, there were 21 medically confirmed fatal cases in persons aged 12-17 years compared to 45 medically confirmed fatal cases in the previous reporting period of the 3rd PSUR, and 40 medically confirmed fatal cases in the 2nd PSUR.

No important new information could be identified regarding the use of Comirnaty in children/adolescents 12-17 years of age.

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.

MAH's 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 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.

Rapporteur assessment comment:

Based on the provided data, MAH's conclusion is endorsed that no important new information could be identified regarding the use of Comirnaty in children and adolescents.

Use in pregnant/lactating women

Search criteria: *Pregnancy cases are identified as cases where:*

- *Patient Pregnant Flag is "Yes";*
- *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.*

Clinical trial data

Incremental review (CT cases)

- Number of pregnancy cases: 11 (3.6% of the total 309 cases from the CT dataset) compared to 41 (6.1% of the total 668 cases from the CT dataset) in the PSUR#3. These 11 cases represent 10 unique pregnancies. 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 (not reproduced here).

Post-authorisation data

Incremental review (Pregnancy)

- 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.

- 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) . 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. 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 case 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 (not reproduced here).

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.

MAH's conclusion

There were no safety signals regarding use in pregnant/lactating women that emerged from the review of these cases or the medical literature.

Rapporteur assessment comment:

Clinical trial data

During the interval period, 11 pregnancy cases (3.6% of the total CT dataset) were retrieved compared to 41 (6.1%) in the 3rd PSUR.

Post-marketing data

During the interval period, 988 pregnancy cases (0.3% of the total PM dataset) compared to 3,642 cases (0.7%) retrieved in the 3rd PSUR.

During the interval period, 302 lactation cases (0.1% of the total PM dataset) compared to 3,771 cases (0.7%) were retrieved in the 3rd PSUR.

Regarding the 125 cases with pregnancy outcome: 47 (37.6%) of these cases reported live birth with congenital anomalies, 10 cases (8%) reported spontaneous abortion, 4 cases (3.2%) reported elective termination of pregnancy, 9 cases (7.2%) reported foetal death/ neonatal death, and 55 cases (44%) reported live birth babies without congenital anomaly. Compared to the pregnancy outcomes in the previous interval period (n=322) these were 39 (12.1%), 37 (11.5%), 23 (7.1%), 21 (6.5%), and 202 (62.7%) respectively.

Literature

No new information.

Overall, based on the information provided by the MAH in the current PSUR, it is agreed that no new safety concerns were identified for use in pregnant/lactating women. The Comirnaty product information reflects that Comirnaty can be used during pregnancy and breastfeeding.

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. None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.

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.
- 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[1] (244), Chills (237), Asthenia (222), Dyspnoea (218), Lymphadenopathy (171), Diarrhoea and Rash (134 each).
- Event outcome: fatal (533), resolved/resolving (5398), resolved with sequelae (511), not resolved (4656), unknown (8168).

MAH's conclusion

No new significant safety information was identified based on a review of these cases.

Rapporteur assessment comment:

No new important safety information could be identified in immunocompromised patients exposed to Comirnaty.

Use in patients with autoimmune or inflammatory disorders

[1] PT selected per case processing conventions to indicate cases reporting third/booster doses.

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. None were assessed as related to BNT162b2 or blinded therapy by the investigator and Sponsor.

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.
- 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 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).

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.
        - Relevant PTs: Condition aggravated (258), Disease recurrence (66), Concomitant disease aggravated (13), Disease progression (4), and Symptom recurrence (1).

- 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.

MAH's 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.

Rapporteur assessment comment:

No new important safety information could be identified in patients with autoimmune or inflammatory disorders.

2.4. Characterisation of risks

2.4.1. Characterisation of important identified and potential risks

- Important Identified Risk: Myocarditis and Pericarditis
- Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Please see Appendix 8 of the PSUR (not reproduced here) 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.

Rapporteur assessment comment:

Please refer regarding the important identified risk - Myocarditis and Pericarditis - to section 2.3.1 'Evaluation of important identified risks' of this AR.

Please refer regarding the important potential risk - Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) – to section 2.3.2 'Evaluation of important potential risks' of this AR.

2.4.2. Description of missing information

Missing information:

- 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.

Rapporteur assessment comment:

Please refer regarding pregnancy and lactation to 2.3. 'Evaluation of risks and new information', section Use in pregnant/lactating women' of this AR. No important new safety information could be identified.

- Use in immunocompromised patients

  The vaccine is being studied in ongoing clinical trials of individuals with immunocompromised conditions.

Rapporteur assessment comment:

Please refer regarding immunocompromised patients to 2.3. 'Evaluation of risks and new information', section 'Use in immunocompromised patients' of this AR. No important new safety information could be identified.

- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

  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.

Rapporteur assessment comment:

In the response to the PRAC request 7 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112) the MAH stated that regarding frail patients with comorbidities no new safety issues/signals or reporting pattern changes were detected.

- 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.

Rapporteur assessment comment:

Please refer regarding patients with autoimmune or inflammatory disorders to 2.3. 'Evaluation of risks and new information', section 'Use in patients with autoimmune or inflammatory disorders' of this AR. No important new safety information could be identified.

- Interaction with other vaccines

  During the reporting interval, 3 PM cases (of which 1 serious) were originated from the same literature article [Alrashdan, et al. The Co-Administration of COVID-19 and Hepatitis B Vaccines, Should Safety Be a Concern? Infect Chemother. 2022;54(3):542-4] 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).

Rapporteur assessment comment:

The information regarding interaction with other vaccines is noted. The study showed that the co-administration of COVID-19 and Hepatitis B vaccines had no additional risks to individuals.

In the response to the PRAC request 7 from the 3rd PSUR (EMEA/H/C/PSUSA/00010898/202112) the MAH stated that regarding interactions with other vaccines no new safety issues/signals or reporting pattern changes were detected.

- 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.

Rapporteur assessment comment:

The information regarding long-term safety data is noted.

3. Benefit evaluation

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS CoV-2 virus in individuals 6 months of age and older.

Rapporteur assessment comment:

There are no new data on efficacy that alters previous assessments which are described in the approved product information of Comirnaty.

4. Benefit-risk balance

During the reporting period of the PSUR:

- The indication of Comirnaty Original (Tris/Sucrose presentation 3 micrograms/dose) was extended to children 6 months - 4 years old. Comirnaty is given as three doses of 3 micrograms each; the first two doses are given three weeks apart, followed by a third dose given at least 8 weeks after the second dose. The injections can be given in the muscles of the upper arm or thigh. (procedure EMEA/H/C/005735/X/0138)
- Two adapted Comirnaty vaccines became available (only to be used in people aged 12 years and older who have received at least a primary vaccination course against COVID-19):
    - Comirnaty Original/Omicron BA.1 contains tozinameran and riltozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0140)
    - Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0143)
        - Booster dose (5/5 micrograms per dose) for people aged from 5 years to 11 years at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/X/0147)

There is a new important safety issue identified, which include that the clinical course and outcome (including very rare fatal outcome) of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months) compared to myocarditis/pericarditis associated with other causes seems to be milder and less severe, respectively. Therefore, the wording concerning myocarditis and pericarditis in section 4.4 of the Comirnaty SmPC should be amended accordingly. Please refer to section 3 Recommendations of this AR.

The important potential risk VAED/VAERD can be removed from the list of safety concerns in both RMP and PSUR, as the available cumulative data (clinical trial and post-marketing) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance.

The risks have been evaluated in the context of the benefits of the vaccine. No additional changes to the Comirnaty risk minimisation measures are warranted.

Based on the PRAC Rapporteur review of the available safety and efficacy/effectiveness data from the current reporting period for the Comirnaty PSUR, the benefit-risk balance of Comirnaty Original (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran and riltozinameran), and Comirnaty Original/Omicron BA.4-5 (tozinameran and famtozinameran) remains unchanged.

The MAH should continue to review the safety of Comirnaty, including all reports of adverse events and should propose an update of the product information if an evaluation of the safety data identifies important new safety information, as applicable.

The current frequency of PSUR submission for Comirnaty should be changed from 6 months to 1 year at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

5. PRAC Rapporteur request for supplementary information

None.

6. Comments from member states

MS#1

We fully endorse the PRAC Rapp assessment, and have no further considerations.

Rapporteur assessment comment:
The endorsement of the PSUR assessment is appreciated.

MS#2

We would like to comment on MAH's cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase, as we do not find the performed analyses sufficient for evaluation of causality. For example, regarding cases of palpitations, there are 35021 cases in the MAH's post-marketing database, of which 20459 cases have a TTO of 0-7 days, which could support a causal association. Nevertheless, the MAH concludes that the data does not support a causal association without looking any case-level data, which we do not find acceptable. Based on the ongoing medical assessment of the ICSRs received in MS#2, it appears that after vaccination with Comirnaty, there are many cases of dyspnoea and/or palpitations and/or tachycardia/increase in heart rate lasting longer than what would be expected for stress related symptoms, and sometimes these symptoms are also accompanied with reduced exercise tolerance. Therefore, we consider that a case-level analysis would be needed before any conclusion of causality can be made. Given the amount of reports we acknowledge that case level analysis is challenging, and therefore we suggest that a case-level analysis would be performed for the cases with positive re-challenge (current number for positive rechallenge cases for tozinameran and PT palpitations in EVDAS is 114).

Further, in the MAH's database there are 5058 cases of palpitations for which the duration of the event can be evaluated. Of these 5058 cases, the MAH has concentrated its further analyses on the 1187 cases

with TTO between 2 and 21 days after vaccination. We don't agree on this approach, as it remains unclear how many of the events with TTO of <2 days lasted longer than what can be considered to represent a symptom of stress-related reaction. Therefore, we suggest that further analysis is conducted also for the cases with TTO of <2 days.

We would also like to point out that the amount of reports with long-lasting symptoms cannot be ascertained by analysing only the 5058 cases for which the duration could be evaluated. Based on the numbers provided in the PBRER, there are 19600 events of palpitations for which the outcome was either not recovered (11586) or unknown (8021), and without looking at these cases at case level it is not possible to know how many of them include events of longer duration.

All the above comments apply also for the analyses of dyspnea and tachycardia/heart rate increase.

As a conclusion, we suggest in the next PSUR, a case level analysis is performed for all positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase. We also suggest that for all these events the "duration and time to onset" analysis is performed also for cases with TTO of <2 days.

Rapporteur assessment comment:

The MS does not find the performed analyses for dyspnoea, palpitations and tachycardia/heart rate increase by the MAH sufficient for evaluation of causality, and states that a case-level analysis would be needed before any conclusion of causality can be made.

It is agreed that the duration of dyspnoea, palpitations and tachycardia/heart rate is not known in cases with a TTO of <2 days, which were removed from further analyses by the MAH. Among the cases with a TTO of <2 days, there could be cases reporting a duration of complaints that are lasting longer than what would be expected for stress/anxiety related symptoms. Indeed is case level analysis challenging for dyspnoea, palpitations and tachycardia/heart rate with a duration of the events not considered stress/anxiety-related reactions, and therefore MS's suggestion is supported that a case-level analysis should be performed for the cases with a positive re-challenge.

Section 4 of the AR is updated in line with MS proposal that a case level analysis should be performed for all cumulative positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a TTO of <2 days. **(Request for next PSUR)**

MS#3

We thank the Rapporteur for the PSUR assessment. The assessment of data regarding the signal of "amenorrhoea" seem to have been left out from the AR, please see detailed comment below. We have some comments, and suggestions for rephrasing of the SmPC 4.4 and PIL for myocarditis and pericarditis.

Amenorrhoea

The evaluation of amenorrhea as was requested by PRAC to be performed in the PSUSA with DLP 18.12.2022 is missing in the Assessment Report. According to the PSUR submitted by the MAH the issue was evaluated, reference is made to appendix 5.3.2.1 of the PSUR. However, we were unable to find any evaluation of this signal by the Rapporteur in the AR.

Myocarditis and pericarditis

Based on the data presented by the MAH, we agree that COVID-19 vaccine associated myocarditis in most cases have a favorable prognosis. Some studies indicate a more benign course of in comparison to "classic" myocarditis, however, other studies demonstrate little or no difference. Most of the studies comparing the two are small and some kind of selection bias is possible. It is also not clear how tx. Studies comparing the two types of myocarditis have been adjusted for confounders. Vaccine associated myocarditis are generally seen in young men with no other baseline risk factors which in part could explain the benign course and good prognosis. The current information regarding differences between the two types of myocarditis is therefore considered sufficient. We agree that no long term (beyond 3 month) data is available and the long-term prognosis for now is not known.

As we consider myocarditis a serious condition, even if the course and prognosis are favorable, we are not in favor of describing the conditions as "mild". We therefore propose the following change to the proposed SmPC update:

SmPC section 4.4 Special warnings and precautions for use

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males **(see section 4.8)**. Available data **indicate** ~~suggest~~ that **most cases** ~~are mild and~~ **tend to recover within a short time. Some cases required intensive care support and fatal cases have been observed. Data also indicate that** the **short-term (≤3 months)** course **and outcome** of myocarditis and pericarditis following vaccination is not different ~~milder and less severe than~~ from myocarditis or pericarditis in general (see section 4.8).

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Package Leaflet section 2

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. **Most cases of myocarditis and pericarditis** ~~are mild and individuals~~ **tend to recover within a short time. Some cases require intensive care support and fatal cases have been observed.** Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Rapporteur assessment comment:

Amenorrhea

We apologize for this, and now included the assessment of MAH's updated cumulative analysis of amenorrhoea in the AR, please refer to page 75 of this AR. Based on the data provided in the updated

cumulative review, a causal association between vaccination with Comirnaty and amenorrhoea is lacking. No new safety information could be identified from the updated review of amenorrhea as requested from the (closed) signal procedure EMEA/H/C/005735/SDA/052 - EPITT 19784. The MAH should continue to be monitor cases reporting amenorrhea after Comirnaty exposure with routine pharmacovigilance and in PASS C4591021

Myocarditis and pericarditis

The MS is not in favor of describing myocarditis and pericarditis as 'mild', and proposes changes to the proposed SmPC update accordingly. We also consider myocarditis and pericarditis serious conditions. However, the word mild refers to the course and outcome of myocarditis and pericarditis after vaccination with Comirnaty and does not refer to the seriousness of the condition as such. Therefore, we do not agree with MS proposal because studies have reported that the clinical course and outcome of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months) compared to myocarditis/pericarditis associated with other causes seems to be milder and less severe, respectively. Therefore, based on the provided information concerning the clinical course (including intensive care support) and outcomes (including fatal outcome) of Comirnaty associated myocarditis/pericarditis, new important safety information was identified, and the Comirnaty PI should be modified to reflect this safety information as proposed.

MS#4

MS#4 endorses the Rapporteur assessment report and supports the proposed update of section 4.4 of the SmPC to amend a warning regarding myocarditis and pericarditis.

Moreover, MS#4 would like to inform PRAC members regarding cases in MS#4 of "hearing loss" and "menstrual disorders".

Hearing loss

The national cross-sectional audiogram-based study, presented in the last PSUSA (PSUSA/00010898/202206) was published in April 2023: https://europepmc.org/article/med/37071555.

In this study, all suspected Sudden Sensorineural Hearing Loss (SSNHL) cases following mRNA COVID-19 vaccination between January 2021 and February 2022 were included. They were retrospectively reviewed based on a comprehensive audiological and medical evaluation by ENT. The aim is to assess the relationship between SSNHL and exposure to mRNA COVID-19 vaccines and to estimate the reporting rates (Rr) of SSNHL after mRNA vaccination per 1,000,000 doses (primary outcome).

Over the study period, 97,840,529 doses of Tozinameran (Pfizer-BioNTech BNT162b2) were administered in MS#4. The Reporting Rates (RR) of mRNA vaccine-induced SSNHL cases were calculated per 1,000,000 injections. Clinical classification was made according to patient history, unilaterality or bilaterality of the hearing loss, its degree, and recovery after a minimum 3-month follow-up.

For these Tozinameran-induced SSNHL cases, the delay onset was ≤21 days for 108 (76%) cases whose median (range) delay onset was 4 (2.0-9.0) days. Women were concerned in 84 (59%) cases. The median (range) age was 51 (13-83) years, and 98 (69%) patients were in the 30-64 years age class. A total of 50 (35%) patients had a medical history, it was otoneurologic in 17 (12%) cases. The vaccination rank was known for 125 cases, the first injection was involved in 60 (42%) cases. Steroids were administered orally in 67 (47%) cases. SSNHL was unilateral in 142 (79%) cases. Detailed audiometric thresholds were available in 98 (69%) cases, with SSNHL being measured as mild to moderately severe

in 61/98 (62%) cases, and as profound in 17 (17%) cases. Tinnitus was associated with SSNHL in 75 (53%) cases and vertigo in 41 (29%) cases. Total recovery was observed in 37 (25%) cases while hearing aid fitting was required in 10 (7%) cases (Table 1). Deafness was more often unilateral than bilateral ($p<0.001$). Neither sex effect nor vaccination rank effect was found. Case follow-up identified 5 (4%) cases of positive rechallenge (Table 2).

The total RR was estimated at 1.45/1,000,000 doses for Tozinameran.

The conclusion is that episodes of SSNHL after COVID-19 mRNA vaccines are very rare adverse events that do not call into question the benefits of mRNA vaccines but deserve to be known given the potentially disabling impact of sudden deafness. It is, therefore, essential to properly characterize any post-injection SSNHL, especially in the case of a positive rechallenge, to provide appropriate individualized recommendations.

In MS#4, the national pharmacovigilance survey about hearing loss following vaccination against COVID-19 with mRNA vaccines is still ongoing.

Menstrual disorders

In the last signal assessment report on heavy menstrual bleeding with COVID-19 mRNA vaccine (october 2022 ; EPITT 19783), MS#4 informed the PRAC that we had been working for several months with various patients' associations and HCP representatives, including obstetrician-gynecologists specialists, to better quantify and characterise the events related to menstrual disorders following COVID-19 vaccination. For this purpose, on 19 July 2022, MS#4 published a guidance on the ANSM website (https://ansm.sante.fr/actualites/troubles-menstruels-apres-la-vaccination-contre-le-covid-19-etat-des-connaissances-et-conseils-aux-femmes-concernees) to improve the recording of basic information when reporting menstrual disorders, in particular for serious cases. Following this publication, relayed by the MS#4 press, 3869 reports of menstrual disorders with Comirnaty were sent to the MS#4 NCA between 19 July 2022 and 31 August 2022.

Of these reports, in addition to cases of heavy menstrual bleeding, already listed in the SmPC, several cases are noteworhty as follows:

- Resurgence of Endometriosis

153 cases of symtomatic relapse of endomestriosis in women with history of endometriosis were reported. The vast majority of women declared that before vaccination, they had no symptom related to endometriosis.

The TTO ranged from few hours after the vaccination to 1 year.

Of these 153 cases, 65 cases needed medical consultation including 5 emergency consultations. 6 cases required surgical intervention: 2 hysterectomies, 2 digestive resections of endometriosis lesions, 1 cyst removal and cauterization of intra uterine lesion and 1 laparoscopic lavage.

A positive rechallenge was reported in 28 cases. Of note, of these 28 cases, 3 mentioned a repeated positive rechallenge after each of the subsequent doses.

The outcomes of these 153 cases were recovery for 31 cases, recovery in progress for 27 cases, no recovery for 93 cases and unknown for 2 cases.

- Menstrual disorders in menaupausal women

56 cases of metrorrhagia in menaupausal women and 2 cases of pelvic pain were reported. The TTO ranged from few hours after the vaccination to 1 year and the duration of metrorrhagia varied from 1 days to 117 days.

Of these 58 cases, an etiological investigation revealed 2 cases of fibroma, 1 case of uterine polyp and 1 case of endometrial cancer.

A positive rechallenge was reported in 2 cases.

The outcomes of these 58 cases were recovery for 28 cases, recovery in progress for 9 cases, no recovery for 20 cases and unknown for 1 case.

MS#4 would like to share this information with the PRAC members. Menstrual disorders are still closely monitored in MS#4.

Rapporteur assessment comment:

The endorsement of the PSUR assessment and our proposed update of section 4.4 of the SmPC to amend a warning regarding myocarditis and pericarditis, is appreciated.

We thank the MS for sharing information of MS#4 cases reporting hearing loss, resurgence of endometriosis or menstrual disorders in menopausal women. At this stage, no new safety information could be identified. The outcome of the ongoing national pharmacovigilance survey about hearing loss following vaccination against COVID-19 with mRNA vaccines in MS#4 is awaited. Nevertheless, the MAH should continue monitoring these adverse events after Comirnaty exposure using routine pharmacovigilance.

MS#5

The PRAC Rapp is thanked for a thorough assessment report. The proposed update of section 4.4 of the SmPC is not supported.

The MAH has presented a thorough review of a lot of new data, from various data sources including large observational studies, smaller case series, and summaries and analyses of spontaneously reported data. Overall, these different datasets continue to support a causal association between vaccination with a Covid-19 mRNA vaccine and myocarditis/pericarditis especially in younger male subjects, as already outlined in the product information. However, all these data sources have limitations which substantially hamper more detailed comparisons of the characteristics of mRNA vaccine induced myo/pericarditis and myo/pericarditis due to other causes. One main aspect is the heterogeny in compared groups where vaccine induced myo/pericarditis mainly occurred in younger, healthier subjects, and myo/pericarditis due to other causes occurred in a substantial proportion in older subjects with underlying health conditions and more frequent use of other medications. In addition, clinical/lab data were not presented for most of the cases in the published literature.

With respect to the ICU and fatal case data presented in the MAH's analysis, several confounding factors and missing data are obvious, and therefore causality assessment is challenging and in most of the cases not possible.

Nevertheless, these cumulative data reviews continue to support that myocarditis /pericarditis due to a Covid-19 mRNA vaccine does not appear to be worse than "myocarditis in general", which is already stated in the product information. It is reassuring. Taken together, we do not find that these new

analyses are sufficiently solid to justify the proposed changes of the product information. Thus, the current wording should be maintained without changes; namely:

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general (see section 4.8).

Rapporteur assessment comment:

Although we agree that presented observational data sources have some limitations regarding comparisons of mRNA vaccine induced myocarditis/pericarditis and myocarditis/pericarditis due to other causes, there are multiple large (EU) population-based cohort studies (12 comparative studies, 3 non-comparative studies and 5 systematic reviews) that all showed that at short term follow-up (up to 3 months), the clinical course (e.g., severity, duration, treatment, length of hospital stay, complications) and outcomes (e.g. recovered without sequelae, recovered with sequela, fatal outcome) of Comirnaty induced myocarditis/pericarditis compared to myocarditis/pericarditis due to other causes seems to be milder and less severe, respectively.

Furthermore, in the warning concerning myocarditis and pericarditis the requirement of intensive care support and the reported occurrence of fatal outcome in both literature and post-marketing reports are not explicitly stated.

Therefore, the warning concerning myocarditis and pericarditis in section 4.4 of the Comirnaty SmPC and section 2 of the package leaflet should be modified as proposed in the AR.

MS#6

We appreciate the thorough assessment of data for this PSUR and overall endorse its conclusions.

However, as previously done in our sent comments for Spikevax PSUSA, we would like to suggest a minor change in the proposed wording for the warning of myocarditis and pericarditis in section 4.4. We feel that the current wording as it is now may be confusing since they refer to mild cases and fatal cases in the same paragraph. This may be solved rephrasing it as follow: "Available data **indicate** suggest that **most cases are mild and tend to recover within a short time. However, sSome cases require intensive care support and fatal cases have been observed. Data also indicate that** the **short-term (≤3 months)** course **and outcome** of myocarditis and pericarditis following vaccination is not different **milder and less severe than** from myocarditis or pericarditis in general".

Rapporteur assessment comment:

The proposed change is endorsed and the recommendation is amended accordingly.