COMIRNATY : Periodic safety update report assessment

19 June 2023 to 18 December 2023

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period 19 June 2023 to 18 December 2023, 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.

EMA/PRAC/345029/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202312

Active substance(s): tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5), raxtozinameran (COMIRNATY Omicron XBB.1.5)

Period covered by the PSUR: 19/06/2023 To: 18/12/2023

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:	14 March 2024	14 March 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 May 2024	13 May 2024
☐	MS/PRAC members and MAH comments	12 June 2024	12 June 2024
☐	PRAC Rapporteur's updated assessment report following comments	27 June 2024	27 June 2024
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	11 July 2024	11 July 2024

Procedure resources	
PRAC Rapporteur	Name: Liana Martirosyan Tel: [redacted] Email:
Contact person - PRAC Rapporteur	Name: Tel: Email:
Assessor – PRAC Rapporteur	Name: Tel: Email:
EMA Procedure Lead	Name: Tel: Email:
EMA Procedure Assistant	Name: Tel: Email:

Table of contents

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), raxtozinameran (COMIRNATY Omicron XBB.1.5).

2. Assessment conclusions and actions

The MAH submitted the 6th EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 15 February 2024) covering the interval period 19 June 2023 through 18 December 2023.

The active substance of Comirnaty 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 lipid nanoparticles, 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.

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

Comirnaty was approved in the EU through a centralised procedure on 21 December 2020.

During the interval period, 224,550,280 doses of Comirnaty vaccines were shipped worldwide. Cumulatively, 4,853,255,325 doses of Comirnaty vaccines were shipped worldwide.

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

The following were ongoing signals during the interval period:

- Pulmonary embolism;
- Post-menopausal haemorrhage (EPITT No. 19989; confirmed signal and closed after the DLP, continue monitoring through routine pharmacovigilance).

The following were closed signals during the interval period:

- Mastitis/Breast swelling;
- Sensorineural hearing loss;
- Retinal vascular occlusion;
- Menstrual irregularities.

For the signals 'Mastitis/Breast swelling', 'Sensorineural hearing loss', 'Retinal vascular occlusion', and 'Menstrual irregularities' no causal relationship could be established based on the available data. No updates of the product information and/or risk management plan are warranted at present.

The safety topics monitored or reviewed are the following:

<u>Hemophagocytic lymphohistiocytosis (HLH)</u>

Based on the data provided in this PSUR no new safety information could be identified on HLH after exposure to Comirnaty. In the next PSUSA, the MAH should provide a cumulative review of all evidence concerning HLH up to data lock point (DLP) of the next PSUSA. A WHO-UMC causality assessment per case (irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc)

should also be included. The MAH should also discuss potential mechanisms and the need to update the product information if appropriate.

Idiopathic Inflammatory Myopathies/Myositis

From 16 January 2023 up to DLP, a total of 156 new cases reporting idiopathic inflammatory myopathies or myositis were identified by the MAH. A compatible time to onset is suggestive in 39 cases. Among the 156 cases, 5 subjects reported idiopathic inflammatory myopathies flares/recurrence: in 2 cases flare was reported after dose 2; in 1 case recurrence was reported after dose 3, dose 4 and dose 5; in 1 case recurrence was reported after 2 doses (unspecified doses) and in 1 case recurrence was reported after dose 2 and dose 3, which might be suggestive of a causal role of the vaccine.

Overall, suggestive TTO has been reported in 5 cases of idiopathic inflammatory myopathies flares, however causality could not be concluded due to the lack of provided information by the MAH. In the next PSUR, the MAH should provide a cumulative review of all evidence concerning Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares from 16 January 2023 up to DLP of PSUR#7. In order to properly establish the causal association, causality assessment should be performed and presented in the PSUR per case (*e.g.* cases without alternative etiologies/confounding factors, or cases reporting of positive rechallenge(s)), irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc). The MAH should also discuss potential biological mechanisms and the need to update the product information, if appropriate.

A Request for supplementary information is included following a submission by the MAH on 18 April 2024 in follow up to the 12 May 2023 adopted PRAC recommendation regarding the signal assessment of myositis with Comirnaty (EMA/PRAC/3178/2023; EPITT no: 19883). The MAH explored the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand trends in recent incidence rates (IRs) of idiopathic inflammatory myopathies (IIM) in the general population. No statistically significant trend in IIM IRs was observed from recent pre-COVID (2019) through COVID-era (2020-2021) timeframes. According to the MAH, the observed to expected analyses in the previous signal evaluation of myositis (EPITT no. 19883) that were based on pre COVID-era background rates were appropriate, and in the low-range of published estimates, hence resulting in a conservative observed to expected estimate, which is supported by the PRAC Rapporteur. Myositis has been included as an AESI/outcome in the MAH-sponsored PASS's C4591009, C4591021, C4591051 and C4591052 (all cat. 3 additional PV studies in the Comirnaty RMP), which is accepted, provided the broader term IIM will also be included in the ongoing PASSs (PRAC Recommendation EPITT no: 19883).

The MAH is requested to provide a cumulative review of all evidence concerning SFN following vaccination with Comirnaty for the next PSUR. A WHO-UMC causality assessment per case (irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc) should also be included. The MAH should also discuss potential mechanisms and the need to update the product information, if appropriate.

Product Lots and AE Reports

Triggered by the quarantine of lot HG2252 for a few days due to possible bubble formation in the solution after updraft in syringes, the MAH provided an elaborated review of the reported lot numbers and their AEs and product quality complaints. Overall, the AEs do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per product information. No new safety issue was identified.

The PSUR cycle is aligned with the EURD, next PSUR will be the first yearly PSUR.

The benefit-risk balance for the use of Comirnaty Original (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran/riltozinameran), Comirnaty Original/Omicron BA.4-5 (tozinameran/famtozinameran), and Comirnaty Omicron XBB.1.5 (raxtozinameran) remains unchanged.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5), raxtozinameran (COMIRNATY Omicron XBB.1.5) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR

The MAH(s) should address the following issues in the next PSUR:

- The MAH should provide a cumulative review of all evidence concerning Hemophagocytic lymphohistiocytosis (HLH) up to DLP of PSUR#7. A WHO-UMC causality assessment per case (irrespective of the source, e.g. spontaneous report, case from literature, case from study, etc) should also be included. Considering O/E-ratios were over 1 for the age groups "12-17 years" and "18-24 years" (21-day risk window) and "12-17 years" (42-day risk window), all cases concerning individuals aged 18 years and younger should be presented in detail and commented upon including causality assessment, as part of the cumulative review. The MAH should also discuss potential mechanisms and the need to update the product information if appropriate.
- The MAH should provide a cumulative review of all evidence concerning Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares from 16 January 2023 up to DLP of PSUR#7. In order to properly establish the causal association, causality assessment should be performed and presented in the PSUR per case, (e.*g.* cases without alternative etiologies/confounding factors, or cases reporting of positive rechallenge(s)), irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc). The MAH should also discuss potential biological mechanisms and the need to update the product information, if appropriate.
- The MAH should provide a cumulative review of all evidence concerning small fiber neuropathy following vaccination with Comirnaty. A WHO-UMC causality assessment per case (irrespective of the source, e.g. spontaneous report, case from literature, case from study, etc) should also be included. The MAH should also discuss potential mechanisms and the need to update the product information, if appropriate.
- The MAH should provide references of relevant key studies discussed within the PSUR in future PSURs.

5. PSUR frequency

☒No changes to the PSUR frequency

The current **1**-year frequency for the submission of PSURs should remain unchanged.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the 6th PSUR for Comirnaty (tozinameran) (also referred to as BNT162b2 Original), Comirnaty Original/Omicron BA.1 (tozinameran/riltozinameran), Comirnaty Original/Omicron BA.4-5 (tozinameran/famtozinameran) and Omicron XBB.1.5 (raxtozinameran) (also referred to as 2023-2024 formula), covering the period 19 June 2023 to 18 December 2023, which is assessed in this report.

The active substance of Comirnaty 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 lipid nanoparticles, 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.

Comirnaty was approved in the EU through a centralised procedure on 21 December 2020 and is currently indicated for active immunisation to prevent COVID-19 disease 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 Range of Recipient and Strength	Vial Cap and Vial Label Color	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation
6 months through 4 years **3 mcg per dose**	Maroon	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (0.4 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
5 through 11 years **10 mcg per dose**	Orange	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (1.3 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Dark blue	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Omicron XBB.1.5
	Light blue	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Omicron XBB.1.5

Age Range of Recipient and Strength	Vial Cap and Vial Label Color	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation
12 years and older **30 mcg per dose**	Dark grey	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Original (Wildtype) • Bivalent (Original + Omicron BA.1) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Purple[a]	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (0.45 mL) contains six 0.3 mL doses after dilution	• Original (Wildtype)
	N/A	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5

a. All presentations are the Tris/Sucrose formulation except the purple cap vials, which are PBS/Sucrose formulation

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

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. Overall, BNT162b2 original received marketing authorisation approval in 104 countries/regions.

In 2022, to address the emergence of Omicron variants, bivalent formulations were developed. Bivalent BNT162b2 (original/Omicron BA.1) and bivalent BNT162b2 (original/Omicron BA.4/BA.5) received marketing authorisation approval in 46 and 73 countries/regions, respectively.

In 2023, to address the emergence of new Omicron variant (XBB.1.5), an adapted monovalent formulation was developed. The BNT162b2 (Omicron XBB.1.5) vaccine was first authorized in the EU countries on 31 August 2023 and as of DLP received marketing authorization approval in 50 countries/regions.

Different dosages are available for use in different age groups.

BNT162b2 original formulations:

- PBS/Sucrose 30 mcg formulation for individuals 12 years and older [Purple cap, 6 doses per vial];
- Tris/Sucrose formulation:
  - at the dosage of 30 mcg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial];
  - at the dosage of 30 mcg for individuals aged 12 years and older [Light grey cap, 1 dose per vial];
  - at the dosage of 10 mcg for individuals aged 5 years to <12 years [Orange cap, 10 doses per vial];
  - at the dosage of 3 mcg for individuals aged 6 months to <5 years [Maroon cap, 10 doses per vial].

BNT162b2 Bivalent (BNT162b2 original/Omicron BA.1) Tris/Sucrose formulation:

- original/Omicron BA.1 at the dosage of 15/15 µg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial].

BNT162b2 Bivalent (BNT162b2 Original/Omicron BA.4/BA.5) Tris/Sucrose formulation:

- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial];
- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Light grey cap, 1 dose per vial];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Orange cap, 10 doses per vial];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Dark blue cap, 6 doses per vial];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Light blue cap, 1 dose per vial];
- original/Omicron BA.4/BA.5 at the dosage of 1.5/1.5 µg for individuals aged 6 months to <5 years [Maroon cap, 10 doses per vial];

BNT162b2 Omicron XBB.1.5 formulations:

- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Dark grey cap, 6 doses per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Light grey cap, 1 dose per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Single dose prefilled syringe];
- Tris/Sucrose 10 mcg/dose (with dilution) – for age 5 years to <12 years [Orange cap, 10 doses per vial];
- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Dark blue cap, 6 doses per vial];
- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Light blue cap, 1 dose per vial];
- Tris/Sucrose 3 mcg/dose (with dilution) – for age 6 months to <5 years [Maroon cap, 10 doses per vial];

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 any authorized BNT162b2 vaccines for safety reasons, either by a HA or by the MAH.

Of note, as a precautionary measure the Danish Medicines Agency (DMA) decided to quarantine lot HG2252 on 17 October 2023 due to possible bubble formation in the solution after updraft in syringes. After careful review, there were no safety issues and the quarantine was lifted on 20 October 2023.

Rapporteur assessment comment:

The provided information is noted.

Further information on the quarantine of Lot HG2252 is provided in Section 2.2 Signal evaluation, Other safety topics not considered signals, of this assessment report.

1.3.2. Changes to reference safety information

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 24.0 dated 21 November 2023, in effect at the end of the reporting period and included in Appendix 1 of the PSUR (not reproduced here).

Three previous CDS versions (version 21.0 dated 25 May 2023, version 22.0 dated 24 July 2023 and version 23.0 dated 19 October 2023) were also in effect during the reporting interval.

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

After the DLP, an updated CDS (version 25.0) was made effective on 26 January 2024. This updated version includes further information on participants from the paediatric study C4591007 reflecting a larger safety population from the 6-month post dose-3 interim study report. Study C4591007, which was conducted with BNT162b2 original vaccine, included individuals 6 months through <12 years of age receiving the primary series or first booster dose. There were no new safety issues identified from the larger safety population of this study.

Rapporteur assessment comment:

The EU SmPC of Comirnaty (version 15 December 2023) is in line with the CDS (version 23.0) in effect during the reporting interval.

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively, 69,995 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

- BNT162b2: 63,842 participants of which 35,272 had received BNT162b2; 26,490 had received BNT162b2 post-unblinding and had received placebo before; 959 had received BNT162b2/placebo; 2 had received BNT162b2/ SIIV; 1119 had received BNT162b2/ SIIV/placebo.

- Variant and variant-adapted vaccines based on BNT162b2: 9581 participants of which 753 had received BNT162b2 (B.1.351); 372 had received BNT162b2 (B.1.617.2); 764 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); 1814 had received BNT162b2 Omi; 1814 had received BNT162b2 original / BNT162b2 Omi; 102 had received BNT162b2 original / BNT162b2 Omi BA.1 (B.1.1.529); 2797 had received BNT162b2 original / BNT162b2 Omi BA.4/BA.5; 725 had received BNT162b2 Omi XBB.1.5; 104 had received BNT162b5 original / BNT162b2 Omi BA.2; 62 had received BNT162b5 original / BNT162b2 Omi BA.4/BA.5; 60 had received BNT162b6 original / BNT162b2 Omi BA.4/BA.5; 63 had received BNT162b7 Omi BA.4/BA.5; 60 had received BNT162b7 original / BNT162b2 Omi 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.
- Other treatments: 6359 participants of which 6352 had received placebo; 7 had received SIIV/placebo.

Post-marketing exposure

Previously publicly available regional information on vaccine doses administered is no longer consistently available for estimation of worldwide exposure. The information about the number of doses cumulatively administered published on the health authorities web sites was last updated with data up to 11 May 2023 (US) and up to 05 October 2023 (EU/EEA countries) and at the DLP (Japan).

Estimated administered doses were provided separately, as available on the public source data.

Worldwide exposure:

- Cumulative exposure:
    - Approximately a total of **4,853,255,325 doses of BNT162b2 (original, bivalent and monovalent) were shipped** worldwide from the receipt of the first temporary authorisation for emergency supply on **01 December 2020 through 18 December 2023**. Out of the cumulative number of shipped doses, 3,945,106,305 were original vaccine (including PBS and Tris/Sucrose), 715,562,080 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations. Cumulatively, there were 4,377,673,725 doses for adult presentations and 475,581,600 doses for paediatric presentations. Overall, 2,520,425,825 doses of BNT162b2 (original, bivalent and monovalent) were shipped to rest of world (ROW).
    - Table 9 below displays the cumulative EU/EEA published data with number of doses administered for each age group and by vaccine type:

Table 1. EU/EEA – Cumulative Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi	BNT162b2 Monovalent XBB.1.5	Total
< 18 years	26778400	17852	61265	29890	87	26887494
0 – 4 years	17829 Error! Reference source not found.	NA	0	0	0	17829
5 – 9 years	4107801 Error! Reference source not found.	NA	2568	0	0	4110369
10 – 14 years	9190473	10283	16490	9457	29	9226732
15 – 17 years	8135504	18382	15494	20192	26	8189598
18 – 24 years	30472234	187764	180313	101585	156	30942052

Table 1. EU/EEA – Cumulative Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi	BNT162b2 Monovalent XBB.1.5	Total
25 – 49 years	138677357	1445486	1379378	878615	3321	142384165
50 – 59 years	67304692	1179266	1789739	975330	2693	71251721
60 – 69 years	55764965	1771316	2497498	2703268	5796	62742843
70 – 79 years	54406191	2196469	2206943	2744582	6664	61560849
≥ 80 years	40987910	1478355	1349603	2139381	4208	45959458
Age Unknown	281706	45	170	0	0	281921
All	498562015	8258623	15316915	9542761	22838	531703162

Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

- **Error! Reference source not found.** through **Error! Reference source not found.** of the PSUR (not reproduced here) provide the cumulative total number of administered Comirnaty doses (original, bivalent and monovalent) in EU/EEA, by age group for each dose (up to dose 7).

- Interval exposure:
  - Approximately a total of **224,550,280 doses of BNT162b2 (original, bivalent and monovalent) were shipped** worldwide during the current reporting interval from 19 June 2023 through 18 December 2023, of which 4,010,600 were original vaccine (Tris/Sucrose), 27,952,740 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations. There were 212,378,080 doses for adult presentations and 12,172,200 doses for paediatric presentations. Overall, 62,659,040 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW.
  - Table 23 below displays the interval EU/EEA published data with number of doses administered for each age group and by vaccine type:

Table 2. EU/EEA – Interval Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi	BNT162b2 Monovalent XBB.1.5	Total
< 18 years	2314	50	505	770	87	3726
0 – 4 years	1494	NA	0 **Error! Reference source not found.**	0	0	1494
5 – 9 years	1929	NA	16	0	0	1945
10 – 14 years	682	0	203	260	29	1174
15 – 17 years	361	5	264	506	26	1162
18 – 24 years	2479	112	1734	2469	156	6950
25 – 49 years	26024	563	7589	8798	3321	46295
50 – 59 years	26090	304	3725	5881	2693	38693
60 – 69 years	72538	689	6134	5414	5796	90571
70 – 79 years	97559	813	10293	3010	6664	118339
≥ 80 years	57697	451	7248	1607	4208	71211
Age Unknown	2953	2	7	0	0	2962
All	282973	2907	69565	27179	22838	405462

Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

- Table 24 through table 27 (not reproduced here) provide for the interval reporting period the total number of administered Comirnaty doses (original, bivalent and monovalent) in EU/EEA, by age group for each dose (up to dose 7).

Rapporteur assessment comment:

Cumulatively, worldwide a total of 4,853,255,325 (4,615,732,025 in previous PSUSA period) doses of Comirnaty were shipped.

During the reporting period, in the EU-EEA countries a total of 405,462 (6,806,370 in previous PSUSA period) doses of Comirnaty were administered and cumulatively 531,703,162 (529,476,191 in previous PSUSA period) doses.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *The MAH should continue to report on the administered 1st, 2nd, 3rd, 4th, etc. doses of Comirnaty as presented in future PSURs*. As requested, the MAH provided the administered 1st, 2nd, 3rd, etc doses, up to dose 7. The MAH should continue to report these numbers in future PSURs.

1.3.4. Data in summary tabulations

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 of the PSUR (not reproduced here) 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 of the PSUR (not reproduced here) 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, and BNT162-21.

Rapporteur assessment comment:

Cumulatively in clinical trials, a total of 2,180 (2,804 in previous PSUSA period) cases with 2,825 (3,682 in previous PSUSA period) SAEs were reported in MAH's safety database.

Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 of the PSUR (not reproduced here) 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 2.2.6 of the PSUR (not reproduced here) 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), BNT162b2 multivalent NOS, BNT162b2 monovalent Omi XBB.1.5]. 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.

Rapporteur assessment comment:

During the interval period, post-marketing there were 107,046 (vs 74,102 previous interval period) cases

reporting 357,748 (vs 242,787 previous interval period) AEs.

Cumulatively, a total of 1,946,152 (vs 1,839,454 previous PSUR) cases with 6,426,327 (vs 6,059,820 previous PSUR) AEs were reported in MAH's safety database.

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.
- Other trials: 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 3 completed clinical trials (C4591001, C4591030, and BNT162-14) with final CSRs (available upon request). No clinically important new information has emerged from these clinical trials.

Ongoing clinical trials

During the reporting period, there were 9 ongoing sponsor-initiated clinical trials.

1. Safety 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 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.
- Original and Bivalent
    - PASS C4591036 [Low-interventional cohort study of myocarditis/pericarditis associated with COMIRNATY in persons less than 21 years of age]. No clinically important information has emerged from this ongoing PASS.

2. Other trials that reported new significant efficacy information:

- Original vaccine
    - 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.
- Original and bivalent vaccines

- C4591031, A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.

  Study C4591031 consists of 6 substudies. All substudies are completed, with final CSRs for substudies C [original] and F [variant-adapted vaccines] available during the reporting interval; no clinically significant safety and/or efficacy information has emerged.

- Variant-adapted vaccines
  - 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 variant-adapted BNT162b2 RNA based vaccine candidate(s) in healthy children.
  - C4591054: A phase 2/3 protocol to investigate the safety, tolerability, and immunogenicity of BNT162b2 RNA-based vaccine candidates for SARS-COV-2 new variants in healthy individuals.

3. Remaining trials

- Original vaccine
  - 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.

No clinically important new safety information has emerged from these 9 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 2 other Pfizer-sponsored clinical development programs (C526 and C548). There was no new clinically important safety information identified for this reporting period.

New safety data related to fixed combination therapies

BNT162b2 was also administered as study vaccine in other Pfizer-sponsored clinical development programs of combinations with an investigational mRNA influenza vaccine in Study C5261001 and with QIV and RSV preF vaccines in Study C5481001 and in another BioNTech sponsored clinical development program of co-administration with BNT162b4.

There was no new clinically important safety information identified for this reporting period from these combination programs.

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 8 ongoing sponsor-initiated non-interventional studies and three non-interventional studies (C4591008, C4591012, C4591061) were completed.

Completed non-interventional study

Safety studies

- The PASSs C4591008[1] and C4591012[2] were completed during the reporting period; the summary of results from these studies is provided in Table 3.

Table 3. Summary of Results from Completed Non-Interventional Safety Studies During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591008	Healthcare Worker Exposure Response and Outcomes (HERO)-Together: A Post-Emergency Use Authorization Observational Cohort Study to Evaluate the Safety of the Pfizer-BioNTech COVID-19 Vaccine in US Healthcare Workers, Their Families, and Their Communities	The study population enrolled in HERO-Together was primarily White, female, and had a low comorbidity burden at baseline. The incidence of positively adjudicated safety events of interest, including hospitalizations, was low and most commonly included arthritis/arthralgia and non-severe allergic reaction. Based on age-adjusted SCRI analyses, there was no observed increased risk of either a composite of any AESI or all-cause hospitalization in the post-vaccination period.
C4591012	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	Overall, no examined safety events of interest were found to be associated with the Pfizer-BioNTech COVID-19 vaccine based on the analyses conducted in the final report.

Other study

- During the reporting period, the study C4591061 was completed. No new safety information emerged from this non-interventional study; the summary of results from this study is provided in Table 4.

Table 4. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591061	Investigating uptake and subsequent health outcomes associated with Pfizer-BioNTech bivalent COVID-19/Influenza vaccine concomitant administration using a claims-based real-world data source in the US.	In this study, coadministration of BNT162b2-biv and SIIV was associated with generally similar effectiveness in the community setting against COVID-19-related and SIIV-related outcomes compared with giving each vaccine alone and may help improve uptake of both vaccines.

[1] 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.
[2] C4591012 and C4591022 are commitments to the US FDA and are Category 3 commitments in the EU RMP v.9.0.

Ongoing non-interventional studies

Safety Studies:

- PASS: Non-interventional studies C4591009, C4591010, C4591021, C4591022, C4591038, C4591049 and C4591055 are ongoing. No clinically important information has emerged from PASS.

Other Studies, 7 ongoing non-interventional studies:

- C4591014, Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.
- C4591025, A prospective, single-arm, open-label, non-interventional, multi-center 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.
- C4591050 , Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance.
- C4591053, The impact of Pfizer-BioNTech (BNT162b2) vaccination on the long-term effects of COVID among adults in England diagnosed with COVID prior to Omicron dominance.
- C4591059, Use and Effectiveness of COVID-19 Vaccines using state vaccine registries and insurance claims data.

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.

Please note that the 5th interim report of the EU PASS C4591021 is currently under assessment in a separate procedure (MEA17.9).

1.3.5.3. Information from other clinical trials and sources

Other clinical trials

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

Medication errors

Clinical trial data

- Number of cases: none; no cases were retrieved in the PSUR#6.

Post-authorisation data

From the global safety database, 7,880 cases reporting 20,168 events (7,4% of 107,046 cases, the total PM dataset for the reporting period) indicative of potential medication errors were retrieved compared to 11,362 relevant cases (15.3%) analysed in the PSUR#5.

Among the medication error cases (7,880 cases), compared to 11,362 medication errors in the PSUR#5, 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)]: 303 cases (3.8%) compared to 360 cases (3.2%) in the PSUR#5. The clinically relevant co-reported events (≥10) were coded to the PTs Vaccination site pain (59), Pain in extremity (42), Fatigue (41), Pyrexia (40), Headache (37), Arthralgia (31), Pain (29), Malaise (27), Myalgia (22), Chills (20), Pruritus, Vaccination site erythema (18 each), Vaccination site swelling (16), Dizziness, Nausea (15 each), Swelling, Rash (13 each), Disturbance in attention, Dyspnoea (12 each), Diarrhoea, Back pain (10 each).
- Medication errors without harm [i.e. not resulting in adverse reaction(s)]: 7571 cases (96.1%) compared to 10,995 (96.8%) in the PSUR #5.
- Potential medication errors: 6 cases (0.1%) compared to 6 cases (0.1%) in the PSUR#5.
- Intercepted medication errors: no cases compared to 1 case (0.01%) in the PSUR #5.

MAH's conclusion:

Overall, among the 7,880 relevant medication error PM cases, 303 cases (0.3% of the total interval cases, 3.8% 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 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, a slight increase of the percentage of medication errors resulting in adverse reaction(s) has been reported, i.e. 3.8% (303 cases) as compared to 3.2% (360 cases) in the previous reporting period. 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.

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 information that presented important 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,

- The ongoing signals (Postmenopausal haemorrhage and Pulmonary embolism) were closed as no risk on 22 December 2023 and on 10 January 2024, respectively.
- The EU-RMP version 11.2 was submitted, as detailed in the table below.

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
EMEA/H/C/005735/II/0206/G RMP update regarding final CSR of study C4591012 and protocol amendments of study C4591052 and C4591021	22 December 2023	RMP v11.2: 22 December 2023 (Gateway)	On-going

- After DLP, CDS version 25.0 was made effective on 26 January 2024. This version includes information of participants from the paediatric study C4591007 reflecting a larger safety population from the 6-month post dose-3 interim study report. Study C4591007, which was conducted with BNT162b2 original vaccine, included individuals 6 months through <12 years of age receiving the primary series or first booster dose. There were no new safety issues identified from the larger safety population of this study. A footnote in Table 48 (Clinical Trial section of CDS) related to the data from the flu vaccine co administration study C4591030, which was added to the CDS in the November 2023 update, was revised to more clearly define the noninferiority criteria.

Rapporteur assessment comment:

Please refer regarding the reported closed signals Postmenopausal haemorrhage and Pulmonary embolism to section 2.2 - Signal evaluation of this AR below.

For the assessment of the Comirnaty EU-RMP version 10.1 please refer to the completed procedure EMEA/H/C/005735/II/0188/G.

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 9.0 adopted 10 Nov 2022 (procedure number EMEA/H/C/005735/II/0147):

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)[a]
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

a: In the PSUR#4, the MAH, based on the review of clinical trial data, cumulative PM data, individual review of cases, and real world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of VAED/VAERD from the list of the safety concerns. In the AR, the PRAC agreed to remove VAED/VAERD from the list of safety concerns in both RMP and PSUR.

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

1. Version 9.4 submitted on 19 June 2023:
    - To update a milestone for study C4591007 following EMA approval of Justification milestone extension (EMEA/H/C/005735/X/0180). Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.
2. Version 9.5 submitted on 21 June 2023:
    - To consolidate the EU-RMP by merging RMP versions 9.3 (RMP v9.1 for EMEA/H/C/005735/X/0176 and RMP version 9.2 for EMEA/H/C/005735/II/0177) and 9.4 (EMEA/H/C/005735/X/0180) as well as to update the EU RMP PART I according to the simplified posology implemented in the SmPC. Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.
3. Up-versioned 10.0 (content-wise similar to RMP version 9.5) submitted on 22 June 2023:

- Covered procedures EMEA/H/C/005735/X/0176, EMEA/H/C/005735/II/0177 and EMEA/H/C/005735/X/0180. Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.

4. Version 10.1 submitted on 09 August 2023 and up-version 11.0 (content-wise similar to version 10.1) submitted on 13 October 2023:
    - To update the Product Information (EMEA/H/C/005735/II/0188/G) with interim 6 months post Dose 2 and final CSR data of study C4591001 including corresponding RMP update to include editorial changes regarding the new strain XBB.1.5 as well as to remove studies/milestone commitments from aPV activities related to the following completed studies: C4591001, BNT-162-01 and WI235284 (Emory). Approved CHMP Opinion: 26 October 2023, EC decision: 29 November 2023.
5. Version 11.1 submitted on 11 December 2023:
    - To update the Product Information based on final CSR data of study C4591030 including corresponding RMP update to remove study C4591030 commitment and missing information related to "Interactions with other vaccines" (EMEA/H/C/005735/II/0201).

After DLP, the MAH submitted the following versions of the EU-RMP:

6. Version 11.2 submitted on 22 December 2023:
    - To update the RMP (EMEA/H/C/005735/II/0206/G) regarding the removal of C4591012 RMP study/milestone commitments following submission of its final CSR, protocol amendments of studies C4591052 (PA #1) and C4591021 (PA #4) as well as the implementation of the following minor RMP changes:
        - C4591022 final CSR milestone update - from 31 December 2024 to 28 February 2026.
        - C4591051 final CSR milestone update from 31 January 2028 to 31 January 2027.
        - C4591024 final CSR milestone change from 30 June 2023 to 31 July 2024 as per PRAC's PAM-MEA-016.5 outcome.
        - C4591011 deletion from the RMP as per PRAC's PAM-MEA-009.1 outcome.
        - C4591009 interim CSR milestone change from 31 Oct 2023 to 30 April 2024 as per PRAC's PAM-MEA-037.5 outcome.
        - C4591044 restriction of RMP commitments to cohorts 2 and 3 only and change of final CSR milestone from 30 September 2023 to 30 June 2024 as per outcome of PRAC's PAM-MEA-059.3.
        - C4591036 final CSR milestone change from 14 November 2029 to 28 February 2031 as per PRAC's PAM-MEA-041.3 outcome.
        - Inclusion of the vaccine presentation COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection in plastic pre-filled syringe based on ongoing procedure EMEA/H/C/005735/II/0205.

Rapporteur assessment comment:

During the reporting period, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of safety concerns in the Comirnaty EU-RMP.

For the assessment of the Comirnaty EU-RMP version 10.1 please refer to the completed procedure EMEA/H/C/005735/II/0188/G.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 19.06.2023 to 18.12.2023.

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
Pulmonary embolism	27 Oct 2023	Ongoing		Enquiry from a Regulatory Authority (SFDA)	Saudi Arabia FDA requested a comprehensive signal evaluation report regarding the occurrence of pulmonary embolism with the use of Comirnaty (BNT 162b2 vaccine).	Postauthorization safety data, medical literature, clinical trial data, nonclinical data, and O/E analysis	Under evaluation
Post-menopausal haemorrhage	30 Oct 2023	Ongoing		Board of Health Alert and Enquiry from a Regulatory Authority (EMA/PRAC)	EMA/PRAC recommendation was received for MAH to perform a cumulative review of postmenopausal haemorrhage.	Postauthorization safety data, medical literature, clinical trial data, nonclinical data, and O/E analysis	Under evaluation
Mastitis/ Breast swelling	05 Jul 2023	Closed	07 Sep 2023	Enquiry from a competent authority (TGA, Australia)	TGAs Pharmacovigilance Branch assessed the risk of mastitis and breast swelling with tozinameran and concluded that there are sufficient safety grounds to request an update to the	Postauthorization safety data, clinical study safety data, medical literature	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and mastitis/breast swelling. An update to product labeling is not warranted at this time.

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
					COMIRNATY PI with mastitis and breast swelling.		Routine monitoring will continue.
Menstrual irregularities	14 Feb 2023	Closed	05 Aug 2023	Spontaneous Data: Non statistical Reports; Other (Safety Risk Lead review of PRAC signal of Amenorrhea and Heavy Menstrual Bleeding) (Internal)	The MAH initiated a review with an expanded focus topic (menstrual irregularities) following closure of the PRAC signals for Amenorrhea and Heavy Menstrual Bleeding	Postauthorization safety data, clinical study safety data, Medical literature	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Menstrual irregularities. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Retinal vascular occlusion	23 May 2023	Closed	07 Sep 2023	Medical literature	Signal evaluation was initiated by MAH based on review of a population-level study (signal detection, medical literature review) (Risk assessment of retinal vascular occlusion after COVID-19 Vaccination by Li Jing-Xing et al https://doi.org/10.1038/s41541-023-00661-7) population level study	Postauthorization safety database, medical literature, Clinical Trial database	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and retinal vascular occlusion. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Sensorineural hearing loss	15 Jun 2023	Closed	05 Aug 2023	Enquiry from a Regulatory Authority (TGA, Australia)	The TGA requested an updated signal analysis on hearing loss cases including age stratified observe versus expected analyses in the next periodic safety update report (i.e., PSUR 5) to enable further evaluation of this signal.	Postauthorization safety data, clinical study safety data, medical literature, Observed versus Expected analyses	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Sensorineural hearing loss. An update to product labeling is not warranted at this time. Routine monitoring will continue.

Rapporteur assessment comment:

During the reporting period, the MAH signals concerning **Mastitis/Breast swelling, Sensorineural hearing loss, Retinal vascular occlusion,** and **Menstrual irregularities** were closed.

After DLP of the current PSUR, the signal management procedure concerning **Post-menopausal haemorrhage** (EPITT 19989) was closed as this was evaluated by PRAC with a recommendation to continue monitoring through routine pharmacovigilance and the MAH signal **Pulmonary embolism** was started and is ongoing.

Other safety topics not considered signals

Hemophagocytic lymphohistiocytosis (HLH) (Appendix 5.2 of the PSUR)

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made:

The MAH should continue to closely monitor hemophagocytic lymphohistiocytosis (HLH) and report all new (literature) cases of HLH including a WHO-UMC causality assessment per case and age-stratified observed/expected analyses using 21-day and 42-day risk intervals.

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of defective apoptosis, a disruption of the regulatory pathway that terminates immune and inflammatory responses and results in excessive immune activation. HLH can be induced by genetic disorders (familial) or environmental causes. Familial HLH is rare, while environmental causes in adults include infection (most commonly EBV), autoimmunity, HIV infection and malignancy. HLH in adults may be confused with or misdiagnosed as sepsis, mainly due to similar clinical manifestations.

Literature

A search of literature was conducted from 19 June 2023 to 18 December 2023 to identify newly available articles describing BNT162b2 and the MedDRA PT Haemophagocytic lymphohistiocytosis in the Medline and Embase database. The search revealed 6 relevant articles.

1. Zhang et al (2023): *An analysis of reported cases of hemophagocytic lymphohistiocytosis (HLH) after COVID-19 vaccination*. The authors performed a systematic review of the literature for case reports of the occurrence of HLH after the administration of any COVID-19 vaccine. A total of 17 articles (25 patients) were included in this qualitative (descriptive) analysis. The mean age of patients who were reported to have developed HLH after COVID-19 vaccination was 48.1 years. Most HLH episodes occurred after the BNT162b2 mRNA COVID-19 vaccination (14/25 cases). The time to onset for symptoms after BNT162b2 vaccination ranged from 2 to 52 days. Almost all affected patients were treated with steroid and antibiotic therapy. Three patients died despite treatment. The authors noted that "the presence of HLH in these patients cannot always be directly attributed to the vaccine, as it may be influenced by underlying medical conditions" and concluded that despite the possibility of very rare HLH following COVID-19 vaccination, that should not discourage the uptake of COVID-19 vaccination.

Rapporteur assessment comment:

In this systematic review, cases of HLH reported after COVID-19 vaccination were analysed by Zang et al to understand the relationship between the two. A total of 25 patients were included in this qualitative analysis. There were 12 women and 13 men, mean age was 48.1 years, most cases were reported in US (9), followed by UK (4) and China (3), 4 patients had medical history of hypertension, 2 had type 2 diabetes and 1 had familial HLH type 3, HLH episodes occurred mainly after Comirnaty (14/25), 8 after 1st dose, 4 after 2nd dose and 2 dose not mentioned.

Four (4) of the published case reports (out of 14 concerning Comirnaty) were already discussed and assessed in previous PSUR AR (PSUSA/00010898/202306):

(i) case report by Park et al was considered probably related;
(ii) case report by Awan et al was considered possible related;
(iii) case report by Shimada et al was considered unlikely related;
(iv) case report by Sassi et al was considered not valid for causality assessment as diagnostic criteria were not met.

The remaining 10 published HLH cases concerning Comirnaty in the systematic review by Zang et al were the following:

1. Beak DW et al (2021), 20 year old male [redacted], symptoms onset after vaccination 2 days, no past medical history;
2. Tin Yu Lin et al (2022), 14 year old female [redacted], symptoms onset after vaccination 15 days, no past medical history;
3. Hieber Marie-Lisa et al (2022), 24-year old female [redacted], symptoms onset after vaccination 21 days after 1st vaccination, no past medical history, outcome discharged 14 days after treatment initiation in good condition;
4. Attwell L et al (2022), reported three cases of HLH following the ChAdOx1 Astrazeneca vaccine, hence this case is considered not valid
5. Giovanni Caocci (2021), 38 year old female [redacted] onset of symptoms after vaccination 21 days after 2nd vaccination, no past medical history, outcome discharged after 1 week, fully recovered within weeks;
6. Wu V et al (2022), 60 year old male [redacted] onset of symptoms after vaccination 6 days after 1st vaccination, past medical history Barrett's oesophagus, outcome discharged;
7. Wu V et al (2022), 32 year old female [redacted] onset of symptoms after vaccination 4 weeks after 2nd vaccination, no past medical history, outcome discharged;
8. Rocco Joseph M (2022), 52 year old male [redacted] onset of symptoms after vaccination 1 day, past medical history viral syndrome, outcome fatal;
9. Rocco Joseph M (2022), 53 year old male [redacted] onset of symptoms after vaccination 4 days, past medical history interstitial lung disease, outcome discharged
10. Rocco Joseph M (2022), 55 year old female [redacted] onset of symptoms after vaccination 3 days, no past medical history, outcome alive (pending chemotherapy, transplantation)

As noted by the authors of this qualitative analysis, one of the limitations is that the included case reports lacked complete data pertaining to the vaccination history, thereby precluding an in-depth analysis, which is acknowledged. The MAH notes in their summary (see further below) that the relevant cases presented in this case series were presented individually in previous PSURs. As far as the assessor is aware of not all Comirnaty cases were discussed previously. Therefore, for the **next PSUR** the MAH is requested to carefully review **all** (published) HLH reports – hence a **cumulative** review – including the review by Zang et al and the published HLH case reports included in the literature search by Hieber et al. A WHO-UMC causality assessment per published case should also be included, as well as a discussion on potential

mechanism (e.g. Hieber et al) plus a discussion whether there is a potential causal relationship between HLH after exposure to Comirnaty (**next PSUR**).

2. Wiwanitkit et al (2023). *Hemophagocytic lymphohistiocytosis (HLH) after COVID-19 vaccination*. Wiwanitkit et al commented on the Zhang et al. article above "An analysis of reported cases of hemophagocytic lymphohistiocytosis vaccination (HLH) after COVID-19". The authors state that specific vaccination components, such as adjuvants or viral vectors, may cause an aberrant immunological response in susceptible individuals and interact with the immune system, resulting in the development of HLH. However, they further state that the temporal link between immunization and the development of HLH does not always imply a causative association, as HLH can happen on its own or be induced by causes unrelated to immunization. The authors conclude that more studies are needed to determine the precise processes underlying HLH following COVID-19 vaccination.

Rapporteur assessment comment:
Wiwanitkit et al commented on the qualitative analysis by Zang et al. Wiwanitkit et al noted it is crucial to note that the temporal link between immunization and the development of HLH does not always imply a causative association, which is fully acknowledged. Indeed, HLH can happen on its own or be induced by causes unrelated to immunization. The authors conclusion is supported that more research is required to determine the true incidence and cause of post-vaccination HLH.

3. Kaizuka et.al: *Pediatric hemophagocytic lymphohistiocytosis after concomitant administration of SARS-CoV-2 vaccine and influenza vaccine*. Kaizuka et al describe a case of HLH in a 12-year-old female patient after co-administration of dose 3 of the bivalent BNT162b2 BA.4-BA.5 vaccine and quadrivalent inactivated influenza vaccine (Influenza HA Vaccine "KMB®"). The patient was reported to be in good physical condition before the vaccinations. For an unspecified reason, 2 doses of flu vaccine were administered in the same season. The patient presented to the hospital on the day after vaccination with fever, developed splenomegaly, cytopenia, bone marrow hemophagocytosis, high ferritin level and was diagnosed with HLH 12 days after vaccination. Various tests ruled out infectious diseases, malignant tumor, and autoimmune disease. The patient was treated with 2 mg/kg/day of oral prednisolone with rapid improvement of the symptoms and blood values. The authors concluded that vaccination was the most likely trigger for HLH, but that the co-administration of vaccines made it impossible to further delineate.

Rapporteur assessment comment:

This case report by Kaizuka et al describe a case of HLH 12 days after vaccination in a 12-year-old female patient [redacted] after simultaneous administration of Comirnaty and quadrivalent inactivated influenza vaccine. Due to the co-administration of Comirnaty and influenza vaccine no clear causality assessment can be performed.

4. Rodrigues et al: *Persistent Fever after COVID-19 Vaccination in a Patient with Ulcerative Colitis: A Call for Attention*. This is a case report of a 23-year-old female who was admitted to the hospital 15 days after receiving a first dose of the BNT162b2 vaccine with persistent fever and arthralgias despite receiving antipyretics. She had a history of ulcerative colitis since 2018 which was complicated by the development of HLH secondary to CMV infection in 2019. She had been in remission since then under vedolizumab therapy. She had no other comorbidities and was only receiving vitamin D supplementation. On presentation, the patient had fever ranging between 39 and 40°C, painless splenomegaly, mild normocytic and normochromic anemia, leukopenia, normal platelet count, hyperferritinemia, elevated CRP and elevated erythrocyte sedimentation rate. No endoscopic activity of ulcerative colitis was identified, and ANA, anti-Sm and anti-dsDNA antibodies were within normal range. CMV serology detected low IgM and IgG antibody titers thus intravenous ganciclovir (5 mg/Kg twice daily) was started for possible CMV reactivation. Cat scratch disease was also deemed a

diagnostic possibility as the patient had regular contact with a cat, so doxycycline was administered. Other infectious causes were excluded. However, after 10 days, there was no clear clinical or biochemical response and the patient felt sick and feverish. Serum PCR obtained at this time was negative for CMV. Further imaging revealed submental, submandibular, and bilateral axillary lymphadenopathy, hepatomegaly and splenomegaly, no evident focus of infection and no functional changes suggestive of high-grade metabolic malignancies or active sarcoidosis. A bone marrow biopsy demonstrated occasional stromal macrophages but no evidence of hemophagocytosis. On the 15th day of hospitalisation, hyperferritinemia, elevated soluble CD25 and elevated fasting triglyceride levels were noted. Taking into account the clinical picture, laboratory and imaging findings in the absence of evidence for infection or malignant disease, a diagnosis of HLH (HLH 2004 criteria) presumptively secondary to recent COVID-19 vaccination was made. Intravenous dexamethasone was started, and the patient became apyretic after 48 hours with concurrent symptomatic and biochemical improvement. She was discharged home after 30 days on a weaning course of oral prednisolone. Genetic testing to rule out hereditary HLH mutations for PRF1, STX11, STXBP2, UNC13D, DCLRE1C, RAG1, and RAG2 was negative.

Rapporteur assessment comment:

The case report by Rodrigues et al concerned a 23-year old female with ulcerative colitis (UC) and a medical history of HLH secondary to CMV infection, who developed HLH 15 days after the 1st dose of Comirnaty. Considering the temporal relationship and the confounding medical history of HLH this case is considered possibly related.

5. Sequeira et al: *Severe Acute Liver Injury due to Secondary Hemophagocytic Lymphohistiocytosis: A Case Report*. A 65-year-old male with a history of low-risk chronic lymphocytic leukemia and rheumatoid arthritis treated with prednisolone, developed fever (>39 C), myalgias and jaundice 1 week after the first dose of COVID-19 vaccine (manufacturer unspecified). The patient presented with liver impairment, characterized by hyperbilirubinemia, transaminases over 1,000 U/L and prolonged INR which prompted investigation and exclusion of autoimmune, toxic, and viral causes of hepatitis. Laboratory workup revealed bicytopenia, hyperferritinemia, which together with organ failure and evidence of hemophagocytosis in bone marrow suggested the diagnosis of HLH. Infectious etiologies, flare of rheumatological disease, and the progression of hematological disease (with bone marrow biopsy) was ruled out. He was successfully treated with etoposide and corticosteroids, with improvement of liver tests. However, after 6 weeks of therapy, the patient developed febrile neutropenia related to immunomodulatory therapy, so etoposide was discontinued and GCSF and antibiotics were started. The patient remained neutropenic and acquired a healthcare-associated pneumonia and died 8 weeks after admission. The authors reported that the recent vaccination for COVID-19 was the likely trigger for HLH.

Rapporteur assessment comment:

This published case report concerned a 65-year old male who presented with persistent high fever (>39°C), myalgias, and jaundice 1 week after 1st dose of COVID-19 vaccine. His medical history included low-risk chronic lymphocytic leukemia (CLL), rheumatoid arthritis previously on prednisolone, and traumatic splenectomy. Diagnosis was challenging given the predominant liver impairment. After excluding malignancy, infections, and rheumatic disorder flare, the authors considered HLH diagnosis, an HLH score of 277 supported the diagnosis. Corrective treatment (etoposide, dexamethasone) started, rapid clinical and liver improvement was observed, as well as neutrophil count and INR normalization. However, after 6 weeks of therapy, patient developed febrile neutropenia related to immunomodulatory therapy, etoposide stopped, granulocyte colony-stimulating factor (GCSF) and broad-spectrum antibiotics started. Patient remained neutropenic and acquired a healthcare-associated pneumonia requiring IC

admission, and died 8 weeks after admission. The authors stated that after exclusion of other causes of secondary HLH, the recent vaccination for COVID-19 was the likely trigger.

As COVID-19 vaccine was not specified, this case report is considered invalid for causality assessment concerning HLH and Comirnaty.

6. Francesca Della Casa et al: *Adult-onset macrophage activation syndrome treated by interleukin-1 inhibition*. Della Casa et al presented a case report/letter to the editor about an otherwise healthy 31-year-old Caucasian man, presenting at the hospital almost 20 days after the third dose of COVID-19 vaccination (manufacturer unspecified). Based on the clinical picture and blood tests, macrophage activation syndrome was suspected as a first manifestation of adult-onset Still's disease, as the patient fit the Yamaguchi criteria of haemophagocytic syndrome. On day 3 of hospitalization, immunosuppressive therapy (methylprednisolone and ciclosporin) was started. Anakinra was started in addition to the ongoing therapy and, on HD 3, intravenous immunoglobulin was started along with fibrinogen, enoxaparin and tranexamic acid to regulate coagulation. After an initial response, the patient's symptoms and blood tests deteriorated, so the patient was transferred to a third-level center on HD 5. Finally, after 7 days of steroid boluses and 5 days of anakinra, the clinical picture improved. After 10 days of anakinra, the patient started therapy tapering until HD 28, when he was discharged in good general clinical condition and with a notable improvement in blood tests. Genetic tests for inherited immunodeficiency and autoinflammatory diseases associated with macrophage activation syndrome development were negative.

Rapporteur assessment comment:

This published case report concerned a 31-year old man who was diagnosed with an EBV (Epstein-Barr Virus) reactivation in the context of secondary HLH/MAS (Macrophage Activating Syndrome).

As COVID-19 vaccine was not specified, this case report is considered invalid for causality assessment concerning HLH and Comirnaty.

MAH Summary

A total of 6 new relevant articles were identified through the literature search, 4 of which were case reports and one which was a commentary on a case series. The relevant cases presented in the case series by Zhang et al. were presented individually in previous PSURs. Of note, the case reports by Della Casa et al. and Sequiera et al. did not specify which brand of COVID-19 vaccine was administered. In the article by Kaizuka et al, in which the patient received BNT162b2 and influenza vaccines concomitantly, it is not explained why the child received 2 doses of influenza vaccine in the same season; this would be unusual in a healthy child as mentioned in the article. Overall, the six new relevant articles of HLH in the literature do not provide significant new safety information.

Rapporteur assessment comment:

Literature summary

A **literature** search during the reporting period revealed **6 new relevant publications on HLH**:

(i) Zang et al.'s systematic review revealed 14 cases of HLH after exposure to Comirnaty;
(ii) Wiwanitkit et al commented on the qualitative analysis by Zang et al.;
(iii) Kaizuka et al described a case report where no clear causality assessment can be performed (by the assessor) due to the co-administration of Comirnaty and influenza vaccine;
(iv) Rodrigues et al described a case report which is considered possibly related to Comirnaty (according to the assessor);

(v) Sequiera et al. described a case report, however, as COVID-19 vaccine was not specified, the case report is considered invalid for causality assessment (by the assessor);

(vi) Della Casa et al. described a case report, however, as COVID-19 vaccine was not specified, the case report is considered invalid for causality assessment (by the assessor);

Although requested, the MAH did not include a WHO-UMC causality assessment per published case, which is not acceptable. In addition, the MAH notes that the case series by Zang et al were presented individually in previous PSURs, however, as far as the assessor is aware of, 4 case reports (included in the review by Zang et al.) were already discussed and assessed in previous PSUR AR (PSUSA/00010898/202306). Therefore, for the next PSUR the MAH is requested to carefully review all (published) HLH reports – hence a cumulative review – including the review by Zang et al and the published HLH case reports included in the literature search by Hieber et al. A WHO-UMC causality assessment per (published) case should also be included, as well as a discussion on potential mechanism (e.g. Hieber et al, Kaizuka et al) plus a discussion whether there is a potential causal relationship between HLH after exposure to Comirnaty.

Refer to Rapporteur's overall conclusion below.

Safety database review

The safety database was searched for BNT162b2 vaccines adverse event reports from 19 June 2023 (the DLP for the previous evaluation of HLH) to 18 December 2023 using the MedDRA (v. 26.1) PT: haemophagocytic lymphohistiocytosis. Six (6) new cases were retrieved.

There were 2 males and 4 females, age ranging from 23 to 85 years (mean age 61.7 years). There were 2 fatal reports and all reports were serious. The reporting countries were Japan (4), Portugal (1) and United Kingdom (1). There were 3 spontaneous and 3 literature reports. One case was a literature report previously described in the literature section of the PSUR 5 (Case report 8: Awan et.al. *COVID-19 vaccination–related hemophagocytic lymphohistiocytosis presenting as acute liver failure*, [redacted] and one case was also retrieved by the literature search (article 4: Rodrigues et al. *Persistent Fever after COVID-19 Vaccination in a Patient with Ulcerative Colitis: A Call for Attention*, [redacted]).

The 6 cases are summarized in the table below. Assessor's comment has been added in the right column in the table below in **blue** font.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

AER Age/Sex Country Dose # Event Outcome	Medical History Concomitant Medications Case Summary	Reported PTs Latency from vaccination	MAH comment WHO UMC assessment	Assessor's comment
[redacted] 33 years / male [redacted] Dose 2 Unknown	Hyperlipidaemia, Seasonal allergy. Concomitant medication not reported. 3 days following D2, the patient had fever(102 F), chills and headache. Two months later he saw a hematologist for persistent cytopenia believed to be sequelae of viral infection and was hospitalized for intermittent fever, myalgia and 15 lb weight loss. Viral, fungal, protozoal, helminthic and bacterial etiologies were ruled out. Rheumatology started him on prednisolone for AOSD however tapering of steroids resulted in AOSD relapse and rehospitalization. Secondary HLH was suspected (H score 274, 99% probability). Etoposide and dexamethasone were started but etoposide was stopped due to severe liver dysfunction. Ultimately, he went into multi-	Haemophagocytic lymphohistiocytosis. 3 days.	The latency of the first symptoms is temporally plausible for being caused by vaccination however they may represent reactogenicity events. HLH was diagnosed 2 months later and it is unknown if the patient had previous recent infection that may have triggered the events. Possible.	This case was already discussed in previous PSUR. Temporal relationship is reasonable: symptoms onset 3 days after vaccination; HLH was diagnosed 2 months later; persistent cytopenia believed to be sequelae of viral infection, hence HLH could also be explained by infection. Comedication not reported. This case is considered possibly related.

AER Age/Sex Country Dose # Event Outcome	Medical History Concomitant Medications Case Summary	Reported PTs Latency from vaccination	MAH comment WHO UMC assessment	Assessor's comment
	organ failure and was transitioned to comfort care.			
[redacted] 69 years / female Japan Dose 4 Fatal	Rheumatoid arthritis. Concomitant medication not reported. Patient with a history of suspected methotrexate-related lymphoproliferative disease (presenting as LAD) developed sustained low grade fever and relapsed multiple areas of LAD at an unspecified time after vaccination. Four weeks after vaccination, soluble IL-2 receptor was high, and EBV-DNA was positive. The patient was hospitalized 6 weeks after vaccination due to fever, dyspnea and distributive shock. HLH was diagnosed based on HLH-2004 diagnostic criteria. On day 2 of hospitalization, etoposide and methylprednisolone were started but the patient died of multiple organ failure on day 3. Left axillary LN biopsy performed on day 2 revealed EBV-positive DLBCL.	Epstein-Barr virus associated lymphoma, Diffuse large B-cell lymphoma, Haemophagocytic lymphohistiocytosis. 6 weeks.	Although there is a plausible temporal relationship with vaccination, EBV infection and DLBCL provide an alternative etiology to HLH. Unlikely.	Temporal relationship is reasonable: onset of symptoms at unspecified time after vaccination, but 6 weeks after vaccination hospitalized and HLH was diagnosed. HLH could also be explained by EBV infection or DLBCL. This case is considered possibly related.
[redacted] 85 years / female	Medical history not reported. Concomitant medication not reported.	Haemophagocytic lymphohistiocytosis, Interchange of vaccine products, Interstitial lung	Data provided are not sufficient to confirm the diagnosis HLH, according to HLH-2004 criteria. The latency (10 months and 11	Temporal relationship is not reasonable: 10 months.

AER Age/Sex Country Dose # Event Outcome	Medical History Concomitant Medications Case Summary	Reported PTs Latency from vaccination	MAH comment WHO UMC assessment	Assessor's comment
[redacted] Dose 5 Not resolved	10 months after receiving Bivalent BNT162b2 OMI BA.1, the patient experienced acute interstitial pneumonia and haemophagocytic syndrome. The event was also complicated by pneumothorax. The patient received steroid pulse therapy and etoposide. 11 months after vaccination HLH was not resolved.	disease, Pneumothorax, Pancytopenia. 10 months and 11 days.	days) is not suggestive of a temporal association between vaccination and HLH. Unlikely.	This case is considered unlikely related.
[redacted] 82 years / female [redacted] Dose 5 Not resolved	Medical history not reported. Concomitant medication not reported. An 82-year-old female patient received the 5th dose of an m-RNA COVID-19 vaccine (dose 1 and 2 Comirnaty, doses 3 and 4 Spikevax, dose 5 BNT162B2 OMI BA.4-5) and approximately 8 months later developed interstitial pneumonia and HLH. The reporter assessed the HLH as related to the vaccine.	Haemophagocytic lymphohistiocytosis, Interchange of vaccine products, Interstitial lung disease. Pyrexia. 244 days.	The latency between vaccination and onset of HLH (8 months) and the previous repeated vaccinations with BNT162b2 are not suggestive of causal relationship between vaccination and HLH. Also, the data provided are not sufficient to confirm the diagnosis HLH, according to HLH-2004 criteria. Two of the eight criteria for HLH were reported as present in the narrative. Unlikely	Temporal relationship is not reasonable: 8 months. This case is considered unlikely related.
[redacted] 23 / female	Colitis ulcerative, Cytomegalovirus infection, Haemophagocytic lymphohistiocytosis, Vitamin D.	Haemophagocytic lymphohistiocytosis.	Latency supports a temporal association with vaccination. However, the patient had a	Temporal relationship is reasonable: 15 days. Medical history of HLH could also be

AER Age/Sex Country Dose # Event Outcome	Medical History Concomitant Medications Case Summary	Reported PTs Latency from vaccination	MAH comment WHO UMC assessment	Assessor's comment
[redacted] Dose 1 Resolving Same case as literature article 4	Hospitalized 15 days after receiving a first dose of BNT162b2, the patient had UC in remission on vedolizumab therapy and a history of HLH secondary to CMV infection. On presentation, she complained of arthralgia and had fever, splenomegaly, mild normocytic and normochromic anemia, leukopenia, hyperferritinemia, elevated CRP and elevated ESR. No endoscopic activity of UC was identified, and ANA, anti-Sm and anti-dsDNA antibodies were within normal range. Empiric treatment with ganciclovir for CMV reactivation and doxycycline for cat scratch disease was administered with no response. Further imaging revealed LAD, hepatomegaly and splenomegaly, no evident focus of infection and no functional changes suggestive of high-grade metabolic malignancies or active sarcoidosis. A bone marrow biopsy demonstrated occasional stromal macrophages but no evidence of hemophagocytosis. On the 15th day of hospitalisation, hyperferritinemia, elevated soluble CD25 and fasting triglyceride levels were noted. A diagnosis of an HLH was made. Intravenous dexamethasone was started, and the patient became apyretic after 48 hours	15 days.	history of autoimmune disease (UC) and was treated with immunosuppressants (vedolizumab) which can be considered trigger factors for HLH. A previous episode of HLH secondary to CMV infection was also reported. Possible.	the cause of the current HLH diagnosis. This case is considered possibly related.

AER Age/Sex Country Dose # Event Outcome	Medical History Concomitant Medications Case Summary	Reported PTs Latency from vaccination	MAH comment WHO UMC assessment	Assessor's comment
	with concurrent symptomatic and biochemical improvement. She was discharged after 30 days on a weaning course of oral prednisolone. Genetic testing to rule out hereditary HLH mutations for PRF1, STX11, STXBP2, UNC13D, DCLRE1C, RAG1, and RAG2 was negative.			
[redacted] 78 / male Japan Dose 2 Fatal	Hypercholesterolaemia, Hypertension. Concomitant medication not reported. At an unspecified time after D2, the patient experienced persistent oropharyngeal discomfort and physical deconditioning and idiopathic thrombocytopenia, haemophagocytic syndrome, acute renal injury, and hepatic function disorder. He presented for evaluation due to general malaise and decreased platelets counts, hepatic function disorder, and acute renal failure; the patient was admitted to the hospital and subsequently died approximately 2 months later.	Haemophagocytic lymphohistiocytosis, Physical deconditioning, Immune thrombocytopenia, Acute kidney injury, Hepatic function abnormal, Oropharyngeal discomfort, Malaise. Not specified.	Missing information on adverse event latency, diagnosis criteria and concomitant medication do not permit a thorough causality assessment. Unclassified.	No information on onset of symptoms, missing information on HLH diagnostic criteria. This case is considered unassessable.

Rapporteur assessment comment:

Spontaneous reports summary

From 19 June 2023 (DLP for previous evaluation of HLH) to 18 December 2023, 6 new HLH cases were retrieved from the MAH's safety database, of which 1 [redacted] was already discussed in previous PSUR and 1 [redacted] was included in the literature section above: 3 cases were considered possibly related, 2 cases were considered unlikely related, and 1 case was considered unassessable.

Routine statistical reports

To support routine signal detection activities, the MAH generates statistical reports including EB05.

The EB05>2 report is a product-specific Bayesian (Multi-Item Gamma Poisson Shrinker) computer-generated statistical data mining report, which provides data on product or adverse event combinations for which there is an emerging statistic of disproportionate reporting, using an EB05>2 as the metric or threshold and using a subtraction option to omit the most previously reviewed events from subsequent views. The objective of this analysis was to identify emerging new events as part of the signal detection.

On cumulative review of the EB05 report for the relevant PT, the obtained value for HLH was 0.727 for BNT162b2, 0.160 for Bivalent BNT162b2 OMI BA.1 and 0.728 for Bivalent BNT162b2 OMI BA.4/BA.5.

The EB05s are less than the EB05>2 threshold, thus indicating no emerging statistical signal of disproportionality for HLH.

Rapporteur assessment comment:

The MAH generates statistical reports including EB05 to support signal detection activities. No date was indicated for the cut off of the cumulative review, hence it is assumed the data cut off is the DLP of this PSUR. As of 18 December 2023, the EB05s are less than the EB05>2 threshold, indicating no emerging statistical signal of disproportionality for HLH.

Observed to expected analyses (O/E analyses)

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 121 hemophagocytic lymphohistiocytosis cases reported cumulatively through 05 October 2023. The observed cases and estimated number of exposed person-years were limited to the European Economic Area (EEA) countries for this analysis due to the availability of updated COVID-19 vaccine administration data in that region at the time of this analysis. Observed cases were defined using the Preferred Term (PT) hemophagocytic lymphohistiocytosis. In Table 2 , O/E results using 21- and 42-day risk windows post Pfizer-BioNTech COVID-19 vaccines are provided using selected population-based background rates for calculation of the expected cases in the denominator and all spontaneous reports of observed cases reported in the EEA in the numerator. The O/E results are further stratified by age.

The overall expected case counts were estimated using background incidence rates (IR) reported by a population-based cohort study from England, including primary and secondary care electronic health records during the years 2000 through 2016. This study identified 214 incident hemophagocytic

lymphohistiocytosis cases during the study period and reported an overall incidence rate that ranged from 0.49 to 3.53 cases per million (0.049-0.353 per 100,000) population per year. The average annual incidence rates during the study period were used for age-specific background estimates. Incidence was higher in infants and young children, as well as in older adults over 75 years. Because an average overall rate across all study years was not reported, to be conservative the median incidence rate was chosen for use in overall O/E analyses (year 2010: 1.41 per million [0.14 per 100,000]). In a literature review, the MAH found that this incidence figure of 1.4 cases per million was consistent with other population-based studies.

The expected case counts of hemophagocytic lymphohistiocytosis were calculated using these background incidence rates, the estimated number of Pfizer-BioNTech vaccine doses reported through 05 October 2023 in the EEA, and the length of risk windows.

Rapporteur assessment comment:

According to UpToDate (16 April 2024), a review of HLH cases from the largest pediatric hospitals in Texas revealed an incidence of 1 in 100,000 children, which is not consistent with the MAH's proposed incidence. Nevertheless, the MAH's conservative approach is acknowledged.

Although HLH is primarily a pediatric disease, it is diagnosed in patients of all ages, including adults as old as 70 years of age. A review of 2197 adult cases worldwide found that approximately half of reported patients were from Japan [source UpToDate].

Based on the selected background rates and the estimated number of exposure person-years through 05 October 2023, O/E ratios were greater than 1 for age groups 12-17 years (within 21- and 42-day risk windows) and 18-24 years (within 21-day risk window) but were less than 1 overall and for all other ages (Table 2). O/E ratios above 1 suggest that the number of observed cases might be higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines. However, the number of observed cases reported in these age groups was small (12-17 years: 5 cases, 18-24 years: 4 cases) resulting in wide 95% CIs that included 1, indicating that these results are not statistically significant.

Table 2. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Hemophagocytic Lymphohistiocytosis Through 05 October 2023 in EEA

Stratification	Observed Cases	Person Years	Background rate	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-day risk window							
EEA							
<5 years	0	3331.2	0.919	0.03	-	-	-
5-11 years	1	713818.8	0.192	1.37	0.730	0.018	4.065
12-17 years	5	1253560.7	0.139	1.74	2.870	0.932	6.697
18-24 years	4	3072550.9	0.086	2.64	1.514	0.412	3.876
25-49 years	16	14356565.8	0.124	17.73	0.902	0.516	1.465
50-59 years	4	7090742.0	0.161	11.42	0.350	0.095	0.897
60-69 years	6	6488700.9	0.161	10.45	0.574	0.211	1.250
70+ years	8	10808689.4	0.191	20.59	0.389	0.168	0.766
Overall, EEA	44	43787959.8	0.141	61.74	0.713	0.518	0.957
42-day risk window							
EEA							
<5 years	0	6634.0	0.919	0.06	-	-	-
5-11 years	1	1427612.2	0.192	2.74	0.365	0.009	2.033
12-17 years	5	2507105.9	0.139	3.48	1.435	0.466	3.348
18-24 years	4	6145054.9	0.086	5.28	0.757	0.206	1.938
25-49 years	21	28712779.6	0.124	35.46	0.592	0.367	0.905
50-59 years	4	14181281.5	0.161	22.83	0.175	0.048	0.449
60-69 years	6	12976653.1	0.161	20.89	0.287	0.105	0.625
70+ years	9	21616089.6	0.191	41.18	0.219	0.100	0.415
Overall, EEA	50	87573210.9	0.141	123.48	0.405	0.301	0.534

CI = confidence interval; EEA=European Economic Area; LL = lower limit; UL= upper limit; US=United States.
Note: The background rate source is West J, 2022. Source age groups of <1 and 1-4 years were averaged for <5; age group 5-14 years used for 5-11; average of 5-14 and 15-44 years used for 12-17; age group 15-44 used for 18-24; average of 15-44 and 45-74 years used for 25-49; age group 45-74 used for 50-59 and 60-69 years; and average of 45-74 and 75+ used for 70+ years.

There are several limitations to O/E analyses for signal detection. The observed case counts are likely to be underestimated due to the spontaneous reporting nature with passive safety surveillance. Furthermore, some observed cases were missing age and/or time to onset detail. Missing values of time to onset were imputed based on observed cases with known time to onset.

Regarding the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. The background rates used in these analyses are derived from a study prior to the COVID-19 era.

The risk windows for hemophagocytic lymphohistiocytosis following Pfizer-BioNTech COVID-19 vaccines are unclear. Misspecification of the risk window as wider than the true risk window could potentially under-estimate the risk estimates. We queried 21- and 42-day risk windows to cover a wide range of periods during which one is expected to be at risk of this acute event if there is a causal association between the event and vaccination.

Rapporteur assessment comment:

The O/E ratios for the age groups 12-17 years (within 21- and 42-day risk windows) and 18-24 years (within 21-day risk window) were above 1, however the 95% CIs are wide due to the limited number of cases (12-17 years: 5 cases, 18-24 years: 4 cases) and the lower level is below 1. The overall O/E ratio in the EEA are below 1 for both the 21-day and 42-day risk window.

MAH summary and conclusion

An updated literature and safety database search including routine statistical reports did not reveal any new significant safety information. There were no statistically significantly elevated O/E ratios; strata with O/E ratios over one had imprecise confidence intervals due to the very small sample size of cases (4-5 cases) in those age categories. A causal relationship between vaccination with BNT162b2 and HLH cannot be concluded based on the evidence. The topic will be monitored using routine pharmacovigilance and presented in future PSURs if any significant new information is identified.

Rapporteur assessment comment:

Literature summary

A **literature** search during the reporting period revealed **6 new relevant publications on HLH**:

(vii) Zang et al.'s systematic review revealed 14 cases of HLH after exposure to Comirnaty;
(viii) Wiwanitkit et al commented on the qualitative analysis by Zang et al.;
(ix) Kaizuka et al described a case report where no clear causality assessment can be performed (by the assessor) due to the co-administration of Comirnaty and influenza vaccine;
(x) Rodrigues et al described a case report which is considered possibly related to Comirnaty (according to the assessor);
(xi) Sequiera et al. described a case report, however, as COVID-19 vaccine was not specified, the case report is considered invalid for causality assessment (by the assessor);
(xii) Della Casa et al. described a case report, however, as COVID-19 vaccine was not specified, the case report is considered invalid for causality assessment (by the assessor);

Although requested, the MAH did not include a WHO-UMC causality assessment per published case, which is not acceptable. In addition, the MAH notes that the case series by Zang et al were presented individually in previous PSURs, however, as far as the assessor is aware of, 4 case reports (included in the review by Zang et al.) were already discussed and assessed in previous PSUR AR (PSUSA/00010898/202306).

Spontaneous reports summary

From 19 June 2023 to 18 December 2023, 6 new HLH cases were retrieved from the MAH's safety database, of which 1 [redacted] as already discussed in previous PSUR and 1 [redacted] was included in the literature section above: 3 cases were considered possibly related, 2 cases were considered unlikely related, and 1 case was considered unassessable.

O/E analyses

The O/E ratios for the age groups 12-17 years (within 21- and 42-day risk windows) and 18-24 years (within 21-day risk window) were above 1, however the 95% CIs are wide due to the limited number of cases (12-17 years: 5 cases, 18-24 years: 4 cases). The overall O/E ratio in the EEA are below 1 for both the 21-day and 42-day risk window.

Overall conclusion

Based on the data provided in this PSUR no new safety information could be identified on HLH after exposure to Comirnaty. Note that for this PSUR only **new** data was requested. Also note that in the observed versus expected analyses section, the MAH notes that cumulatively 121 hemophagocytic lymphohistiocytosis cases were reported through 05 October 2023 in the EEA countries. To enable assessment of **all available** data, in the next PSUR the MAH should provide a cumulative review of all evidence concerning HLH up to DLP of PSUR#7. A WHO-UMC causality assessment per case (irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc) should also be

included. The MAH should also discuss potential mechanisms and the need to update the product information if appropriate.

(**Issue to be addressed in the next PSUR**).

Idiopathic Inflammatory Myopathies/Myositis

The following was requested by Health Canada (MHPD):

BioNTech Manufacturing GmbH is requested to commit to the following: To continue to closely monitor idiopathic inflammatory myopathies/myositis, and idiopathic inflammatory myopathies flares through routine pharmacovigilance in the upcoming PSURs/PBERs including (but not restricted to): Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms, as appropriate.

Considering the cumulative review done up to 15 January 2023 of all evidence concerning the association between myositis and vaccination with Comirnaty provided to PRAC in the context of the signal evaluation request (EPITT 19883), the Pfizer safety database was searched from 16 January 2023 to the DLP of this PSUR (18 December 2023).

Rapporteur assessment comment:

Concerning the Myositis signal procedure (EPITT 19883), in May 2023, it was concluded by PRAC that based on the totality of the available evidence a causal association between COMIRNATY and autoimmune myositis could not be concluded at that moment. Therefore, the MAH was requested to continue close monitoring of Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares through routine pharmacovigilance, including (but not restricted to) any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms, as appropriate.

The MAH's review is presented below.

Clinical Trial Data

No cases.

Post-Authorisation Data

From 16 January 2023 up to 18 December 2023, the MAH received 156 idiopathic inflammatory myopathies/myositis cases (original [135]; bivalent Omi BA.1 [7]; bivalent Omi BA.4/BA.5 [10]; multivalent NOS [3], monovalent Omi XBB.1.5 [2]), of which 78 cases were medically confirmed and 78 cases non-medically confirmed. 118 cases were considered serious and 46 were non-serious cases.

Country/region of incidence (≥ 2%): Germany (47); Sweden, UK (14 each); Japan (12); Australia (9); US (8); France (7); Finland, New Zealand (5 each); Denmark, Norway (4 each); Brazil, Italy, Turkey (3 each); Canada, Czech Republic, Greece, Poland, Romania, and Spain (2 each); the remaining 6 cases were distributed among 6 unique countries.

The events were reported in females for 101 (64.7%) cases and in males for 50 (32.1%) cases. The other (5) cases did not report the gender of the patient.

Age was reported in 151 cases, ranging from 10-85 years (mean: 52.5; median: 53.0).

Medical history was reported in 67 cases, of which the most frequently (≥ 4) reported medical conditions included Hypertension (14); Depression (10); Anxiety (8); Autoimmune thyroiditis (7); Arthropathy, Hypersensitivity, Immunodeficiency, and Panic attack (4 each).

In 6 cases (suspected) COVID-19 was reported as medical history.

Reported relevant PTs: Myositis (87), Dermatomyositis (32), Polymyositis (13), Autoimmune myositis (8), Antisynthetase syndrome, Orbital myositis (6 each), Immune-mediated myositis (4), Anti-melanoma differentiation-associated protein 5 antibody positive, Overlap syndrome (2 each), Focal myositis, Idiopathic inflammatory myopathy, Inclusion body myositis, and Necrotising myositis (1 each).

Time to event onset could be retrieved in 51 cases (range: <24 hours to 499 days, median: 4 days): <24 hours after vaccination for 12 events (1 of which had a fatal outcome), 1 day for 4 events, 2-7 days for 13 events, 14 days for 4 events, 15-30 days for 6 events, 31-100 days for 6 events, and 101-499 days for 6 events.

In 2 cases the duration of the relevant events could be retrieved (events with outcome of resolved and resolved with sequelae); 1 event of 2 days duration and 1 event of 4 days duration.

Relevant event outcome: fatal (2), resolved/resolving (37), resolved with sequelae (6), not resolved (65), unknown (54).

The 2 cases with fatal outcome reporting 2 relevant events Dermatomyositis and Necrotising myositis, involved elderly subjects (67 and 69 years). In one of these 2 cases, influenza vaccine was reported as co-suspect and relevant medical history included malignancies (breast cancer and squamous cell carcinoma of the skin).

The reported causes of death were Abdominal distension, Dermatomyositis, Pneumonia aspiration, Acute kidney injury, Autoimmune disorder, Autoimmune hepatitis, Blood pressure systolic decreased, Dyspnoea, Erythema, Hepatic necrosis, Hepatitis, Hypoaesthesia, Hypoxia, Interchange of vaccine products, Intervertebral disc annular tear, Intervertebral disc protrusion, Malaise, Necrotising myositis, Nerve compression, Neuropathy peripheral, Paraneoplastic syndrome, Pleural effusion, Pneumothorax, Pruritus, Respiratory failure, Respiratory tract infection, Rhabdomyolysis, Spinal stenosis, Troponin increased (1 each).

Of the 69 cases reporting co-suspect medications and/or medical history, 22 cases reported relevant medical history/risk factors (e.g., autoimmune disorders, infections, malignancies, rheumatoid arthritis, muscular disorders, underlying dermatomyositis) and/or co-suspect vaccines which may have contributed to the development of the events indicative of idiopathic inflammatory myopathies/myositis.

Cases with idiopathic inflammatory myopathies flares

Among the 156 cases, 5 subjects reported idiopathic inflammatory myopathies flares. In 2 cases flare of juvenile idiopathic inflammatory myopathy and of dermatomyositis was reported after administration of dose 2 (1 each). Additionally, recurrences of myositis were reported in a subject after dose 3, 4 and 5 of vaccine and in further 2 subjects after 2 doses of vaccines (unspecified dose numbers for the first subject and dose 2 and 3 for the second subject).

Analysis by age group

Paediatric (3), Adults (103), Elderly (45) and Unknown (5).

No notable difference was observed in the reporting proportion of idiopathic inflammatory myopathies/myositis 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.

Literature

Review of the literature did not identify any significant new information regarding the COVID-19 mRNA vaccine and idiopathic inflammatory myopathies/myositis, and no scientific literature on possible pathogenic mechanisms.

Conclusion by the MAH

No new significant safety information was identified based on the review of the new cases reporting idiopathic inflammatory myopathies/myositis (including those reporting rechallenge information). This topic will continue to be monitored with routine pharmacovigilance activities and presented in future PSURs only if any significant new information is identified.

Rapporteur assessment comment:

From 16 January 2023 up to DLP, a total of 156 new cases reporting idiopathic inflammatory myopathies or myositis were identified by the MAH. The events were reported in females for 101 (64.7%) cases and in males for 50 (32.1%) cases. The other (5) cases did not report the gender of the patient. The gender distribution is in-line with the distribution of IMM irrespective of vaccination.

Time to event onset (TTO) could be retrieved in 51 cases (range: <24 hours to 499 days, median: 4 days): <24 hours after vaccination for 12 events (1 of which had a fatal outcome), 1 day for 4 events, 2-7 days for 13 events, 14 days for 4 events, 15-30 days for 6 events, 31-100 days for 6 events, and 101-499 days for 6 events. From these data, a compatible time to onset is suggestive in 39 cases (<24 hours to 30 days; comparable risk window as in Myositis Signal procedure).

The 2 cases with fatal outcome (reporting dermatomyositis and necrotising myositis), involved elderly subjects (67 and 69 years). In one of these 2 cases, influenza vaccine was reported as co-suspect and relevant medical history included malignancies (breast cancer and squamous cell carcinoma of the skin).

According to the MAH, 22 cases reported relevant medical history/risk factors (e.g., autoimmune disorders, infections, malignancies, rheumatoid arthritis, muscular disorders, underlying dermatomyositis) and/or co-suspect vaccines which may have contributed to the development of the events indicative of idiopathic inflammatory myopathies/myositis. Although the presence of alternative etiologies hampers assessment of a causal role of the vaccine in these 22 cases, a worsening effect of vaccination cannot be excluded.

In 6 cases (suspected) COVID-19 was reported as medical history. COVID-19 infection has been associated as a potential trigger of autoimmune diseases.

Among the 156 cases, 5 subjects reported idiopathic inflammatory myopathies flares/recurrence: in 2 cases flare was reported after dose 2; in 1 case recurrence was reported after dose 3, dose 4 and dose 5; in 1 case recurrence was reported after 2 doses (unspecified doses) and in 1 case recurrence was reported after dose 2 and dose 3. This might be suggestive of a causal role of the vaccine.

Overall, causality is possible based on suggestive TTO and 5 cases reporting idiopathic inflammatory myopathies flares, but inconclusive due to the lack of causality assessment per case by the MAH. The list of data as provided by the MAH is not appropriate to properly establish a causal association; the MAH should provide per case the causality assessment. However, considering the thorough assessment of all evidence in the Myositis signal procedure (EPITT 19883) which was completed recently, and the confounding factors in the new cases, a further assessment of this topic will be made in the next PSUR.

In conclusion, based on the new cases reporting idiopathic inflammatory myopathies or myositis the causal association cannot be confirmed neither refuted and therefore the signal should remain open. In

the next PSUR, the MAH should provide a cumulative review of all evidence concerning Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares from 16 January 2023 up to DLP of PSUR#7. In order to properly establish the causal association, causality assessment should be performed and presented in the PSUR per case (e.*g.* cases without alternative etiologies/confounding factors, or cases reporting of positive rechallenge(s)), irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc). The MAH should also discuss potential biological mechanisms and the need to update the product information, if appropriate.

(Issue to be addressed in the next PSUR)

RfSI included following submitted document by MAH in follow up to the 12 May 2023 adopted PRAC recommendation regarding the signal assessment of myositis with Comirnaty (EMA/PRAC/3178/2023; EPITT no: 19883)

Product Lots and AE Reports

Most frequently reported Lot Numbers

The most frequently reported lot numbers in PM case reports (>320 cases) are listed in Table 5 below.

Table 5. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases[b]
EK9788	1442
EM0477	969
HD9871	628
EL8723	373
EM6950	370
FH3023	324

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium).
b. Multiple lots were reported in the same case; hence the sum of the cases exceeds the real number of cases.

Out of total 4103 cases (11,109 AEs) with these lot numbers, the clinical AEs most frequently reported (≥ 5%) included Headache (1529), Pain (1474), Myalgia (1193), Pyrexia (1054), Fatigue (571), Arthralgia (569), Malaise (295), Chills (235), Diarrhoea (227), Lymphadenopathy (217) and Nausea (211).

These AEs do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per the RSI.

Of note, out of 4103 cases, there were 331 non-serious cases reporting PTs indicative of potential product quality issues including:

- three hundred and twenty-two (322) cases reported PT Product temperature excursion issue,[3] all involving lot FH3023 and without any co-reported clinical AEs;
- eight (8) cases reported PT Product packaging quantity issue,[4] all involving lot HD9871 without any co-reported clinical AEs;
- a single case reported PT Product substitution issue involving lot HD9871 with a single non serious co-reported event (PT Arthralgia).

There were no safety signals related to product quality defects or issues identified with product complaint investigations.

[3] Originated from a single cluster from Japan.
[4] Originated from a single cluster from Ireland.

Lot HG2252

As a precautionary measure the Danish Medicines Agency (DMA) decided to quarantine lot HG2252 on 17 October 2023 due to possible bubble formation in the solution after updraft in syringes. After careful review, there were no safety issues and the quarantine was lifted on 20 October 2023.

There were one hundred and eighty-three (183) cases reported with lot number HG2252. The clinical AEs most frequently reported (≥ 3%) were Fatigue (23), Headache and Malaise (22 each), Pyrexia (20), Vaccination site pain (18), Myalgia (16), Arthralgia, Asthenia, Chills and Nausea (11 each), Pain in extremity and Vaccination site swelling (10 each), Dizziness and Vomiting (9 each), Dyspnoea and Pruritus (8 each), Erythema and Vaccination site inflammation (7 each), Diarrhoea, Rash papular, and Vaccination site erythema (6 each).

There were no cases reporting a PT indicative of a product quality issue nor cases suggesting a suspected association between quality complaints and the AEs. In addition, the cases reviewed made no mention of bubbles in the syringes.

The reported AEs for HG2252 do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per the RSI.

AE reports and product quality complaints

Overall, the most frequently (≥ 22 occurrences) reported events potentially indicative of product issues regardless of lot number included the following PTs: Product temperature excursion issue (2561), Product counterfeit (37), and Product packaging quantity issue (22).

- Cases reporting the PT Product temperature excursion issue described product storage deviations.
- Cases reporting PT Product counterfeit originated from a single cluster of non-serious legal cases from Greece. These cases described a possible administration of counterfeit vaccine as it was not administered in the designated governmental facilities and the vaccination certificate recorded incorrect data on vaccination dates and facility. A product quality complaint (PQC) investigation cannot be performed due to absence of lot number/sample.
- Cases reporting the PT Product packaging quantity issue described volume overfill in vials.

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 original and bivalent primary series/booster doses are adequately described on the product packaging/labelling.

Surveillance for any correlation ("AE/PC [product complaint] alert") between the number of AE reports and the number of product quality complaints received in the review period is performed through review of AE/PC Lot and Lot profile reports and SAE/PC reports, and review of AE-batch/lot trending by Country reports. In support to this process as needed, a review of AE data related to respective PCs may be requested to support Trend Alert analysis and Trend Notifications.

AE/PC alerts are reviewed and evaluated to establish whether there is an association between the reported adverse event and a product quality defect or complaint. Upon safety evaluation, it is determined whether an alert does or does not constitute a potential safety signal and any required further evaluation and escalation as per standard procedures.

Conclusion by the MAH

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

Rapporteur assessment comment:

Triggered by the quarantine of lot HG2252 for a few days due to possible bubble formation in the solution after updraft in syringes, the MAH provided an elaborated review of the reported lot numbers and their AEs and product quality complaints. Overall, the AEs do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per product information.

No new safety issue was identified.

2.2.1. Evaluation of closed signals

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined Not to be Risks	
Mastitis/Breast swelling	Following communication from a regulatory authority (Australia TGA) on 05 July 2023 that the TGA's Pharmacovigilance Branch had assessed the risk of mastitis and breast swelling with tozinameran and concluded that there were sufficient safety grounds to request an update to the COMIRNATY PI with mastitis and breast swelling, the MAH evaluated this signal. Evaluation consisted of the review of preclinical toxicity studies that showed no signs of enlarged mammary glands, either clinically or microscopically in rats treated with up to 100 mcg BNT162b2 on Study Days 1, 8 and 15 and DART study data from dams treated with 30 mcg BNT162b2 21 and 14 days prior to mating and on gestation days 9 and 20 that showed no clinical signs of mastitis. The clinical trial database of blinded, placebo-controlled clinical trial data for studies C4591001, C4591031 substudy A and C4591015 was searched for reports of breast swelling, breast enlargement, breast oedema and mastitis. Four AE reports of mastitis were retrieved from the 3 studies: 1 from the BNT162b2 group and the remaining 3 from placebo groups. The literature search retrieved few articles apart from case reports (which are included in the post-authorization database review). The 2 most relevant articles described prospective cohort studies of lactating women who had been vaccinated with BNT162b2 or another mRNA COVID-19 vaccine; one focused on solicited AEs of relevance to lactating women (e.g. breast engorgement, mastitis) and found the incidence of mastitis/breast engorgement was not increased compared to published global estimates and axillary lymphadenopathy was not associated with mastitis or breast engorgement. The other prospective cohort study was smaller and focused on determination of Anti-SARS-CoV-2 antibody levels in milk and serum; in this study 1 mother developed mastitis and 1 developed a lump/swelling of the breast on the same side as the vaccination. The global safety database retrieved over 3100 AE reports of reports of breast swelling, breast enlargement, breast oedema and/or mastitis (breast swelling was the most frequently reported of the 4 PTs), the vast majority reported for BNT162b2 (original). Most of the reports were not medically confirmed and were reported by women between 31 and 50 years of age (80 cases in pregnant women) and a minority of cases described any kind of imaging study. The AE reports were examined for co-reported events of local vaccination reactions and lymphadenopathy in an attempt to determine if, for example, there were reports of local swelling severe enough to cause breast swelling or axillary lymphadenopathy contributing to breast swelling. A small minority of the reports (47) described local swelling/oedema that extended to the breast and a minority of reports (154) described ipsilateral lymphadenopathy and breast swelling however the chronology of the events was unclear.

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	Disproportionality analyses did not indicate any statistical signal. Overall, based on the totality of the information available, a causal relationship between vaccination and mastitis/breast swelling in women could not be concluded. Routine pharmacovigilance will continue.

Rapporteur assessment comment:

The signal of Mastitis/Breast swelling was opened based upon an enquiry from the Australian regulatory authority after the DLP of the previous PSUR (EMEA/H/C/PSUSA/00010898/202306).

The MAH reviewed all available data. No signs of enlarged mammary glands or mastitis was identified in the preclinical toxicity studies. A search in the clinical trial database of blinded, placebo-controlled clinical trial data for studies C4591001, C4591031 substudy A and C4591015, resulted in 4 reports of mastitis, of which 1 was reported in the BNT162b2 group, the remaining 3 reports were from the placebo groups. A literature search identified a few articles, apart from case reports, which were included in the post marketing database review. The MAH described 2 of the most relevant studies. These concerned prospective cohort studies of lactating women vaccinated with BNT162b2 or another mRNA COVID-19 vaccine. The first focused on solicited AEs of relevance to lactating women (e.g. breast engorgement, mastitis), the incidence found was not increased compared to published global estimates and axillary lymphadenopathy was not associated with mastitis or breast engorgement. The other study focused on determination of Anti-SARS-CoV-2 antibody levels in milk and serum; in this study 1 mother developed mastitis and 1 developed a lump/swelling of the breast on the same side as the vaccination. Disproportionality analysis did not indicate any signal.

In the global safety database, 3100 AE reports of breast swelling, breast enlargement, breast oedema and/or mastitis were retrieved. Most reports concerned BNT162b2 (original). Most of the cases concerned women between 31 and 50 years of age (80 cases in pregnant women) and were not medically confirmed. The MAH examined the reports for co-reported events, that could contribute or explain the breast swelling, such events were local vaccination reactions and lymphadenopathy. For 47 reports local swelling/oedema that extended to the breast was reported and ipsilateral lymphadenopathy and breast swelling was reported for 154 reports, however the chronology of the events were unclear. Review of the available data by the MAH did not support a causal relationship between vaccination and mastitis/breast swelling. This conclusion is endorsed. The MAH should continue to monitor mastitis/breast swelling through routine pharmacovigilance.

During the current 6th PSUR, the signal was closed on 5 August 2023 which is accepted.

Sensorineural hearing loss	Following communication from a regulatory authority (Australia TGA) on 15 June 2023 that the TGA's MaVIS section was reviewing the signal of sensorineural hearing loss, the MAH evaluated this signal with review of medical literature, AE reports in the global safety database, clinical trial data and O/E analyses. Participants in the placebo-controlled, blinded periods of the pivotal, Pfizer-led clinical studies reported a low number of hearing loss events in the vaccination and placebo groups, with no meaningful difference apparent between the two groups. The literature, consisting of 13 articles, not including case reports, enabled evaluation of population level data. While preliminary disproportionality findings were positive in 2 articles, a 3rd study did not, and the remaining

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	large observational studies were not supportive of an increased occurrence of hearing loss post-vaccination. No signal of disproportionate reporting was observed in the Pfizer safety database for any of the preferred terms included in the safety database search. The O/E analyses on deafness and sensorineural hearing loss supports that the reports of hearing loss and tinnitus in the stratified populations and doses are not greater than would be expected as background occurrences. The spontaneously reported cases received in the safety database are of variable quality. There are individual cases that report events close to the time of vaccination and provide detailed information without alternative explanations for hearing loss, however, due to the nature of sensorineural hearing loss and its myriad etiologies and the sheer number of vaccination doses administered globally, this is not unexpected, and the possibility of coincidental occurrence (of hearing loss and vaccination) cannot be discounted. The number of vaccine doses administered, and the subsequent number of adverse event reports received for the vaccine are unprecedented and raise the importance of population level data. Considering the totality of the data available, a causal association between Comirnaty and sensory neural hearing loss is not supported. Routine pharmacovigilance will continue.
Rapporteur assessment comment: A review of hearing loss was included in the previous 3rd PSUR in which PRAC endorsed the MAH conclusion that a causal association between Comirnaty and hearing loss or tinnitus could not be concluded (procedure EMEA/H/C/PSUSA/00010898/202206). In the prior 5th PSUR, the MAH reported the results of an updated review of sensorineural hearing loss requested by TGA (Australia) through 18 Jun 2023 including literature (13 articles), post-marketing cases (BC level 1: 132 cases; BC level 2: 9; BC level 3: 1; BC level 4: 205; BC level 5: 72 cases) and O/E analyses (all O/E ratios well below 1). It was concluded that based on provided data, MAH's conclusion is endorsed that a causal association between Comirnaty and sensorineural hearing loss is not supported at this time and that the MAH should continue to monitor sensorineural hearing loss through routine pharmacovigilance. During the current 6th PSUR, the signal was closed on 5 August 2023 which is accepted.	
Retinal vascular occlusion	Prompted by a literature article entitled Risk assessment of retinal vascular occlusion after COVID 19 vaccination by Li Jing-Xing et al. (Li J-X, Wang Y-H, Bair H, Hsu S-B, Chen C, Wei JC-C, et al. Risk assessment of retinal vascular occlusion after COVID-19 vaccination. npj Vaccines. 2023;8[1]:64) the MAH has undertaken an evaluation of retinal vascular occlusion on 22 June 2023. Evaluation consisted of review of the available data from clinical trials, the global safety database, the published literature and an observed versus expected analysis. Two cases of retinal artery occlusion were reported in the blinded placebo-controlled period of the pivotal clinical study C4591001: one in the >23,000 participant placebo group and one in the >23,000 participant BNT162b2 group. The participant in the vaccine group had received BNT162b2 (dose 2) 12 weeks previously and had a medical history of risk factors for retinal artery occlusion; the event was assessed as unrelated to BNT162b2 by the investigator.

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	A critical assessment of published large epidemiological studies was undertaken and one of the 5 studies concluded there may be an increased risk of retinal vascular occlusion after vaccination with a COVID-19 vaccine however, taken together, the literature did not provide strong evidence for an increased risk. The review of post-authorization data revealed the majority of retinal vascular occlusion events occurred in patients aged greater than 50 years, occurring most frequently in the 14 days after dose 1 and dose 2. Many cases were confounded by the presence of known risk factors in the medical history or provided insufficient detail on the clinical work-up to exclude other potential aetiologies. A small number of well-documented cases, with exclusion of the main known aetiologies, occurred with a temporal association to vaccination. Observed versus expected analyses were well below one for retinal arterial and retinal venous occlusion across all age stratifications and both the 21- and 42-day risk windows. Considering the totality of data in the context of global vaccine administration, the MAH did not consider that the currently available information supports a causal association between retinal vascular occlusion and Comirnaty. Routine pharmacovigilance will continue.
Rapporteur assessment comment: A review of Retinal vascular occlusion was performed by the MAH following the publication of Risk assessment of retinal vascular occlusion after COVID 19 vaccination by Li Jing-Xing et al. There were 2 cases identified in the clinical trials. One case concerned a participant in the placebo group. The other participant experiences retinal vascular occlusion 12 weeks after receiving BNT162b2 (dose 2). The case was assessed as unrelated by the investigator due to the medical history of risk factors. An assessment of published epidemiology studies was performed by the MAH. One of the 5 studies showed an increased risk of retinal vascular occlusion after a Covid-19 vaccination. The MAH did not provide information which epidemiological publication it concerned. Relevant key studies should be provided with references in future PSURs. The majority of cases from post marketing data occurred in patients over 50 years of age in the 14 days after the 1st or 2nd dose. Only a small number of cases was well documented, excluding other ethiologies and with a temporal association. The O/E analyses were below one for the 21- and 42- day risk windows for all age stratifications. Review of the available data by the MAH did not support a causal relationship between vaccination and retinal vascular occlusion. This conclusion is endorsed. The MAH should continue to monitor retinal vascular occlusion through routine pharmacovigilance. During the current 6th PSUR, the signal was closed on 7 Sep 2023, which is accepted.	
Menstrual irregularities	Following signal evaluations and follow-up query responses to EMA/PRAC for the signals heavy menstrual bleeding and amenorrhea in February 2022, the MAH considered that a separate overview of AE reports using a more inclusive MedDRA search strategy indicative of menstrual irregularities was warranted in February 2023.

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	Menstrual irregularities were not widely reported in the clinical trials in adults, and no imbalance between BNT162b2 and placebo groups occurred in the placebo-controlled period of the large pivotal C4591001 study. There were many spontaneously reported cases, and most were non-medically confirmed and non-serious without trends toward events of clinical significance. There were notable differences in regional reporting, with the bulk of reports from the UK and Western European countries and significantly fewer from the US, Australia and Japan, which are countries with robust pharmacovigilance systems and which account for an overall high proportion of ICSRs received in the global safety database. Review of the accumulating literature, supported by epidemiology, focused on studies robustly conducted but also included a look at other studies such as cross-sectional surveys based on convenience samples that generally did not have comparator groups or adjusted analyses. The literature provided reassurance that menstrual abnormalities reported following vaccination do not appear to be clinically consequential. Study observations included: weak/small observations of temporary changes in menstrual cycle length, inconsistent (some point toward, and others do not) changes in the length of reported menses, inconsistent (some point toward, and others do not) observations of heavier than usual menstrual bleeding. The difficulties of discerning causality of menstrual irregularities to the vaccine have been discussed in other reviews and evaluation documents produced by Pfizer and include that menstrual irregularities are common and may be multifactorial in etiology. Based on the totality of information, including the regional reporting differences, lack of signal in the pivotal studies and inconsistencies in the medical literature, the strength and quality of evidence was not supportive of a causal association between menstrual irregularities and Comirnaty. Routine pharmacovigilance will continue.

Rapporteur assessment comment:

Please refer to the closed signal procedure heavy menstrual bleeding (EPITT 19783) in which heavy menstrual bleeding was added as an ADR in Comirnaty PI, the closed signal procedure amenorrhoea (EPITT 19784), and the updated review of amenorrhea in the previous 4th PSUR concluding that a causal association between vaccination with Comirnaty and amenorrhoea was lacking.

In the prior 5th PSUR, the MAH reported the results of a repeated review of menstrual irregularities (not limited to heavy menstrual bleeding and amenorrhoea) through 31 Mar 2023 for post-marketing cases (731 serious medically confirmed cases with a reasonable latency between 1-90 days post vaccination) and through 11 Jul 2023 for relevant literature (6 high quality articles). Based on the provided data, MAH's conclusion was endorsed in the prior PSUR AR.

During the current 6th PSUR, the signal was closed on 5 August 2023 which is accepted.

Of note, during the period under review, a safety signal concerning postmenopausal haemorrhage after COVID-19 mRNA vaccine (nucleoside-modified) was ongoing (EPITT 19989). After DLP of the current PSUR, in the PRAC meeting of February 2024, the PRAC agreed that the overall evidence is insufficient to establish a casual association between COVID-19 mRNA vaccine (nucleoside-modified) and postmenopausal haemorrhage. No updates of the product

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
information and/or risk management plan are warranted at present. The MAH should continue to monitor postmenopausal haemorrhage through routine pharmacovigilance.	
Important Risks	
None	
Risks Not Categorised as Important	
None	

2.2.2. Signal evaluation plan for ongoing signals

Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Pulmonary embolism	Following a request from a regulatory authority (Saudi FDA) on 27 October 2023, a signal evaluation including review of post-authorization AE reports, medical literature, clinical study data, non-clinical data and O/E analyses was conducted. The signal was closed by the MAH as "not a risk" on 10 January 2024 (after the PSUR #6 DLP).
Rapporteur assessment comment: The evaluation of the signal pulmonary embolism by the MAH is awaited.	
Post-menopausal haemorrhage	Following a request from a regulatory authority (EMA/PRAC) on 30 October 2023, a signal evaluation including review of post-authorization AE reports, medical literature, clinical study data, non-clinical data and O/E analyses was conducted. The signal was closed by the MAH as "not a risk" on 22 December 2023 (after the PSUR #6 DLP). EPITT No. 19989
Rapporteur assessment comment: During the current 6th PSUR, the signal of post-menopausal haemorrhage was closed during a signal procedure (EPITT 19989). After DLP of the current PSUR, in the PRAC meeting of February 2024, the PRAC agreed that the overall evidence is insufficient to establish a casual association between COVID-19 mRNA vaccine (nucleoside-modified) and postmenopausal haemorrhage. No updates of the product information and/or risk management plan are warranted at present. The MAH should continue to monitor postmenopausal haemorrhage through routine pharmacovigilance.	

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Evaluation of important identified risks

Important Identified Risks – Myocarditis and Pericarditis

There were 843 potentially relevant cases of myocarditis and pericarditis: 482 cases reported myocarditis and 432 cases reported pericarditis (in 71 of these 843 cases, both myocarditis and pericarditis were reported).

Literature Data

During the reporting interval, there were no significant new safety data received from literature sources.

Important Identified Risks – Myocarditis

Search criteria - 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, no cases were retrieved in the PSUR #5.
- **Post-Authorisation Data**
    - Number of cases: 482 (original [424], bivalent Omi BA.1 [8], bivalent Omi BA.4/BA.5 [15], multivalent NOS [9], monovalent Omi XBB.1.5 [26]; 0.5% of 107,046 cases, the total PM dataset), compared to 711 cases (1.0%) retrieved in the PSUR #5.
    - Reported relevant PTs: Myocarditis (404), Myopericarditis (77), Carditis (7), Autoimmune myocarditis, Chronic myocarditis, Eosinophilic myocarditis (1 each).
    - Relevant event outcome: fatal (23), resolved/resolving (172), resolved with sequelae (31), not resolved (121), unknown (144).

Important Identified Risks – Pericarditis

Search criteria - 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 #5.
- **Post-Authorisation Data**
    - Number of cases: 432 (original [373], bivalent Omi BA.1 [13], bivalent Omi BA.4/BA.5 [16], multivalent NOS [4], monovalent Omi XBB.1.5 [26]; 0.4% of 107,046 cases, the total PM dataset), compared to 379 cases (0.5%) retrieved in the PSUR #5.
    - Reported relevant PTs: Pericarditis (424), Pericarditis constrictive (5), Pleuropericarditis (3).
    - Relevant event outcome: fatal (6), resolved/resolving (169), resolved with sequelae (11), not resolved (148), unknown (98).

O/E analysis

Cumulative for myocarditis in the EEA, O/E ratios were above 1 for the following groups (although the 95% CI crossed 1 for some groups)

- 14-day risk window:
    - Males 5+ years
    - Females 5+ years
    - Overall, monovalent dose 1, dose 2, and dose 3
    - Overall
- 21-day risk window:
    - Males 5+ years
    - Females 5+ years

- Overall, monovalent dose 1, dose 2, and dose 3
- Overall

Cumulative for myocarditis/pericarditis in the EEA, O/E ratios were above 1 for the following groups (although the 95% CI crossed 1 for some groups)

- 14-day risk window:
  - Males 12-24 years
  - Females 12-49 years
  - Overall, monovalent dose 2
  - Overall
- 21-day risk window:
  - Males 12-24 years
  - Females 12-49 years
  - Overall, monovalent dose 2

These results are consistent with those in the most recent PSUR.

Conclusion

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

This risk and appropriate action to take is communicated in the BNT162b2 CDS, in:

- Section 4.4, Special warnings and precautions for use - Myocarditis and pericarditis: "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".
- Section 4.8, Undesirable effects as adverse drug reaction in the post authorisation experience.
- Appendices A and B.

This risk will continue to be monitored through routine and additional pharmacovigilance activities as per EU-RMP v. 9.0 adopted on 10 November 2022.

Rapporteur assessment comment:

During the interval period, 843 potentially relevant cases of myocarditis and pericarditis were retrieved: 482 cases reporting myocarditis and 432 cases reporting pericarditis. In 71 of these 843 cases, both myocarditis and pericarditis were reported.

Myocarditis and pericarditis are included as ADRs in the Comirnaty EU SmPC section 4.8 with frequency very rare, and a warning/precaution regarding myocarditis and pericarditis in section 4.4:

"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 that most cases recover. Some cases required intensive

care support and fatal cases have been observed.

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."

Based on provided data concerning myocarditis and pericarditis, MAH's conclusion is endorsed that no new safety information could be identified. The MAH should continue to monitor cases reporting myocarditis and pericarditis after Comirnaty exposure with routine and additional pharmacovigilance.

2.3.2. Evaluation of Important Potential Risks

During the reporting period there were no important potential risks for BNT162b2.

2.3.3. Evaluation of Other Risks (not categorised as important)

Adverse events of special interest (AESIs)

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made: *for future PSURs, in 'Adverse Events of Special Interest (AESIs)' of section 'Evaluation of Other Risks (not categorised as important)', the AESIs should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal*.

MAH Response

Upon review of the incremental data in cases potentially reflective of AESIs, no new safety issues/signals or reporting pattern changes were detected. Section 16.3.3.1 Adverse Events of Special Interest has been removed from this document of the PSUR.

O/E analyses were conducted by the MAH for all AESIs that were previously included in the PSUR 5. Current analyses were restricted to the EEA countries only due to lack of availability of up-to-date exposure data from other regions. No new safety issue was identified; therefore, the MAH has included O/E results in the Appendix 5.4 of the PSUR (not included in this AR) for Myocarditis and Pericarditis only, as part of continuous monitoring.

Rapporteur assessment comment:

Noted.

As part of the approval letter for the emergency use of Tozinameran – COVID-19 mRNA vaccine (nucleoside modified) – COMIRNATY® on 26 January 2021, 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.*

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

MAH Response

Upon review of the incremental data in cases evaluated for these topics, no new safety issues/signals or reporting pattern changes were detected. These topics will continue to be monitored with routine pharmacovigilance activities and presented in future PSURs only if any significant information is identified. These topics have been removed from this Section of the PSUR.

Rapporteur assessment comment:

No new safety issues/signals or reporting pattern changes were detected concerning the 'AESIs in subjects with Malnutrition; HIV infection'. Thes topics will continue to be monitored with routine pharmacovigilance activities and presented in future PSURs only if any significant information is identified, which is noted.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

MAH 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 this Section of the PSUR.

Rapporteur assessment comment:

Noted.

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.*

MAH 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.

Rapporteur assessment comment:

Noted.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

MAH Response

Upon review of the incremental data of cases indicative of death, no new safety issues/signals or reporting pattern changes were detected. This topic has been removed from the evaluation of special situations discussed in Section 16.3.4 Evaluation of Special Situations of the PSUR.

Rapporteur assessment comment: Noted.

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made: *For future PSURs, in 'Evaluation of special situations' of section 'Evaluation of Other Risks (not categorised as important)', lack of therapeutic efficacy should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

MAH Response

Upon review of the incremental data of cases indicative of lack of therapeutic efficacy, no new safety issues/signals or reporting pattern changes were detected. This topic has been removed from the evaluation of special situations discussed in Section 16.3.4. Evaluation of Special Situations of the PSUR.

Rapporteur assessment comment: Noted.

Update on Special Patient Populations

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 '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 Response

Upon review of the incremental data of cases reported in frail patients with co-morbidities 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.

Rapporteur assessment comment: Noted.

In the AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

MAH Response

Upon review of the incremental data of cases reported in elderly population, no new safety issues/signals or reporting pattern changes were detected. This population has been removed from the populations discussed in Section 16.3.5 Update on Special Patient Populations of the PSUR.

Rapporteur assessment comment: Noted.

Paediatric Subjects <5 Years of Age

Clinical Trial Data

- Number of cases: 5 (original [2] and bivalent Omi BA.4/BA.5 [3] originated from clinical studies C4591007-OPENLABEL, C4591048-SSB [2 each], and C4591048-SSA [1]; 26.3% of 19 cases, the total CT dataset), compared to 41 cases (50.0%) retrieved in the PSUR #5. All events were assessed as unrelated to BNT162b2 or bivalent Omi BA.4/BA.5.

Post-Authorisation Data

- Number of cases: 395 (original [136], bivalent Omi XBB.1.5 [194], and bivalent Omi BA.4/BA.5 [72]; 0.4% of 107,046 cases, the total PM dataset), compared to 396 cases (0.5%) retrieved in the PSUR #5.
- Most frequently reported PTs (≥ 2) in subjects with ages of 5 months through 4 years (n=847):
  - Following dose 1
    - Formulation 3 mcg (Maroon cap) (n=30): Poor quality product administered (10), Overdose (6), Product administration error, Product temperature excursion issue (5 each), Product preparation error, Pyrexia (3 each), Concomitant disease aggravated, Expired product administered, Product preparation issue, Seizure, and Urticaria (2 each).
    - Formulation other/unknown (n=87): Overdose (47), Product preparation error (38), Poor quality product administered (29), Product administered to patient of inappropriate age (20), Product administration error, Product preparation issue (9 each), Expired product administered (7), Underdose (6), Accidental overdose, Product administered inappropriate site, and Vaccination error (2 each).
  - Following dose 2
    - Formulation 3 mcg (Maroon cap) (n=24): Poor quality product administered (9), Inappropriate schedule of product administration (8), Product administration error (6), Overdose (4), Product preparation error, Product temperature excursion issue, Pyrexia (3 each), COVID-19, and Vaccination failure (2 each).
    - Formulation other/unknown (n=17): Overdose (8), Inappropriate schedule of product administration, Product administered to patient of inappropriate age (4 each), Incorrect dose administered, Product preparation error (3 each), Accidental overdose, Fatigue, Interchange of vaccine products, Off label use, Pain, Poor quality product administered, and Wrong product administered (2 each).
  - Following dose 3
    - Formulation 3 mcg (Maroon cap) (n=16): Poor quality product administered (11), Product administration error (10), COVID-19, Inappropriate schedule of product administration, Overdose, Vaccination failure, and Wrong product administered (2 each).
    - Formulation other/unknown (n=13): Overdose (7), Product administered to patient of inappropriate age, Product preparation error (4 each), Incorrect dose administered (3), Accidental overdose, Fatigue, Interchange of vaccine products, Pain, Poor quality product administered, and Pyrexia (2 each).
  - Following dose other/unknown
    - Formulation 3 mcg (Maroon cap) (n=83): Poor quality product administered (77), Product temperature excursion issue (65), Product administration error (12), Overdose, and Product preparation error (4 each).

- Formulation other/unknown (n=135): Overdose (54), Product preparation error (50), Poor quality product administered (48), Product administered to patient of inappropriate age (21), Expired product administered (17), Product administration error (13), Product preparation issue (9), Underdose (8), Pyrexia (6), Off label use (5), Infant irritability, Product use issue (4 each), Rash, Wrong product administered (3 each), Accidental overdose, Decreased appetite, Incorrect dose administered, Infantile diarrhoea, Interchange of vaccine products, Musculoskeletal pain, Product administered at inappropriate site, Product packaging quantity issue, Product temperature excursion issue, and Sleep disorder (2 each).

- Event outcome: fatal (1), resolved/resolving (69), not resolved (12), unknown (765).

Fatal case (1)

- Age: 14 months (1).
- NMC case (1).
- Gender: unknown (1).
- Country/region of incidence: US (1).
- Fatal PT: Death (1).
- Medical history: none.

This case reported PT Death only as the fatal AE. Neither cause of death nor information on autopsy was provided in this case involving a 14-month-old subject (unspecified gender) who died after getting the vaccine bivalent Omi BA.4/BA.5. Timing of vaccination and date of death was not reported. Limited information was provided, precluding any meaningful assessment.

Rapporteur assessment comment:

During the interval period, post-marketing 395 cases were retrieved including 1 fatal case not medically confirmed. In the previous 5th PSUR there were reported 3 fatal cases of which 2 medically confirmed fatal case.

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: 4 (blinded therapy [2], original, and bivalent Omi BA.4/BA.5 [1 each], originated from clinical studies C4591007 [2], C4591007-OPENLABEL, and C4591048-SSB [1 each]; 21.1% of 19 cases, the total CT dataset), compared to 7 cases (8.5%) retrieved in the PSUR #5. All events were assessed as unrelated to BNT162b2, bivalent Omi BA.4/BA.5, or blinded therapy.

Post-Authorisation Data

- Number of cases: 1697 (original [1345], bivalent Omi BA.4/BA.5 [201], bivalent Omi XBB.1.5 [174], bivalent Omi BA.1 [3], and BNT162b2 Multivalent NOS [2]; 1.6% of 107,046 cases, the total PM dataset), compared to 1225 cases (1.7%) retrieved in the PSUR #5.

- Most frequently reported PTs (≥3% of cases): Poor quality product administered (507), Product temperature excursion issue (372), Dizziness (208), Nausea (175), Product administration error (154), Overdose (123), Product administered to patient of inappropriate age (122), Vomiting (121), Headache (114), Chest discomfort (98), Pyrexia (91), Abdominal pain, Vaccination site pain (82 each), Pallor (81), Syncope (75), Presyncope (66), Drug ineffective (51), and COVID-19 (50).
- Relevant event outcome: resolved/resolving (347), resolved with sequelae (3), not resolved (152), unknown (3120).

Rapporteur assessment comment:

During the interval period, post-marketing 1,697 cases were retrieved. No fatal cases were identified. In the previous 5th PSUR there were reported 2 fatal cases of which 1 medically confirmed fatal cases.

No important new information could be identified regarding the use of Comirnaty in children 5-11 years of age.

Paediatric Subjects ≥12 to ≤ 17 Years of Age

Clinical Trial Data

- Number of cases: none, compared to 5 cases (6.1%) retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 4690 (original [4502], bivalent Omi BA.4/BA.5 [114], bivalent Omi XBB.1.5 [77], BNT162b2 Multivalent NOS [7], bivalent Omi BA.1 [5]; 4.4% of 107,046 cases, the total PM dataset), compared to 1287 cases (1.7%) retrieved in the PSUR #5.
- Most frequently reported PTs (≥3%): Dizziness (1466), Nausea (838), Poor quality product administered (768), Headache (738), Product temperature excursion issue (736), Syncope (538), Pyrexia (450), Vaccination site pain (424), Lethargy (421), Chest discomfort (398), Vomiting (316), Anxiety (255), Abdominal pain (254), Pallor (229), Dyspnoea (226), Presyncope (218), Influenza like illness (213), Lymphadenopathy (177), Feeling of body temperature change (153), and Vision blurred (143).
- Relevant event outcome: fatal (20), resolved/resolving (1572), not resolved (1479), resolved with sequelae (69), unknown (9778).

Fatal cases (8)

  - Age: 13 years (3), unknown (2), 12 years, 14 years, and 15 years (1 each).
  - MC cases (3), NMC cases (5).
  - Gender: female (1) and males (7).
  - Country/region of incidence: Spain (3), Germany (2), Austria, Hong Kong, and Philippines (1 each).
  - Fatal PTs (20): reported AEs included Myocarditis, Pyrexia, Hypertrophic cardiomyopathy (2 each), Brain oedema, Brain herniation, Chest pain, Circulatory collapse, Drug ineffective, COVID-19, Muscular weakness, Dyspnoea, Use of accessory respiratory muscles, Guillain-Barre syndrome, Acute respiratory failure, Hypoxia, Asphyxia, and Arrhythmia (1 each).
  - Medical history (n=2): Obesity and Attention deficit hyperactivity disorder (1 each).

The 8 fatal cases are summarised below:

In 1 MC and 1 NMC case, limited information was provided, precluding any meaningful assessment. The subjects' medical history/underlying conditions, concomitant medications, or date of death were not reported. Lab data are limited (body temperature: 38-39 centigrade), and information on autopsy was not provided in these 2 cases.

In 6 cases, potential explanations other than vaccination for death are not evident in the reports:

- In 1 NMC case, a 13-year-old female subject experienced pyrexia, chest pain, and circulatory collapse 51 days after receiving BNT162b2 as dose 2, single for COVID-19 immunisation and died on the 52nd day. The subject's medical history, concomitant medications, and information on autopsy were not reported.
- In 3 NMC cases, 3 separate parents reported their children (12, 13, and 14 years of age) died suddenly while playing sports after receiving BNT162b2 (unknown dose number, lot number FG9428 [2] and FG7898 [1]) for COVID-19 immunisation. Fatal events in these 3 cases were Hypertrophic cardiomyopathy (2), Asphyxia, and Arrhythmia (1 each). All subjects had no relevant medical history. Concomitant medications and information on autopsy were not provided and date of death was unknown. No related quality issues were identified on this lot during the investigation.
- In the remaining 2 MC cases originated from 1 literature, the 2 adolescent male subjects experienced myocarditis after receiving BNT162b2 vaccination dose 2, single (lot number: unknown) for COVID-19 immunisation (see section 2.3.1). The latency time were 3 days and 4 days, respectively. One subject had the medical history of obesity, and another had attention deficit hyperactivity disorder. Concomitant medications were not reported in both cases. The autopsy results included microscopic myocardial findings (myocardial fibrosis in boy A and cardiac hypertrophy in boy B) and the subjects died suddenly and unexpectedly without resuscitation within the first week after receiving the second dose.

Rapporteur assessment comment:

During the interval period, post-marketing 4,690 cases were retrieved including 8 fatal cases, of which 3 were medically confirmed. Two of the medically confirmed cases concerned myocarditis, in one case the child had medical history of obesity and in the other one history of ADHD and the concomitant medications were not reported in these cases. The third case was not discussed due to limited information. In the previous 5th PSUR there were reported 13 fatal cases of which 9 medically confirmed fatal cases.

Section 4.4 of the SmPC contains the warning:

"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 that most cases recover. Some cases required intensive care support and fatal cases have been observed.

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."

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 6,791 cases involving paediatric subjects, 385 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (185 cases) and/or underlying medical history (282 cases).

Literature

During the reporting period, the review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

Conclusion

Upon review, the most frequently reported AEs indicative of vaccination errors had a higher reporting proportion in paediatric groups < 5 years and ≥5 Years and ≤ 11 Years of Ages compared to the ≥ 12 years of age; while the most frequent AEs indicative of reactogenicity type had a higher reporting proportion in paediatric group ≥ 12 years of age compared to groups of < 5 years and ≥5 Years and ≤ 11 Years of Ages. Of the frequently reported AEs (≥2%) in the paediatric dataset, no clinical AEs had a higher reporting proportion compared to the non-paediatric dataset. The medication errors reported in this population were in large majority not associated with harm.

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 and safety profile 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 RSI.

Rapporteur assessment comment:

Based on provided data, the MAH's conclusion is endorsed that no important new information could be identified regarding the use of Comirnaty in paediatric groups <5 years, ≥5 years - ≤11 years, and ≥12 years of age.

Use in Pregnant/Lactating Women

Clinical Trial Data

There was no pregnancy or lactation cases in the clinical trial dataset for this reporting period compared to 2 cases (2.4%) retrieved in the PSUR #5.

Post-Authorisation Data

- Number of pregnancy cases: 232 (original [160], bivalent Omi BA.1 [10], bivalent Omi BA.4/BA.5 [24], monovalent Omi XBB.1.5 [38]; 0.2% of 107,046 cases, the total PM dataset), compared to 464 cases (0.6%) retrieved in the PSUR #5. These 232 cases represent 201 unique pregnancies (2 cases [a mother case and a foetus/baby case] were created for 31 pregnancies).
- Country/region of incidence (>10 occurrences): UK (38), US (31), New Zealand (24), Germany (19), Netherlands (16), Australia (15), France (12), Slovakia (11).

- Of the 196 mother cases, 34 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 (19), Maternal exposure timing unspecified (12), Maternal exposure before pregnancy (2), Exposure during pregnancy (1).
- There were 162 mother cases of which 97 were serious and 65 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. The pregnancy exposure events (>10 occurrences) were coded to the PTs Maternal exposure during pregnancy (71), Maternal exposure timing unspecified (20), Maternal exposure before pregnancy (12). Additional pregnancy related events reported in these cases (>10 occurrences) were coded to the PTs Abortion spontaneous (34). Other frequently reported clinical events (≥10 occurrences) were coded to PTs Fatigue (23), Headache (22), Vaccination site pain (17), Malaise (14), Nausea (13), COVID-19, Myalgia, Pyrexia (10 each).
- Thirty-six (36) baby/foetal cases, 35 serious and 1 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: 18 of these cases reported 26 congenital anomalies that coded to the PTs Syndactyly, Ventricular septal defect (2 each), Accessory auricle, Aorta hypoplasia, Aplasia cutis congenita, Bicuspid aortic valve, Cardiac septal defect, Cerebellar hypoplasia, Cerebral palsy, Cleft lip, Cleft palate, Congenital anomaly, Congenital tracheomalacia, Congenital umbilical hernia, Cytogenetic abnormality, Dysmorphism, Foetal malformation, Foetal vascular malperfusion, Gnathoschisis, Laryngomalacia, Respiratory tract malformation, Rib deformity, Sensory level abnormal, Vascular compression (1 each). Of these 18 cases, information regarding trimester of exposure was available in 3 cases. Of these 3 cases, in 2 cases foetus was exposed during 1st trimester and remaining 1 case, foetus was exposed during 3rd trimester. Of these 18 cases, in 1 case mother of the baby was on multiple co-suspect/concomitant medications (i.e., acetylsalicylic acid, DTP vaccine, tetanus toxoid vaccine, levothyroxine etc.) which might have contributed to the reported event i.e., supraventricular tachycardia. In the remaining 17 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
    - Pregnancy outcome: Spontaneous abortion: 2 cases reported spontaneous abortion. In both these cases information regarding trimester of exposure was unknown. The clinical events in these 2 cases other than exposure related events were coded to PTs Foetal death, Foetal malformation (2 each). In these 2 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.
    - Pregnancy outcome: Elective termination: 1 case reported elective termination of pregnancy due to foetal defects. In this case information regarding trimester of exposure was unknown. The events reported in case other than exposure related events were coded to PTs Multiple congenital abnormalities, Chromosomal deletion, Hydrops foetalis, Congenital foot malformation, Heart disease congenital, Congenital hand malformation, Amniotic fluid volume increased, Dysphagia (1 each). In this case there was limited information regarding mothers' obstetric history which precluded meaningful causality assessment.
    - Pregnancy outcome: Stillbirth: 5 cases reported foetal death/ neonatal death. Of these 5 cases, 2 cases reported stillbirth with foetal defect and 3 cases reported stillbirth without foetal defect. The information regarding trimester of exposure was available in 2 cases and in these cases, foetus was exposed during 2nd and 3rd trimester. The events reported in these

cases other than exposure related events were coded to PTs Foetal growth restriction (2), Congenital anomaly, Foetal cystic hygroma, Foetal death, Premature baby death (1 each). Of these 5 cases, in 1 case mother of the baby had underlying urinary tract infection, which might have contributed to the reported event. In the remaining 4 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Live birth without congenital anomaly: 10 cases reported live birth babies without congenital anomaly. Of these 10 cases, information regarding trimester of exposure was available in 3 cases. In these 3 cases, foetus was exposed during the 1st, 2nd and 3rd trimester each. The events reported in these 10 cases other than exposure related events were coded to PTs Foetal hypokinesia (4), Premature baby (2), Foetal growth restriction, Ischaemic stroke, Sebaceous naevus (1 each). In all these 10 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 232 cases, 172 cases provided pregnancy outcomes which are provided in **Error! Reference source not found.** of the PSUR (not included in this AR). Pregnancy outcome was pending or not provided in the remaining 60 cases.

Lactation cases

- Number of lactation cases: 94 (original [81], bivalent Omi BA.1 [2], bivalent Omi BA.4/BA.5 [8], monovalent Omi XBB.1.5 [3]; 0.1% of 107,046 cases, the total PM dataset), compared to 119 cases (0.2%) retrieved in the PSUR #5.
    - Breast feeding baby cases: 80, of which:
    - Sixty-eight (68) cases reported exposure to vaccine during breastfeeding Exposure via breast milk) without the occurrence of any clinical events.
    - Twelve (12) cases, 1 serious and 11 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 (>1 occurrence) other than exposure related events were coded to PTs Infantile diarrhoea, Pyrexia (3 each), Infant irritability, Anxiety, Abdominal pain, Urticaria (2 each).
    - Breast feeding mother cases: 14, of which
    - Six (6) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
        - Eight (8) cases, 2 serious and 6 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (≥2 occurrences) other than exposure related events were coded to PTs Dizziness (3), Mastitis, Pyrexia, Vomiting, Arthralgia (2 each).

Literature

Review of the literature did not identify any new safety information regarding the use of BNT162b2 in pregnant/lactating women.

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, no pregnancy cases were retrieved compared to 2 cases (2.4%) retrieved in the PSUR #5.

Post-marketing data

During the interval period, 232 pregnancy cases (0.2% of the total PM dataset) were retrieved compared to 464 pregnancy cases (0.6%) retrieved in the 5th PSUR.

During the interval period, 94 lactation cases (0.1% of the total PM dataset) were retrieved compared to 119 lactation cases (0.2%) retrieved in the 5th PSUR.

Regarding the 36 cases with pregnancy outcome: 18 (50%) of these cases reported live birth with congenital anomalies, 2 cases (6%) reported spontaneous abortion, 1 case (3%) reported elective termination of pregnancy, 5 cases (14%) reported foetal death/ neonatal death, and 10 cases (28%) reported live birth babies without congenital anomaly. Compared to the pregnancy outcomes in the previous interval period (n=57) these were 12 (21%), 14 (25%), 3 (5%), 1 (2%), and 27 (47%) respectively.

Literature

No new safety information.

Overall, based on provided data 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.

2.4. Characterisation of risks

2.4.1. Characterisation of important identified and potential risks

- Important Identified Risk: Myocarditis and Pericarditis
- Important Potential Risk: *None*

Please see Appendix 8 of the PSUR (not reproduced here) for the characterisation of the important identified risks of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 11.2 in effect at the end of the reporting period (EMEA/H/C/005735/II/0206/G submitted 22 December 2023, after DLP).

Rapporteur assessment comment:

Please refer regarding the important identified and potential risks to section 2.1 'Summary of safety concerns' of the AR above. During the reporting period, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of safety concerns in the Comirnaty EU-RMP.

2.4.2. Description of 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:

The information on the missing information has been updated with no consequences on the known safety profile. The missing information remain unchanged.

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.

During the reporting period, in August 2023, an adapted Comirnaty vaccine targeting the Omicron XBB.1.5 subvariant named Comirnaty Omicron XBB.1.5 (raxtozinameran) has been authorised (procedure EMEA/H/C/005735/II/0183) to be used for preventing COVID-19 in adults and children from 6 months of age. In line with previous recommendations by EMA and the European Centre for Disease Prevention and Control (ECDC), adults and children from 5 years of age who require vaccination should have a single dose, irrespective of their COVID-19 vaccination history. Children from 6 months to 4 years of age may have one or three doses depending on whether they have completed a primary vaccination course or have had COVID-19.

Rapporteur assessment comment:

There are no new data on efficacy that alters previous assessments as described in the approved product information of Comirnaty.

4. Benefit-risk balance

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/riltozinameran), Comirnaty Original/Omicron BA.4-5 (tozinameran/famtozinameran), and COMIRNATY Omicron XBB.1.5 (raxtozinameran) 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.

In the previous 4th PSUSA (procedure EMEA/H/C/PSUSA/00010898/202212) changes of the PSUR frequency was proposed: one additional 6-monthly PSUR (DLP December 2023) will be submitted, then a first yearly PSUR (DLP December 2024), to be followed by further yearly PSURs according to the list of Union reference dates (EURD).

5. Rapporteur Request for supplementary information

This Request for supplementary information is included following a submission by the MAH on 18 April 2024 in follow up to the 12 May 2023 adopted PRAC recommendation regarding the signal assessment of myositis with Comirnaty (EMA/PRAC/3178/2023; EPITT no: 19883) with the following recommendation in part:

The MAH should explore the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand the occurrence of IIM/myositis in a broad population. The MAH should provide proposals to obtain more recent IIM/myositis background incidence rates (i.e., during the pandemic/immunisation campaigns).

The MAH should include and follow-up on IIM/myositis in any of the ongoing PASSs listed in the pharmacovigilance plan (e.g., C4591009; C4591010; C4591011; C4591012; C4591021).

The response to this question will be assessed for the updated AR.

6. MAH responses to Request for supplementary information

BACKGROUND INCIDENCES OF MYOSITIS

In accordance with the June 2023 updated PRAC recommendation regarding the signal assessment of myositis with Comirnaty (EPITT no: 19883), the MAH has continued to monitor the background incidence of idiopathic inflammatory myopathies (IIM) both in the published literature and using a real-world healthcare database.

Literature prior to the COVID-19 era

A 2015 systematic review and meta-analysis comprehensively summarized population-based studies of IIM IRs from across the world during the period 1966 to 2013[1]. IRs varied widely depending upon a number of factors, including case definition and study design. The systematic review reported an IR range of 1.16-19 per million PY across studies that included all ages (Table **1**). Studies that included primarily adults reported higher rates (Table **2**). Studies in the U.S. using administrative claims data reported the highest IRs (42.7-66 per million-PY for 18+ years). Literature published after the Meyer et al. 2015[1] systematic review reported estimates within the range of those in the systematic review for all ages among study populations captured in similar calendar periods, including Svensson et al. 2017[2] with an IR of 11 cases per million-PY in Sweden, Kronzer et al. 2021[3] with an IR also of 11 cases per million PY in the US for dermatomyositis only[3], and Cho et al. 2019[4] with an IR of 2.9-5.2 per million-PY in South Korea.

Table 6. Incidence of inflammatory myopathies (all ages) Error! Bookmark not defined.

Country	Reference	Year of publication	Period of study	Size of study population	Incidence /million-PY (95% CI)
US; California	Pearson	1966	9-year period	10 million	1.16
North England	Rose and Walton	1966	1954-64	3 294 000	2.46
US; Minnesota (Rochester)	Kurland et al.	1969	1951-67	~50 000	6
US; Tennessee (Shelby County)	Medsger et al.	1970	1947-68	0.4-0.7 million	5

Table 6. Incidence of inflammatory myopathies (all ages) Error! Bookmark not defined.					
Country	**Reference**	**Year of publication**	**Period of study**	**Size of study population**	**Incidence /million-PY (95% CI)**
Israel	Benbassat et al.	1980	1960–76	2.3 million	2.18
Libya; Benghazi	Radhakrishnan et al.	1987	1983–85	0.52 million	8.8
US; Pennsylvania (Allegheny County)	Oddis et al.	1990	1963–82	1.3–1.6 million	5.5 (0.3, 10.7)
Japan; Tottori Prefecture	Kusumi et al.	1995	1988–92	614 725	10.1 (4.50, 15.70)
Sweden; Gävleborg County	Weitoft et al.	1997	1984–93	307 018	7.6
Australia; Victoria	Patrick et al.	1999	1989–91	4 420 373	7.4 (6.0, 9.0)
Taiwan	Kuo et al.	2011	2003–07	22.7 million	11.5
England	Tran et al.	2012	2000–09	1.72 million	19 (17, 21)
Taiwan	Yu et al.	2013	2000–08	1 million randomly sampled from 23 753 407	15 (12, 17)
Hungary	Vincze et al.	2013	1999–2010	9.82 million	9.5
New Zealand; Counties Manukau	Gupta et al.	2013	2004–08	464 000	5.1
Japan	Ohta et al.	2013	2003–10	127 million	6.8 (2003) to 13.4 (2008)
Meta-analysis	Present article	—	1951–2010	186 million	7.98 (7.38, 8.66)
CI: confidence interval; IM: inflammatory myopathy; PY: Person-years; US: United States; **Note:** Reproduced from Table 1 in Alain Meyer et al Error! Bookmark not defined.					

Table 7. Incidence of adult inflammatory myopathies Error! Bookmark not defined.					
Singapore	Koh et al.	1993	1986–91	1.62 million	7.70 adjusted for ≥16 years of age
Finland	Kaipiainen-Seppänen et al.	1996	1990	~1 million	3.7 (1.1, 10.2) adjusted for ≥16 years of age
New Zealand, North Canterbury region	Lynn et al.	2005	1989–2001	430 000	8.7
South Australia	Limaye et al.	2007	1990–2004	1 491 418	5.4
US	Furst et al.	2012	2003–08	Sample of ~35 million	66 (62, 69) adjusted for ≥18 years of age
US	Smoyer-Tomic et al.	2012	2004–08	~14 million	42.7 (40.9, 44.4) adjusted for >18 years of age
South Australia	Tan et al.	2013	1980–2009	1.47 million	8 (7.2, 8.9)
Argentina, City of Buenos Aires	Rosa et al.	2013	1999–2009	146 747	10.7 (5, 18.4) adjusted for >18 years of age
Meta-analysis	Present article	—	1986–2009	24 million	19.97 (18.82, 21.34)
CI: confidence interval; IM: inflammatory myopathy; PY: Person-years; US: United States; **Notes:** Reproduced from Table 2 in Alain Meyer et al Error! Bookmark not defined.					

Literature during and after the COVID-19 era

The MAH conducted an updated literature review to understand the incidence of IIM during and after the COVID-19 pandemic (01 Dec 2019 onwards). No published population-based background IRs during this time period were identified as of December 2023.

Healthcare database analysis prior to and during the COVID-19 era

To explore the feasibility of using healthcare data prior to and during the COVID-19 era to better understand the trends in recent/contemporaneous background IIM IRs in a broad population, the MAH conducted an analysis using the US Optum Clinformatics closed claims database for the timeframe 01 Jan 2018 to 31 Dec 2022, which allowed calculation of annual IRs for 2019 to 2021 (Table **3**). IIM cases were defined as insured individuals with at least one of the myositis ICD 10-CM codes listed in Table **4** present

during 2 or more specialist visits (rheumatology, neurology, internal medicine, dermatology, or pediatric) with subsequent visit occurring within 1-12 months of the first qualifying visit with myositis diagnosis (index date). Patients were required to have continuous enrollment for at least 365 days prior to cohort entry and prevalent cases of IIM were excluded using a washout period of 365 days prior to the index date. The timeframe for the study allowed for at least 365 days of continuous enrollment before the first eligible index date (01 Jan 2019), and for subsequent follow-up time for a second visit through 31 Dec 2022. The case definition for this analysis was based on Svensson et al, 2017[2], which was used in a prior regulatory response (Appendix 1) and modified based on internal clinical input with additional IIM codes.

During the 2019 pre-COVID era, the IIM IR was 48.6 (95% CI: 41.1, 57.5) cases per million-PY (Table **3**). Annual IRs during the COVID-19 period did not show a consistent temporal pattern, with each of the years having IR estimates statistically indistinguishable from 2019 (all Wald Chi-Sq test of differences in IR p>0.2). Furthermore, the range of IIM IRs (48.4-55.0 per million-PY) in this analysis were within the range of pre-COVID-19 era IRs of 42.7-66 cases per million-PY estimated from administrative claims data in the US as reported in the Meyer et al 2015[1] systematic review (see Table **2**).

There are limitations to this analysis, which include that cases were not clinically confirmed, but rather were defined by ICD-10 codes in adjudicated closed claims which may be subject to coding errors and misclassification of cases. As found in the review by Meyer et al 2015[1], IRs from administrative data sources tend to be in the high range of published estimates compared to studies that include case reviews. In addition, claims data are collected for administrative and billing reasons, and not for research purposes. Finally, these analyses are for a 3-year period using US data and may not be representative of trends in myositis incidence over a longer period of time post 2020 and/or in different geographic regions. Strengths include the large underlying population size in the database covering all ages allowing ascertainment of this rare outcome to compare annual incidence rates prior to and during the COVID-19 era.

In summary, the MAH conducted a feasibility analysis of administrative real-world data, the results of which did not show a statistically significant trend in IIM IRs from recent pre-COVID (2019) through COVID-era (2020-2021) timeframes. Since no trend was exhibited, background IIM IRs from studies during the pre-COVID-era timeframes should be comparable to the background IIM IRs during the COVID-era. In conclusion, the results from the observed to expected analyses in the previous signal evaluation of myositis (Appendix 1) that relied on pre COVID-era background rates were appropriate to use and are in the low-range of published estimates, which would result in a conservative observed to expected estimate.

Table 8. Incidence of inflammatory myopathies (all ages) in Optum Clinformatics US Claims Database

Country	Data Source	Period of study	Cases (N)	Time at Risk (PY)	Incidence/ million-PY (95% CI)
US	Optum Claims	2019	136	2,799,653	48.6 (41.1, 57.5)
		2020	135	2,788,310	48.4 (40.9, 57.3)
		2021	159	2,891,498	55.0 (47.1, 64.2)

CI: confidence interval; IM: inflammatory myopathy; PY: Person-years; US: United States
Wald chi-square test for difference: 2020 vs. 2019: p=0.9782; 2021 vs. 2019: p=0.2885
Notes: Estimates from Optum Clinformatics closed claims during the study period 01 Jan 2018 – 31 Dec 2022. A 25% random sample of all patients with claims in this period was selected to ensure efficiency of analyses.

Table 9. Diagnosis Codes (ICD-10) Used to Identify Incident Cases of Potential Idiopathic Inflammatory Myopathy in Optum Closed Claims Database

ICD-10 Code	Description
M33.10	Other dermatomyositis, organ involvement unspecified
M33.11	Other dermatomyositis, with respiratory involvement

M33.12	Other dermatomyositis with myopathy
M33.13	Other dermatomyositis without myopathy
M33.19	Other dermatomyositis with other organ involvement
M33.00	Juvenile dermatomyositis, organ involvement unspecified
M33.01	Juvenile dermatomyositis with respiratory involvement
M33.02	Juvenile dermatomyositis with myopathy
M33.03	Juvenile dermatomyositis without myopathy
M33.09	Juvenile dermatomyositis with other organ involvement
M33.20	PM with organ involvement unspecified
M33.21	PM with respiratory involvement
M33.22	PM with myopathy
M33.29	PM with other organ involvement
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.93	Dermatopolymyositis, unspecified without myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
G72.41	Inclusion Body Myositis
G72.49	Other inflammatory and immune myopathies, not elsewhere classified

MYOSITIS IN POST-AUTHORISATION SAFETY STUDIES

Myositis has been included as an AESI/outcome in the following MAH sponsored non interventional PASS's: C4591009, C4591021; C4591051 and C4591052.

APPENDIX 1

V Doc_Mar 2023_Response to EMA PRAC PAM SDA-XXX Myositis (not reproduced here, see EPITT no: 19883).

References

[1]Meyer A, Meyer N, Schaeffer M, et al. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford). 2015;54(1):50-63.

[2]Svensson J, Arkema EV, Lundberg IE,et al. Incidence and prevalence of idiopathic inflammatory myopathies in Sweden: a nationwide population-based study. Rheumatology (Oxford). 2017;56(5):802-10.

[3]Kronzer VL, Kimbrough BA, Crowson CS, et al. Incidence, prevalence, and mortality of dermatomyositis: a population-based cohort study. Arthritis Care Res (Hoboken). 2023;75(2):348-55.

[4]Cho SK, Kim H, Myung J, et al. Incidence and prevalence of idiopathic inflammatory myopathies in Korea: a nationwide population-based study. J Korean Med Sci. 2019;34(8):e55.

Rapporteur assessment comment:

The MAH explored the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand trends in recent incidence rates (IRs) of idiopathic inflammatory myopathies (IIM) in the general population. No statistically significant trend in IIM IRs was observed from recent pre-COVID (2019) through COVID-era (2020-2021) timeframes. According to the MAH, the observed to expected analyses in the previous signal evaluation of myositis (EPITT no. 19883) that were based on pre COVID-era background rates were appropriate, and in the low-range of published estimates, hence resulting in a

conservative observed to expected estimate, which is supported by PRAC Rap. Note that for this analysis US data were used for a 3-year period and may not be representative of trends in myositis incidence over a longer period of time post 2020 and/or in different geographic regions. This is acknowledged and accepted.

Myositis has been included as an AESI/outcome in the following MAH sponsored non-interventional PASS's (included as cat. 3 additional PV studies in the Comirnaty RMP):

C4591009: a study using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System (final CSR 31 March 2026);

C4591021 (former ACCESS/VAC4EU): a Comirnaty safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol (final CSR 30 Sep 2024);

C4591051: a Comirnaty Original /Omicron BA.4-5 safety surveillance study to be conducted using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System (final CSR 31 Jan 2028);

C4591052: a Comirnaty Original/Omicron BA.1 and Comirnaty Original /Omicron BA.4-5 safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol (final CSR 31 Oct 2025).

This is accepted, provided the broader term IIM will also be included in the ongoing PASSs (PRAC Recommendation EPITT no: 19883)

Issue resolved with commitment.

7. Comments from Member States

MS1

We endorse the PRAC Rapp´s AR and have no further comments.

MS2

We fully endorse the PRAC Rapp assessment, and have the following additional comments:

Menstrual irregularities

During the PSUR interval under review, the MAH closed the signal "menstrual irregularities". This signal was presented and evaluated in the previous PSUSA, where the MAH had presented 731 serious medically confirmed cases (as of 31 March 2023) and 6 relevant publications (as of 11 July 2023). In that procedure, the MAH's conclusion that the data did not support a causal association was endorsed. It appears that no significant new data regarding this signal have been presented in the current procedure, and it seems that the only reason that the signal has been presented again is that the signal was closed after the DLP of the previous PSUR. For this reason, we agree that no further action is warranted at present.

Hemophagocytic lymphohistiocytosis (HLH)

The safety topic "hemophagocytic lymphohistiocytosis" was presented and evaluated in the current procedure due to a request made in the previous PSUSA procedure. Based on the MAH's presentation of data, the Rapporteur of Comirnaty concludes that no new safety information could be identified. However, as the evaluated data only includes new data (i.e. interval data) and as it appears that not all previous HLH case reports have been evaluated in previous PSURs, the Rapporteur has requested a cumulative review of hemophagocytic lymphohistiocytosis (HLH) for presentation in the next PSUR. Based on the Rapporteur's summary and assessment of the most recent data, we agree that no significant new safety information regarding HLH has been identified. However, we fully endorse the Rapporteur's suggested approach of requesting a full cumulative review for presentation in the next PSUR.

Of note, the MAH has presented O/E-ratios for this topic and the overall O/E-ratios are below 1. However, for the age groups "12-17 years" and "18-24 years" (21-day risk window) and "12-17 years" (42-day risk window), the O/E-ratios are above one. It is acknowledged that the confidence intervals are wide, however, for the age group "12-17 years" the lower bound is almost 1 (i.e. implying borderline statistical significance). However, the estimated number of expected cases may be too low for the youngest age groups due to the used incidence rate. The MAH has used an incidence rate of 0.049-0.353 per 100,000 persons per year. However, the Rapporteur of Comirnaty points out that UpToDate lists a paediatric incidence of 1 in 100,000 children. Provided that the incidence listed on UpToDate is more correct, this could (at least in part) explain the O/E-ratios over 1. However, in order to not miss a potential signal of HLH in children and adolescents, we propose that as part of the MAH's cumulative review, all cases concerning individuals aged 18 years and younger should be presented in detail and commented upon including causality assessment by the MAH.

Idiopathic Inflammatory Myopathies/Myositis

The MAH has presented the most recent data related to "Idiopathic Inflammatory Myopathies/Myositis". The Rapporteur of Comirnaty concludes that a causal association with Comirnaty can neither be confirmed nor refuted based on the data presented by the MAH. It is noted in the AR that some cases have plausible TTOs (i.e. <24 hours to 30 days) and a few cases also exhibit positive re-challenge, however, the data provided by the MAH are not considered appropriate to properly establish a causal association due to the lack of causality assessment per individual case. Therefore, the MAH has been requested to provide a cumulative review of all evidence from 16 January 2023 up to DLP of PSUR#7. We agree that the lack of case details of individual cases and the lack of the MAH's causality assessment per individual case preclude proper assessment of causality and the request for a cumulative review for presentation in the next PSUR is supported. Of note, in the AR it is stated that as part of the myositis signal procedure (EPITT 19883), a cumulative review was conducted up to 15 January 2023. Therefore, the chosen start date in the request for the cumulative review is considered appropriate.

Rapporteur assessment comment: The endorsement and additional comments are appreciated. Comments on the cases concerning individuals aged 18 years and younger have been added to the Request for next PSUR.

MS3

MS3 fully endorses the PRAC Rapp assessment report and have further comments about the risk of small fibre neuropathy.

Small fibre neuropathy is a rare form of peripheral neuropathy disease, it damages small nerve fibres in the skin, causing symptoms like painful tingling or burning sensations notably in hands and feet. Given the rarity of the disease, the difficulty of making the diagnosis and the time required to make it, this potential signal has only recently been detected by the French pharmacovigilance system after Comirnaty vaccination.

A total of 32 cases of small fibre neuropathy were reported after a vaccination with Comirnaty. Of the 32 cases, 9 were medically confirmed by a neurologist and with positive skin biopsy, with no other ethiological causes retrieved (no diabetes, systemic disease, monoclonal gammopathy, folate or B9 deficiency, or dysimmune origin):

Moreover, cases were retrieved in the literature[1,2,3,4] especially in the publication of Mastropaolo et al.[3] with:

- progressive and extensive symptoms such as paraesthesia, numbness, dysesthesias with burning sensations, following vaccination in a 39-year-old man,
- a biopsy showing a significant reduction in the density of epidermal nerve fibres and a significant reduction in the density of sweat gland nerve fibres,
- a negative extensive aetiological test,
- evidence of anti-FGRF3 (anti-fibroblast growth factor) IgG at 17,000 (N < 3,000) and negative for the other autoantibodies in the neuropathy panel,
- treatment with immunoglobulins,
- a favourable clinical outcome,
- a post-treatment biopsy with Ig showing healing and normal epidermal nerve fibre density.

Furthermore, in Eudravigilance, a statistical disproportionality was retrieved with tozinameran as active substance and small fibre neuropathy as preferred termed (ROR (-) : 6.03).

Taking these elements into account and especially the latency of diagnosis (sometimes more than a year), MS3 is of the opinion that further investigations should be considered. Therefore, MS3 suggests that the MAH performs an analysis of these small fibre neuropathy adverse events (including data from literature and spontaneous reporting) for the next PSUR, and discuss the need to update the SmPC.

[1]Finsterer J et al. Small fiber neuropathy with long-term, multifocal paresthesias after a SARS-CoV-2 vaccination. Clinics (Sao Paulo). 2023 Mar 13;78:100186.

[2]Waheed W, Carey ME, Tandan SR, Tandan R. Post COVID-19 vaccine small fiber neuropathy. Muscle Nerve. 2021 Jul;64(1):E1-E2.

[3]Mastropaolo M et al. Small Fiber Neuropathy Triggered by COVID-19 Vaccination: Association with FGFR3 Autoantibodies and Improvement during Intravenous Immunoglobulin Treatment. Case Rep Neurol. 2023 Jan 27;15(1):6-10.

[4]Schelke MW et al. Post-COVID-19 vaccine small-fiber neuropathy and tinnitus treated with plasma exchange. Muscle Nerve. 2022 Oct;66(4):E21-E23.

*Rapporteur assessment comment:*The endorsement and further comments on small fibre neuropathy (SFN) are appreciated.

SFN can be primary (hereditary) or secondary (acquired). Infectious, metabolic, toxic, immunological paraneoplastic, and neoplastic disorders have been described as causes of acquired SFN (Finsterer et al). Among the immunological causes, several vaccines have been identified as the cause of SFN, however, the possible association between vaccination and small fiber polyneuropathy is not well defined (Kafaie J et al. 2016). As indicated by MS3, some published case reports of patients with COVID-19 vaccination-related SFN have been reported in literature. In addition, SFN has been disproportionally reported in Eudravigilance. Therefore, MS3 suggestion is supported, and the MAH is requested to provide a cumulative review of all evidence concerning SFN following vaccination with Comirnaty for the next PSUR.

A WHO-UMC causality assessment per case (irrespective of the source (e.g. spontaneous report, case from literature, case from study, etc) should also be included. The MAH should also discuss potential mechanisms and the need to update the product information if appropriate (**Issue to be addressed in the next PSUR**).

PERIODIC SAFETY UPDATE REPORT #6
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (BNT162b2)[1]

BNT162b2 Original – BNT162b2 Bivalent (Original and Omicron BA.1) – BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) – BNT162b2 Monovalent Omicron XBB.1.5

ATC CODE: J07BN01
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 2023 through 18 DECEMBER 2023
DATE OF THIS REPORT: 15 FEBRUARY 2024

SIGNATURE: [redacted] Date: 15 FEBRUARY 2024

NAME AND CONTACT DETAILS OF THE QPPV:	
EU Qualified Person Barbara De Bernardi, MD Worldwide Medical & Safety Pfizer srl Via Anna Maria Mozzoni 12 20152 Milan (Italy)	telephone: [redacted] fax number: [redacted] email: [redacted]
EU Qualified Person Deputy [redacted] Worldwide Medical & Safety Pfizer srl Via Anna Maria Mozzoni 12 20152 Milan (Italy)	telephone: [redacted] fax number: [redacted] email: roberta.[redacted]

Marketing Authorisation Holder:
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

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 6th Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (Coronavirus disease 2019 messenger ribonucleic acid) COMIRNATY®, also referred to as BNT162b2 Original (tozinameran),[3] BNT162b2 (Original and Omicron BA.1) (tozinameran/riltozinameran), BNT162b2 (Original and Omicron BA.4/BA.5) (tozinameran/famtozinameran)[4] or BNT162b2 (Omicron XBB.1.5)[5] covering the reporting interval 19 June 2023 through 18 December 2023.

COMIRNATY® approved presentations include:

Original (BNT162b2)

- phosphate buffered saline (PBS)/Sucrose 30 micrograms/dose – for age 12 years and older [Purple cap, 6 doses per vial];
- tromethamine (Tris)/Sucrose 30 micrograms/dose – for age 12 years and older [Dark grey cap, 6 doses per vial];
- tromethamine (Tris)/Sucrose 30 micrograms/dose – for age 12 years and older [Light grey cap, 1 dose per vial];
- Tris/Sucrose 10 micrograms/dose – for age 5 years to <12 years [Orange cap, 10 doses per vial];
- Tris/Sucrose 3 micrograms/dose – for age 6 months to <5 years [Maroon cap, 10 doses per vial].

Bivalent (Original + Omicron)

Original +

- Tris/Sucrose BA.1 (15/15 micrograms/ dose) – for age 12 years and older [Dark grey cap, 6 doses per vial];
- Tris/Sucrose (BA.4/BA.5 15/15 micrograms/ dose) – for age 12 years and older [Dark grey cap, 6 dose per vial];
- Tris/Sucrose (BA.4/BA.5 15/15 micrograms/ dose) – for age 12 years and older [Light grey cap, 1 dose per vial];[6]

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

[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.

[5] Also referred to as "2023-2024 formula".

[6] First approved in European Union (EU) on 22 June 2023.

- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/ dose) – for age 5 years to <12 years [Orange cap, 10 doses per vial];
- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/dose) – for age 5 years to <12 years [Dark blue cap, 6 doses per vial];[6]
- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/dose) – for age 5 years to <12 years [Light blue cap, 1 dose per vial];[6]
- Tris/Sucrose BA.4/BA.5 (1.5/1.5 micrograms/dose) – for age 6 months to <5 years [Maroon cap, 10 doses per vial].[6]

Omicron XBB.1.5 (BNT162b2)

- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Dark grey cap, 6 doses per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Light grey cap, 1 dose per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Single dose prefilled syringe]; Tris/Sucrose 10 mcg/dose (with dilution) – for age 5 years to <12 years [Orange cap, 10 doses per vial];
- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Dark blue cap, 6 doses per vial];
- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Light blue cap, 1 dose per vial];
- Tris/Sucrose 3 mcg/dose (with dilution) – for age 6 months to <5 years [Maroon cap, 10 doses per vial].

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 deoxyribonucleic acid (DNA) template, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Original).

The nucleoside-modified mRNA in Original BNT162b2 and variant-adapted BNT162b2 is formulated in lipid nanoparticles (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.

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

Age Range of Recipient and Strength	Vial Cap and Vial Label Color	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation
6 months through 4 years **3 mcg per dose**	Maroon	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (0.4 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
5 through 11 years **10 mcg per dose**	Orange	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (1.3 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Dark blue	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Omicron XBB.1.5
	Light blue	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Omicron XBB.1.5
12 years and older **30 mcg per dose**	Dark grey	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Original (Wildtype) • Bivalent (Original + Omicron BA.1) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Purple[a]	Concentrate for dispersion for injection. Must dilute. IM	Multidose vial (0.45 mL) contains six 0.3 mL doses after dilution	• Original (Wildtype)
	N/A	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5

a. All presentations are the Tris/Sucrose formulation except the purple cap vials, which are PBS/Sucrose formulation

Cumulatively, it is estimated that 69,995[7] participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with:

- 63,842 participants exposed to BNT162b2;
- 9581 participants exposed to clinical candidates developed as variant and variant-adapted vaccines based on BNT162b2 (BNT162b2 [B.1.351], BNT162b2 [B.1.617.2], BNT162b2 [B.1.1.7 + B.1.617.2], BNT162b2 [B.1.1.7], BNT162b2 [B.1.1.529], BNT162b2 Omi, BNT162b2 original / BNT162b2 Omi, BNT162b2 original / BNT162b2 Omi BA.1, BNT162b2 original / BNT162b2 Omi BA.4/BA.5, BNT162b2 Omi XBB.1.5, BNT162b5 original / BNT162b2 Omi BA.2, BNT162b5 original / BNT162b2 Omi BA.4/BA.5, BNT162b6 original / BNT162b2 Omi BA.4/BA.5, BNT162b7 Omi BA.4/BA.5, and BNT162b7 original / BNT162b2 Omi BA.4/BA.5);
- 633 participants exposed to other early development candidates (including BNT162a1, BNT162b1, BNT162b3 and BNT162c2), and
- 6359 participants exposed to other study treatments (including placebo and seasonal inactivated influenza vaccine [SIIV]/placebo).

BNT162b2 is also being utilised in 3 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026,[8]
- C526: 858 participants received bivalent BNT162b2 (original / Omi BA.4/BA.5)/quadrivalent influenza vaccine (QIV), BNT162b2 (original / Omi BA.4/BA.5)/ quadrivalent influenza modRNA vaccine (qIRV), BNT162b2 (original / Omi BA.4/BA.5)/QIV/ bivalent influenza modRNA vaccine (bIRV), BNT162b2 (original / Omi BA.4/BA.5)/tIRV as a study vaccine in the clinical study C5261001[9] and

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

[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. This clinical study is completed before the current reporting period and therefore it is not included in Section 7.4.

[9] A phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of combined modified RNA vaccine candidates against COVID-19 and influenza in healthy individuals.

- C548: 1073 participants[10] may have received BNT162b2 original or bivalent BNT162b2 original/Omi BA.4/BA.5 as a study vaccine in the clinical study C5481001.[11]

BNT162b2 is also being utilised in 1 other BioNTech clinical development program:

- BNT162b4: 358 participants received bivalent BNT162b2 original/Omi BA.4/BA.5/BNT162b4, BNT162b2 original/Omi BA.4/BA.5 alone or monovalent Omi XBB.1.5/BNT162b4 as a study vaccines in the clinical study BNT162-21.[12]

From the receipt of the first temporary authorisation for emergency supply on 01 December 2020[13] through 18 December 2023, approximately 4,853,255,325 doses of BNT162b2 (original, bivalent and monovalent vaccines) were shipped from BioNTech and Pfizer worldwide. Considering the current status of the vaccination schedule and the availability of only partial data published on the European Centre for Disease Prevention and Control (ECDC) websites for doses of BNT162b2 vaccines (original, bivalent and monovalent) administered in the EU- European economic area (EEA) countries up to 05 October 2023, it is no longer applicable to estimate the number of doses administered from those shipped. Out of the cumulative number of shipped doses, 3,945,106,305 were original vaccine (including PBS and Tris/Sucrose), 715,562,080 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations; cumulatively, there were 4,377,673,725 doses for adult[14] presentations and 475,581,600 doses for paediatric[15] presentations. Overall, 2,520,425,825 doses of BNT162b2 (original, bivalent and monovalent) were shipped to rest of world (ROW).[16]

During the current reporting interval (19 June 2023 through 18 December 2023), approximately 224,550,280 doses of BNT162b2 original, bivalent and monovalent vaccines were shipped worldwide. Out of the doses shipped during the reporting period, 4,010,600 were original vaccine (Tris/Sucrose), 27,952,740 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations; there were 212,378,080 doses for adult[14]

[10] This number of participants considers all study treatments administered in the study. The study treatments are reported as Blinded Therapy in Appendix 2.3.1.

[11] A study to evaluate the safety, tolerability, and immunogenicity of combined vaccine candidate(s) against infectious respiratory illnesses, including COVID-19 and RSV, in healthy individuals.

[12] 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.

[13] BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the United Kingdom (UK) on this date.

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

[15] Approved for 6 months through <12 years.

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

presentations and 12,172,200 doses for paediatric[15] presentations. Overall, 62,659,040 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW.[16]

Additionally, as per data provided by contractual party (CP) in Hong Kong, Macau, and Taiwan, 32,348,209 doses of original BNT162b2, bivalent Omi BA.4/BA.5 and monovalent Omi XBB.1.5 were administered cumulatively through the DLP, and 67862 doses were administered in the interval reporting period.

The marketing authorisation holders (MAHs) of BNT162b2 Original and Bivalent vaccines (BNT162b2 Original/Omicron BA.1 and BNT162b2 Original/Omicron BA.4/BA.5 and Monovalent Omicron XBB.1.5) in different countries/regions are the following: BioNTech, Pfizer, the local Ministry of Health (MoH), the local Government, the CP Fosun Pharma, and the CP Hemas.

Marketing Authorisation Holders of BNT162b2 Original, BNT162b2 Bivalent Vaccines and Omicron XBB.1.5

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)	BNT162b2 Omicron XBB.1.5
BioNTech	58	37	47	40
Pfizer	34[a]	8	27	9
Fosun Pharma	1	0	1	1
Local MoH	3	0	0	0
Local Government	3	1	1	0
Hemas (CP)	1	0	0	0
All	**100**	**46**	**76**	**50**

a. Compared to the previous reporting period, authorization replacements for the BNT162b2 Original vaccine to the new BNT162b2 Omicron XBB.1.5 vaccine were issued in four countries. The BNT162b2 Omicron XBB.1.5 vaccine was authorized in Thailand on 17 November 2023, in Brazil and in Dominican Republic after DLP respectively on 19 December 2023 and on 28 December 2023. In Jordan no active licenses were in place as of DLP for BNT162b2 Original vaccine, however an application for the BNT162b2 Omicron XBB.1.5 vaccine authorization was submitted.

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 24.0 dated 21 November 2023, in effect at the end of the reporting period. Three (3) previous CDS versions (version 21.0 dated 25 May 2023, version 22.0 dated 24 July 2023 and version 23.0 dated 19 October 2023) were also in effect during the reporting period. No safety-related changes were made to CDSs version 22.0 and 23.0.

Safety-related changes in the CDS version 24.0 included updates of the following sections: 4.5. Interaction with other medicinal products and other forms of interaction, 4.8. Undesirable effects, and Appendix A and Appendix B.

During the reporting period, the following signals were evaluated:

- Signals determined not to be risks: Mastitis/Breast swelling, Menstrual Irregularities, Retinal Vascular Occlusion, Sensorineural Hearing Loss.

- Ongoing signals: Pulmonary Embolism, and Post-menopausal haemorrhage.

During the reporting period, no action was taken with respect to any authorized BNT162b2 vaccine presentations for safety reasons.

Regulatory and health authority requests addressed in this PSUR were received from the European Medicines Agency (EMA)/Pharmacovigilance Risk Assessment Committee (PRAC), WHO, Health Canada, Medsafe [New Zealand Medicines and Medical Devices Safety Authority], Therapeutic Goods Administration, Australia [TGA] and SAHPRA (South Africa). The WHO requests were received in the EUL Procedure. The requests are summarised in the table below.

Regulatory authority procedure	Request(s)
EMA PSUR #5 Final AR EMEA/H/C/PSUSA/ 00010898/202306	The MAH should continue to closely monitor hemophagocytic lymphohistiocytosis (HLH) and report all new (literature) cases of HLH including a WHO-UMC causality assessment per case and age-stratified observed/expected analyses using 21-day and 42-day risk intervals.
	For future PSURs, in 'Adverse Events of Special Interest (AESIs)' of section 'Evaluation of Other Risks (not categorised as important)', the AESIs 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, in 'Evaluation of special situations' of section 'Evaluation of Other Risks (not categorised as important)', lack of therapeutic efficacy should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
Health Canada	*BioNTech Manufacturing GmbH* is requested to commit to the following: To continue to closely monitor idiopathic inflammatory myopathies/myositis, and idiopathic inflammatory myopathies flares through routine pharmacovigilance in the upcoming PSURs/PBERs including (but not restricted to): Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms, as appropriate.
SAHPRA (South Africa)	While the MAH's undertaking to monitor the risk of mastitis/breast swelling with the use of BNT162B2 using routine pharmacovigilance activities is noted, the Authority recommends that the MAH includes this safety issue in the subsequent BNT162B2 PBRER.
	Following the deliberations on this matter (risk of retinal vascular occlusion), the Authority recommend that the safety signal should not be dismissed without further investigation. The Authority, therefore, recommend that: - the applicant re-evaluates the signal, include an updated review in their next PSUR and submit the PSUR for evaluation.

Regulatory authority procedure	Request(s)
EMA PSUR #4 AR EMEA/H/C/PSUSA/ 00010898/202212	For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition; HIV infection, Tuberculosis 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 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.
	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.
	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.
	The MAH should continue to report on the administered 1st, 2nd, 3rd ,4th, etc. doses of Comirnaty as presented in future PSURs.
	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%.
EMA PSUR #3 AR EMEA/H/C/PSUSA/ 00010898/202206	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.
	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.
	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.
	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.
WHO	Pregnancy outcome in clinical trials.
Health Canada/Marketed Health Products Directorate (MHPD)	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.
Medsafe (New Zealand)	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.

Regulatory authority procedure	Request(s)
Medsafe (New Zealand) AR of 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 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 maroon 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.
EMA/PRAC/202255/2022 13th Summary Safety Report	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.

The European Union Risk Management Plan (EU-RMP) in effect at the beginning of the reporting period is version 9.0 adopted on 10 November 2022 (Procedure number EMEA/H/C/005735/II/0147). The safety concerns in the EU-RMP for BNT162b2 are:

- Important identified risk: Myocarditis and Pericarditis.
- Important potential risk: None.[17]
- 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.

No new safety concerns for inclusion in the EU-RMP were identified during the reporting period.

After the DLP,

- The ongoing signals (Pulmonary embolism and Postmenopausal haemorrhage) were closed as no risk on 10 January 2024 and on 22 December 2023, respectively.
- The EU-RMP version 11.2 was submitted, as detailed in the table below.

[17] The important potential risk of VAED/VAERD was removed from the list of safety concerns in EU-RMP version 10.0 (procedures EMEA/H/C/005735/X/0176, EMEA/H/C/005735/II/0177, and EMEA/H/C/005735/X/0180). Additionally, the Rapporteur agreed to remove the important potential risk of VAED/VAERD from the list of safety concerns for the PSUR #5 reporting period [as per PSUR #4 PRAC AR (EMEA/H/C/PSUSA/00010898/202212)]. This risk is not included in the safety concerns at the beginning of the reporting period according to the explanatory note on PSURs, in the EU regional appendix in GVP Module section VII.C.5.3.

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
EMEA/H/C/005735/II/0206/G RMP update regarding final CSR of study C4591012 and protocol amendments of study C4591052 and C4591021	22 December 2023	RMP v11.2: 22 December 2023 (Gateway)	On-going

- CDS version 25.0 was made effective on 26 January 2024. This version includes further information from paediatric study C4591007 that reflects a larger safety population from the 6-month post-dose-3 interim study report. Study C4591007, which was conducted with BNT162b2 original vaccine, included individuals 6 months through <12 years of age receiving the primary series or first booster dose. There are no new safety issues identified from the larger safety population of this study. Also, a footnote in Table 48 (Clinical Trial section of CDS) related to the data from the flu vaccine co-administration study C4591030, which was added to the CDS in the November 2023 update, was revised to more clearly define the noninferiority criteria.

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, bivalent vaccines (Omi BA.1 and Omi BA.4/BA.5) and monovalent Omi XBB.1.5, the overall benefit-risk profile of the BNT162b2 vaccines remains favourable. No further changes to the BNT162b2 RSI or additional risk minimisation measures are warranted in addition to those above mentioned.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Term
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	assessment report
ARDS	acute respiratory distress syndrome
ATC	anatomical therapeutic chemical
bIRV	bivalent influenza modRNA vaccine
CDC	Centres for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMI	Charlson comorbidity index
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	coronavirus disease 2019
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
CP	contractual party
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial
D	dose
DART	developmental and reproductive toxicity
DLP	data lock point
DMA	Danish Medicines Agency
DNA	deoxyribonucleic acid
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECMO	extracorporeal membrane oxygenation
EEA	European economic area
EMA	European Medicines Agency
EPITT	European pharmacovigilance issues tracking tool
EU	European Union
EUA	emergency use authorisation
EUL	emergency use listing
EURD	European Union reference date
FDA	Food and Drug Administration
GFP	green fluorescent protein
GMC	geometric mean concentration

Abbreviation	Term
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
GVP	Good pharmacovigilance practices
HA	Health Authority
HAI	Hemagglutination-inhibition
HCP	healthcare professional
HBV	hepatitis B virus
HCV	hepatitis C virus
HERO	Healthcare Worker Exposure Response and Outcomes
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HLGT	high level group term
HLT	high level term
IBD	International Birth Date
ICH	International Council for Harmonisation; intracerebral haemorrhage
ICU	Intensive care unit
ID	Identifier
Ig	Immunoglobulin
IM	intramuscularly
IIM	idiopathic inflammatory myopathies
iPSC-CM	induced pluripotent stem cell-derived cardiomyocytes
JNJ	Johnson & Johnson
JST	Japan Standard Time
LMIC	low- and middle-income country
LNP	lipid nanoparticles
MAA	marketing authorisation application
MAH	marketing authorisation holder
MC	medically confirmed
ME	medication error
MEA	additional pharmacovigilance activity in the risk-management plan
Medsafe	Medicines and Medical Devices Safety Authority
MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
MIS	multisystem inflammatory syndrome
MIS-C	multisystem inflammatory syndrome in children
MoH	ministry of health
mRNA	messenger ribonucleic acid
NA or N/A	not applicable
NAAT	nucleic acid amplification test
NEC	not elsewhere classified
NIS	non interventional study

Abbreviation	Term
NMC	non-medically confirmed
NOS	not otherwise specified
NT50	50% neutralising titer
O/E	observed versus expected
Omi	omicron
OR	odds ratio
PAM	post-authorisation measure
PASS	post-authorisation safety study
PBRER	periodic benefit-risk evaluation report
PBS	phosphate buffered saline
PC	product complaint
PI	product information
PM	post-marketing
PQC	Product quality complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PVC	Pharmacovigilance Advisory Committee
preF	prefusion F
PSUR	periodic safety update report
PSUSA	periodic safety update report single assessment
PT	Preferred Term
PVP	pharmacovigilance plan
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QPPV	qualified person for pharmacovigilance
RA	Regulatory Authority
RMP	risk management plan
ROW	rest of world
RNA	ribonucleic acid
RSI	reference safety information
RSV	respiratory syncytial virus
RT-PCR	reverse transcription-polymerase chain reaction
RVO	retinal vascular occlusion
S	spike
SAE	serious adverse event
SAG	surface antigen
SAHPRA	South African Health Products Regulatory Authority
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBSR	summary bimonthly safety report
SCRI	Self-Controlled Risk Interval
SIIV	seasonal inactivated influenza vaccine
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SMSR	summary monthly safety report
SOC	system organ class

Abbreviation	Term
SSR	summary safety report
TGA	Therapeutic Goods Administration
TGF	Transforming growth factor
tIRV	trivalent influenza modRNA vaccine
Tris	Tromethamine
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US	United States
USG	United States Government
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VE	vaccine efficacy
WHO	World Health Organization
WT	wild type

1. INTRODUCTION

This is the 6th PSUR for the COVID-19 mRNA vaccine, COMIRNATY®, also referred to as BNT162b2,[3] covering the reporting interval 19 June 2023 through 18 December 2023.

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]),[18] and Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance v. 3.1 (EMA/PRAC/73244/2022 [01 September 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.

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

Age Range of Recipient and Strength	Vial Cap and Vial Label Color	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation
6 months through 4 years 3 mcg per dose	Maroon	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.4 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
5 through 11 years 10 mcg per dose	Orange	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (1.3 mL) contains ten 0.2 mL doses per vial after dilution	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Dark blue	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Omicron XBB.1.5

[18] The corePSUR19 guidance, was discontinued on 30 March 2023.

Age Range of Recipient and Strength	Vial Cap and Vial Label Color	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation
5 through 11 years 10 mcg per dose *Cont'd*	Light blue	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Omicron XBB.1.5
12 years and older 30 mcg per dose	Dark grey	Dispersion for injection. Do not dilute. IM	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	• Original (Wildtype) • Bivalent (Original + Omicron BA.1) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent (Original + Omicron BA.4/BA.5) • Omicron XBB.1.5
	Purple[a]	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.45 mL) contains six 0.3 mL doses after dilution	• Original (Wildtype)
	N/A	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5

a. All presentations are the Tris/Sucrose formulation except the purple cap vials, which are PBS/Sucrose formulation

Pfizer is responsible for the preparation of the PSUR on behalf of contractual parties according to the Safety Data Exchange Agreement(s) in place. Data from respective contractual party(s) are included in the report when applicable.

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
4	19 June 2022 through 18 December 2022
5	19 December 2022 through 18 June 2023

2. WORLDWIDE MARKETING APPROVAL STATUS

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK[19] 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. Overall, BNT162b2 original received marketing authorisation approval in 104 countries/regions.

In 2022, to address the emergence of Omicron variants, bivalent formulations were developed. Bivalent BNT162b2 (original/Omicron BA.1) and bivalent BNT162b2 (original/Omicron BA.4/BA.5) received marketing authorisation approval in 46 and 73 countries/regions, respectively.

The approved indication is for active immunisation to prevent COVID-19 caused by SARS-CoV-2. Of note, on 18 April 2023, US FDA has simplified the vaccination schedule for most individuals, and granted EUA for BNT162b2 original/Omicron BA.4/BA.5 to be used for all doses administered to individuals 6 months of age and older. The approved indication in terms of age limits and the recommended posology may vary in countries where COVID-19 vaccine is available.

In 2023, to address the emergence of new Omicron variant (XBB.1.5), an adapted monovalent formulation was developed. The BNT162b2 (Omicron XBB.1.5) vaccine was first authorized in the EU countries on 31 August 2023 and as of DLP received marketing authorization approval in 50 countries/regions.

The MAHs and the number of countries where the different MAHs hold the authorisation are presented in Table 2.

Different dosages are available for use in different age groups.

<u>BNT162b2 original formulations:</u>

- PBS/Sucrose 30 mcg formulation for individuals 12 years and older [Purple cap, 6 doses per vial];
- Tris/Sucrose formulation:
  - at the dosage of 30 mcg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial];

[19] Conditional marketing authorisation approval was also granted in the UK on 01 January 2021 and converted to standard marketing authorisation on 9 November 2022.

- at the dosage of 30 mcg for individuals aged 12 years and older [Light grey cap, 1 dose per vial];
- at the dosage of 10 mcg for individuals aged 5 years to <12 years [Orange cap, 10 doses per vial];
- at the dosage of 3 mcg for individuals aged 6 months to <5 years [Maroon cap, 10 doses per vial].

BNT162b2 Bivalent (BNT162b2 original/Omicron BA.1) Tris/Sucrose formulation:

- original/Omicron BA.1 at the dosage of 15/15 µg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial].

BNT162b2 Bivalent (BNT162b2 Original/Omicron BA.4/BA.5) Tris/Sucrose formulation:

- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Dark grey cap, 6 doses per vial];
- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Light grey cap, 1 dose per vial];[6]
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Orange cap, 10 doses per vial];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Dark blue cap, 6 doses per vial];[6]
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Light blue cap, 1 dose per vial];[6]
- original/Omicron BA.4/BA.5 at the dosage of 1.5/1.5 µg for individuals aged 6 months to <5 years [Maroon cap, 10 doses per vial];[6]

BNT162b2 Omicron XBB.1.5 formulations:

- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Dark grey cap, 6 doses per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Light grey cap, 1 dose per vial];
- Tris/Sucrose 30 mcg/dose (no dilution) – for age 12 years and older [Single dose prefilled syringe];
- Tris/Sucrose 10 mcg/dose (with dilution) – for age 5 years to <12 years [Orange cap, 10 doses per vial];
- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Dark blue cap, 6 doses per vial];

- Tris/Sucrose 10 mcg/dose (no dilution) – for age 5 years to <12 years [Light blue cap, 1 dose per vial];
- Tris/Sucrose 3 mcg/dose (with dilution) – for age 6 months to <5 years [Maroon cap, 10 doses per vial];[6]

Table 2. Marketing Authorisation Holders of BNT162b2 Original, BNT162b2 Bivalent Vaccines and Omicron XBB.1.5

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)	BNT162b2 Omicron XBB.1.5
BioNTech	58	37	47	40
Pfizer	34[a]	8	27	9
Fosun Pharma	1	0	1	1
Local MoH	3	0	0	0
Local Government	3	1	1	0
Hemas (CP)	1	0	0	0
All	**100**	**46**	**76**	**50**

a. Compared to the previous reporting period, authorization replacements for the BNT162b2 Original vaccine to the new BNT162b2 Omicron XBB.1.5 vaccine were issued in four countries. The BNT162b2 Omicron XBB.1.5 vaccine was authorized in Thailand on 17 November 2023, in Brazil and in Dominican Republic after DLP respectively on 19 December 2023 and on 28 December 2023. In Jordan no active licenses were in place as of DLP for BNT162b2 Original vaccine, however an application for the BNT162b2 Omicron XBB.1.5 vaccine authorization was submitted.

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 any authorized BNT162b2 vaccines for safety reasons, either by a HA or by the MAH.

Of note, as a precautionary measure the Danish Medicines Agency (DMA) decided to quarantine lot HG2252 on 17 October 2023 due to possible bubble formation in the solution after updraft in syringes. After careful review, there were no safety issues and the quarantine was lifted on 20 October 2023 (see Section 15 *Product Lots and AE Reports*).

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID-19 mRNA vaccine CDS version 24.0 dated 21 November 2023, in effect at the end of the reporting period and included in Appendix 1.

Three (3) previous CDS versions (version 21.0 dated 25 May 2023, version 22.0 dated 24 July 2023 and version 23.0 dated 19 October 2023) in effect during the reporting period,

are included in Appendix 1.2, Appendix 1.3 and Appendix 1.4, respectively. No safety-related changes were made to CDS version 22.0 and 23.0.

Safety-related changes in the CDS version 24.0 (presented in Appendix 1.1) included updates of the following sections:

- Section 4.5. *Interaction with other medicinal products and other forms of interaction*, based on Study C4591030, updated to state that the adult presentation (30 mcg) may be administered concomitantly with seasonal influenza vaccine at different injection sites (see Section 5.1).

- Section 4.8. *Undesirable effects*,

  - Based on safety results from study C4591007, information added regarding number and follow-up time for participants 12 to 15 years of age who completed the original vaccine 2-dose course and received a booster dose of original vaccine approximately 11.2 months after receiving Dose 2; no new adverse reactions were identified from this data.

  - Based on safety results from study C4591030, information added regarding a higher frequency of reactogenicity events in participants receiving original vaccine co-administered with seasonal inactivated influenza vaccine (SIIV) compared to participants receiving original alone; the most common adverse reactions reported in both groups were injection site, fatigue and headache.

- Appendix A – minor numerical changes in frequencies for some ADRs in the age group >55 years.

- Appendix B to include ADR frequencies and frequency categories (Very Common, Common, Uncommon or Rare) for Study C4591030: individuals 18 to 64 years of age receiving BNT162b2 co-administered with SIIV or alone.

After the PSUR #6 DLP, CDS version 25.0 was made effective on 26 January 2024. This version includes further information on participants from the paediatric study C4591007 reflecting a larger safety population from the 6-month post dose-3 interim study report. Study C4591007, which was conducted with BNT162b2 original vaccine, included individuals 6 months through <12 years of age receiving the primary series or first booster dose. There were no new safety issues identified from the larger safety population of this study. A footnote in Table 48 (Clinical Trial section of CDS) related to the data from the influenza vaccine co administration study C4591030, which was added to the CDS in the November 2023 update, was revised to more clearly define the noninferiority criteria.

5. ESTIMATED EXPOSURE AND USE PATTERNS

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *The MAH should continue to report on the administered 1st, 2nd, 3rd, 4th, etc. doses of Comirnaty as presented in future PSURs.*

Response

Please refer to Section 5.2.1.2 *Health Authority Public Data – Cumulative Exposure* and to Section 5.2.2.2 *Health Authority Public Data – Interval Exposure*, where information about the total number of doses administered of all BNT162b2 vaccine presentations is provided cumulatively in Table 10 through Table 14 for the EU/EEA countries and in Table 15 through Table 18 for Japan; Table 23 through Table 27 display the incremental number of doses (reported as first, second, third, fourth, fifth, sixth and seventh, respectively) of BNT162b2 original and bivalent vaccine presentations administered in the EU/EEA countries.

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 69,995[7,20] participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

BNT162b2: 63,842 participants of which

- 35,272 had received BNT162b2;[21]
- 26,490 had received BNT162b2 post-unblinding and had received placebo before;[22]
- 959 had received BNT162b2/placebo;
- 2 had received BNT162b2/ SIIV;
- 1119 had received BNT162b2/ SIIV/placebo.

[20] From the total number of participants to the BNT162b2 clinical development, those accounted to the study BNT162-21 receiving bivalents BNT162b2 and included in the total of PSUR #5, are now evaluated under other BioNTech clinical development programs (BNT162b4 co-administered with bivalent Omi vaccines). The clinical exposure related to this study is provided in Appendix 2.3.1B.

[21] There were 2 subjects in the treatment arm original BNT162b2 were counted twice in 2 studies due to different subject ID number in the PSUR 5. These subjects are now identified with the same subject ID number and counted once.

[22] There was 1 subject in this treatment arm that was not included in the calculation done for PSUR 5. It has been assigned to this treatment arm by using the actual treatment arms for the sub-studies B and D of study C4591031.

Variant and variant-adapted vaccines based on BNT162b2: 9581 participants of which

- 753 had received BNT162b2 (B.1.351)[23];
- 372 had received BNT162b2 (B.1.617.2);
- 764 had received BNT162b2 (B.1.1.7 + B.1.617.2);[24]
- 20 had received BNT162b2 (B.1.1.7);
- 71 had received BNT162b2 (B.1.1.529);[25]
- 1814 had received BNT162b2 Omi;[26]
- 1814 had received BNT162b2 original / BNT162b2 Omi;[27]
- 102 had received BNT162b2 original / BNT162b2 Omi BA.1 (B.1.1.529);
- 2797 had received BNT162b2 original / BNT162b2 Omi BA.4/BA.5;[28]
- 725 had received BNT162b2 Omi XBB.1.5;
- 104 had received BNT162b5 original / BNT162b2 Omi BA.2;
- 62 had received BNT162b5 original / BNT162b2 Omi BA.4/BA.5;
- 60 had received BNT162b6 original / BNT162b2 Omi BA.4/BA.5;
- 63 had received BNT162b7 Omi BA.4/BA.5;
- 60 had received BNT162b7 original / BNT162b2 Omi BA.4/BA.5.

Early development candidates: 633 participants of which

- 30 had received BNT162a1;
- 411 had received BNT162b1;

---

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

[24] There were 4 subjects in the treatment arm BNT162b2 (B.1.1.7 + B.1.617) that were counted twice in 2 studies due to different subject ID number in the PSUR 5. These subjects are now identified with the same subject ID number.

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

[26] There was 1 subject in the sub-study D of study C4591031, that, in PSUR 5 was assigned to the treatment arm BNT162b2, based on the randomization files; this subject, using the actual treatment arms approach, is now assigned to BNT162b2 OMI.

[27] In the sub-study D of study C4591031, there was 1 subject that, in PSUR 5 was assigned, based on the randomization files to the treatment arm BNT162b2/ BNT162b2 OMI; this subject, using the actual treatment arms approach, is now assigned to BNT162b2 OMI.

[28] The difference of 69 subjects is largely due to study C4591044 that has a new treatment arm (BNT162b2 Bivalent OMI BA.4/BA.5) in this most recent PBRER with 62 additional subjects. The remaining additional 7 subjects are from study C4591048.

- 96 had received BNT162b3;
- 96 had received BNT162c2.

Other treatments: 6359 participants of which

- 6352 had received placebo;
- 7 had received SIIV/placebo.

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 3 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026;[29]
- C526: 858 participants received bivalent BNT162b2 (original / Omi BA.4/BA.5)/QIV, bivalent BNT162b2 (original / Omi BA.4/BA.5)/qIRV, bivalent BNT162b2 (original / Omi BA.4/BA.5)/QIV/bIRV, bivalent BNT162b2 (original / Omi BA.4/BA.5)/tIRV in the clinical study C5261001,[9] as a study vaccine.
- C548: 1073 participants[10] may have received BNT162b2 original or bivalent BNT162b2 (original / Omi BA.4/BA.5) as a study vaccine in the clinical study C5481001.[11]

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

Of note, BNT162b2 is also being utilised in 1 other BioNTech clinical development program:

- BNT162b4: 358 participants received bivalent BNT162b2 original/Omi BA.4/BA.5/BNT162b4, BNT162b2 original/Omi BA.4/BA.5 alone or monovalent Omi XBB.1.5/BNT162b4 as study vaccines in the clinical study BNT162-21.[12]

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

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

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1. Cumulative Exposure

5.2.1.1. MAH and Contractual Party Data – Cumulative Exposure

MAH Data

Previously publicly availab le regional information on vaccine doses administered is no longer consistently available for estimation of worldwide exposure. The information about the number of doses cumulatively administered published on the health authorities web sites was last updated with data up to 11 May 2023 (US[30]) and up to 05 October 2023 (EU/EEA countries[31]) and at the DLP (Japan[32]). Estimated administered doses were provided separately (Section 5.2.1.2 *Health Authority Public Data – Cumulative Exposure* and Section 5.2.2.2 *Health Authority Public Data – Interval Exposure*, as available on the public source data.

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)[33] through 18 December 2023 is showed in Table 3. Approximately a total of 4,853,255,325[34] doses of BNT162b2 (original, bivalent and monovalent) were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 December 2023. Out of the cumulative number of shipped doses, 3,945,106,305 were original vaccine (including PBS and Tris/Sucrose), 715,562,080 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations; cumulatively, there were 4,377,673,725 doses for adult[14] presentations and 475,581,600 doses for paediatric[14] presentations. Overall, 2,520,425,825 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW.[16]

Table 3. Cumulative Estimated Number of Shipped Doses by Vaccine Presentation, Region and Age Group

Age Group	Paediatrics				Adults			
Vaccine Presentation → Region/Country ↓	Original	Bivalents	Monovalent	Total	Original	Bivalents	Monovalent	Total
EU/EEA, US, Japan	165255500	21606900	7025480	193887880	1519291620	478411740	141238260	2138941620
ROW	277832200	2352400	1509120	281693720	1982726985	213191040	42814080	2238732105
Total	443087700	23959300	8534600	475581600	3502018605	691602780	184052340	4377673725

[30] CDC COVID Data Tracker: Vaccinations in the US. Accessed 21 January 2024.

[31] Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed 21 January 2024.

[32] COVID-19 Vaccines (kantei.go.jp). Accessed 29 December 2023.

[33] 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 Germany, Hong Kong, Macau and Taiwan were provided by BioNTech.

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

Table 4 through Table 7 show the worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group.

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

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years[b]	All
Europe	**30.8**	**4377600**	**69969600**	**1139427555**	**1213774755**
European Union (27)	22.4	3355200	57535200	820856760	881747160
European Economic Area Countries (3)	0.3	9600	452400	12007185	12469185
Switzerland	0.3	9600	609600	11397330	12016530
UK	3.3	1003200	10993200	117557895	129554295
Other Countries	3.2	0	57600	126781515	126839115
Commonwealth of Independent States	1.3	0	321600	50826870	51148470
North America	**14.9**	**15379300**	**70749800**	**501181515**	**587310615**
US	13	13669300	64199800	433518135	511387235
Canada	1.9	1710000	6550000	67663380	75923380
Central and South America	**15.6**	**24934800**	**87128300**	**502158915**	**614222015**
Asia	**29.9**	**15606600**	**135667000**	**1027296240**	**1178569840**
Japan	7.1	10017600	16016400	252909540	278943540
Other Countries	22.8	5589000	119650600	774386700	899626300
Oceania	**2.2**	**1195200**	**12246600**	**75019230**	**88461030**
Australia/New Zealand	2.2	1195200	12172800	73598760	86966760
Other Countries	0	0	73800	1420470	1494270
Africa	**6.7**	**0**	**5832900**	**256935150**	**262768050**
Total	**100**	**61493500**	**381594200**	**3502018605**	**3945106305**

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

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

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

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

Region/Country	≥12 years	All
Oceania	**4700160**	**4700160**
Australia/New Zealand	4700160	4700160
Other Countries	0	0
Africa	**0**	**0**
Total	**127889550**	**127889550**

Table 6. Cumulative Estimated Number of 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	**37.1**	**0**	**1814400**	**215953200**	**217767600**
European Union (27)	33.1	0	1795200	192998160	194793360
European Economic Area Countries (3)	0.4	0	19200	2554560	2573760
Switzerland	0	0	0	48960	48960
UK	2.4	0	0	13999680	13999680
Other Countries	0.1	0	0	852480	852480
Commonwealth of Independent States	0.9	0	0	5499360	5499360
North America	**23.9**	**5321400**	**13278700**	**121649880**	**140249980**
US	21.4	5321400	12455100	108015120	125791620
Canada	2.5	0	823600	13634760	14458360
Central and South America	**11.8**	**57600**	**300000**	**68695500**	**69053100**
Asia	**22.8**	**0**	**3187200**	**131006490**	**134193690**
Japan	17.1	0	2016000	98662590	100678590
Other Countries	5.7	0	1171200	32343900	33515100
Oceania	**3.8**	**0**	**0**	**22282560**	**22282560**
Australia/New Zealand	3.8	0	0	22245120	22245120
Other Countries	0	0	0	37440	37440
Africa	**0.7**	**0**	**0**	**4125600**	**4125600**
Total	**100**	**5379000**	**18580300**	**563713230**	**587672530**

Table 7. Cumulative Number of Estimated Shipped Doses of BNT162b2 Monovalent Omi XBB.1.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**48.3**	**1233600**	**1589760**	**90175680**	**92999040**
European Union (27)	39.6	782400	1330560	74223360	76336320
European Economic Area Countries (3)	1	4800	8640	1984320	1997760
Switzerland	0.2	0	0	460800	460800
UK	7.4	446400	250560	13504320	14201280
Other Countries	0	0	0	2880	2880
Commonwealth of Independent States	0	0	0	0	0
North America	**21.6**	**1996410**	**2279630**	**37362420**	**41638460**
US	15.8	1862010	1813070	26844660	30519740
Canada	5.8	134400	466560	10517760	11118720
Central and South America	**0.3**	**0**	**0**	**616320**	**616320**
Asia	**26.1**	**537600**	**897600**	**48764160**	**50199360**
Japan	20.5	441600	782400	38185920	39409920
Other Countries	5.6	96000	115200	10578240	10789440
Oceania	**3.7**	**0**	**0**	**7133760**	**7133760**
Australia/New Zealand	3.7	0	0	7133760	7133760
Other Countries	0	0	0	0	0
Africa	**0**	**0**	**0**	**0**	**0**
Total	**100**	**3767610**	**4766990**	**184052340**	**192586940**

CP Data

Cumulative CP (Fosun) data on the number of original BNT162b2 and bivalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 8.

Table 8. Cumulative Administered Doses of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Vaccine – Contractual Party Data

Region Country *-Vaccine Presentation*	Number of Administered Doses
Asia	**32348209**
Hong Kong[a]	12052065
- BNT162b2 (Original)	*11445300*
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	*606765*
Macau [b]	402444
- BNT162b2 (Original) + Bivalent (Original + Omi BA.4/BA.5)	399182
BNT162b2 (Omicron XBB.1.5) (30 mcg/dose)	3262
Taiwan[c]	19893700
- BNT162b2 (Original)	*19893700*

a. Cumulative period: through 15 December 2023.
b. Cumulative period: through 17 December 2023; for Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. Cumulative period: through 30 August 2023.

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, and Japan on the respective Health Authorities' websites.[35]

Table 9 below displays the cumulative EU/EEA published data up to 05 October 2023 with number of doses administered for each age group and by vaccine presentation.

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

- BNT162b2 original was approved in 12 years of age and older on 21 December 2020 (2020 week 52),
- BNT162b2 original was approved children 5 to less than 12 years of age on 26 November 2021 (2021 week 47),
- BNT162b2 original was approved in infants and children aged 6 months to 4 years on 20 October 2022 (2022 week 42),
- BNT162b2 bivalent Omi BA.1 was approved in 12 years of age and older on 01 September 2022 (2022 week 35),
- BNT162b2 bivalent Omi BA.4/BA.5 was approved in 12 years of age and older on 12 September 2022 (2022 week 37), and
- BNT162b2 bivalent Omi BA.4/BA.5 was approved in children 5 to less than 12 years of age on 10 November 2022 (2022 week 45).
- BNT162b2 bivalent Omi BA.4/BA.5 was approved in infants and children aged 6 months to 4 years on 08 August 2023 (2023 week 32).[36]
- BNT162b2 monovalent Omi XBB.1.5 was approved in infants and children aged 6 months to 4 years, in children 5 to less than 12 years of age, and in 12 years of age and older on 30 August 2023 (2023 week 35).

Table 9. EU/EEA – Cumulative Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[d]	BNT162b2 Monovalent XBB.1.5[e]	Total
< 18 years	26778400	17852	61265	29890	87	26887494
0 – 4 years	17829[f]	NA	0	0	0	17829
5 – 9 years	4107801[g]	NA	2568	0	0	4110369
10 – 14 years	9190473	10283	16490	9457	29	9226732
15 – 17 years	8135504	18382	15494	20192	26	8189598

[35] The CDC COVID Data Tracker: Vaccinations in the US is no longer updated since 11 May 2023. US data related to the cumulative number of doses of original and bivalents vaccines are not included.

[36] The interval number of doses shipped of BNT162b2 bivalent Omi BA.4/BA.5 for infants and children aged 6 months to 4 years and the interval number of doses shipped of BNT162b2 monovalent Omi XBB.1.5 (all age groups) overlap with the cumulative dose number of shipped doses. Only cumulative numbers are displayed.

Table 9. EU/EEA – Cumulative Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[d]	BNT162b2 Monovalent XBB.1.5[e]	Total
18 – 24 years	30472234	187764	180313	101585	156	30942052
25 – 49 years	138677357	1445486	1379378	878615	3321	142384165
50 – 59 years	67304692	1179266	1789739	975330	2693	71251721
60 – 69 years	55764965	1771316	2497498	2703268	5796	62742843
70 – 79 years	54406191	2196469	2206943	2744582	6664	61560849
≥ 80 years	40987910	1478355	1349603	2139381	4208	45959458
Age Unknown	281706	45	170	0	0	281921
All	498562015	8258623	15316915	9542761	22838	531703162

a. Cumulative period: 2020 week 52 through 2023 week 40 (05 October 2023).
b. Cumulative period: 2022 week 35 through 2023 week 40 (05 October 2023).
c. Cumulative period: 2022 week 37 through 2023 week 40 (05 October 2023).
d. Not specified if BA.1 or BA.4/BA.5. Cumulative period: from 2022 week 35 through 2023 week 40 (05 October 2023).
e. Cumulative period: 2023 week 35 through 2023 week 40 (05 October 2023).
f. BNT162b2 Original in infants and children aged 6 months to 4 years was approved in EU/EEA on 20 October 2022; correspondent data for BNT162b2 original evaluated from 2022 week 42 through 2023 week 40 (05 October 2023).
g. Line extension 5-11 years old Tris/Sucrose Paediatrics approved on 03 December 2021 (week 48); cumulative period: from 2021 week 48 through 2023 week 40 (05 October 2023).

Cells highlighted in grey reports values lower than those reported in the previous PSUR reporting period.
The European Centre for Disease Prevention and Control alerts that data displayed in the COVID-19 Vaccine Tracker website are subject to retrospective corrections and that corrected datasets are released every four weeks as soon as the processing of updated national data has been completed at ECDC level.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 10 through Table 14 provide the cumulative total number of administered doses for each vaccine presentations in EU/EEA, by age group and dose number. Individual country data are provided in Appendix 5.1.

Table 10. EU/EEA – Cumulative Number of Administered Doses of BNT162b2 Original by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	12654581	11666935	2447248	8458	147	7	2	1022
18 – 24 years	12352627	11487751	6489379	137281	1175	52	4	3965
25 – 49 years	54812888	52342452	30180654	1286824	16403	1025	172	36939
50 – 59 years	25215059	24606147	16225201	1204295	24133	2344	310	27203
60 – 69 years	17461274	17315669	17465115	3424549	48247	16719	1621	31771
70 – 79 years	17253828	17103698	15745433	4171891	54021	21206	26930	29184
≥80 years	13131029	12912237	11021843	3799197	63813	12189	17642	29960
Age Unknown	103417	82603	62396	32704	107	0	0	479
All	178841476	173665567	125158937	20194022	312854	53535	46679	288945

Cumulative period: 2020 week 52 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 11. EU/EEA – Cumulative Number of Administered Doses of BNT162b2 Bivalent Omi BA.1 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	283	453	10660	6210	246	0	0	0
18 – 24 years	362	484	37035	145740	4100	4	0	39
25 – 49 years	1747	1885	130894	1267615	43116	48	1	180
50 – 59 years	530	570	43262	1080473	54289	72	0	70
60 – 69 years	601	458	49182	1486253	234240	423	3	156
70 – 79 years	584	463	37849	1784089	372312	794	8	370
≥80 years	588	566	26819	657636	788246	966	2	3532
Age Unknown	2	3	5	27	4	0	0	4
All	4408	4423	325023	6421805	1496303	2307	14	4340

Cumulative period: 2022 week 35 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 12. EU/EEA – Cumulative Number of Administered Doses of BNT162b2 Bivalent Omi BA.4/BA.5 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	768	1166	29390	29622	307	12	0	0
18 – 24 years	1276	1991	40302	133544	3035	47	0	118
25 – 49 years	4648	5484	157530	1172628	37476	878	8	726
50 – 59 years	1180	1475	79577	1652355	53509	1173	13	457
60 – 69 years	1278	1135	89974	2201357	197516	5221	76	941
70 – 79 years	1044	983	61337	1740411	344423	57704	486	555
≥80 years	1083	1221	32677	824244	453305	36074	316	683
Age Unknown	4	3	15	123	18	0	0	7
All	48158	61386	704475	11153338	3244088	101097	899	3474

Cumulative period: 2022 week 37 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 13. EU/EEA – Cumulative Number of Administered Doses of BNT162b2 Bivalent Omi by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5
< 18 years	18	28	27600	2087	157
18 – 24 years	18	40	46828	53871	828
25 – 49 years	93	178	170374	695476	12494
50 – 59 years	14	32	71388	887519	16377
60 – 69 years	12	25	67586	2612104	23541
70 – 79 years	11	28	37899	2692259	14385
≥80 years	23	31	36922	2095928	6477
Age Unknown	0	0	0	0	0
All	171	334	430997	9037157	74102

Cumulative period: 2022 week 35 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 14. EU/EEA – Cumulative Number of Administered Doses of BNT162b2 Monovalent Omi XBB.1.5 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	10	4	20	30	23	0	0	0
18 – 24 years	5	1	12	50	88	0	0	0
25 – 49 years	255	6	82	876	2102	0	0	0
50 – 59 years	179	2	45	590	1876	0	0	1
60 – 69 years	184	4	71	952	4585	0	0	0
70 – 79 years	144	3	52	884	5581	0	0	0
≥80 years	179	8	75	692	3254	0	0	0
All	946	24	337	4044	17486	0	0	1

Cumulative period: 2023 week 35 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 15 and Table 16 show the cumulative number of all vaccine presentations administered as dose 1 and as dose 2 in Japan, respectively.

Table 15. Japan - Cumulative Number of Administered Dose 1 by Populations and Vaccine Presentation

Population(s)	All Vaccine Presentations	BNT162b2 Original and Bivalent Omi	Bivalent Omi BA.1	Bivalent Omi BA.4/BA.5	Monovalent Omi XBB.1.5
General population[a]	81831833		261	1747	20203
Elderly	32164636		112	698	4747
Child (5 to < 12 years)	1768834			331	2811
Infant (6 months – 4 years)	186581				7253
Medical workers[b]	6378205	6378205			

Table 15. Japan - Cumulative Number of Administered Dose 1 by Populations and Vaccine Presentation

Population(s)	All Vaccine Presentations	BNT162b2 Original and Bivalent Omi	Bivalent Omi BA.1	Bivalent Omi BA.4/BA.5	Monovalent Omi XBB.1.5

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers ended on 30 July 2021.
Cells highlighted in grey reports values lower than those reported in the previous PSUR reporting period. Administration data corrected between PSUR #5 and PSUR #6.
Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 29 December 2023, 9:15 [JST].

Table 16. Japan - Cumulative Number of Administered Dose 2 by Populations and Vaccine Presentation

Population(s)	All Vaccine Presentations	BNT162b2 Original and Bivalent Omi	Bivalent Omi BA.1	Bivalent Omi BA.4/BA.5	Monovalent Omi XBB.1.5
General population[a]	81416301		163	1076	16113
Elderly	32091097		71	334	3492
Child (5 to < 12 years)	1714512			250	2267
Infant (6 months – 4 years)	172998				5545
Medical workers[b]	5709228	5709228			

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers ended on 30 July 2021.
Cells highlighted in grey reports values lower than those reported in the previous PSUR reporting period. Administration data corrected between PSUR #5 and PSUR #6.
Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 29 December 2023, 9:15 [JST].

Table 17 and Table 18 provide the cumulative total number of administered doses for all vaccine presentations and for monovalent Omi XBB.1.5 by age group and dose number in Japan.

Table 17. Japan - Cumulative Number of Administered Doses (All Vaccine Presentations)

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7
General population[a]	81831833	81416301	52836878	43385948	35263200	18596811	14246532
Elderly	32164636	32091097	20742629	20559085	24982264	15447959	12974812
Child (5 to < 12 years)	1768834	1714512	731304	220421	63547	497	NA
Infant (6 months – 4 years)	186581	172998	136119	30343	NA	NA	NA
Medical workers[b]	6378205	5709228	NA	NA	NA	NA	NA
All[c]	88210038	87125529	52836878	43385948	35263200	18596811	14246532

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers ended on 30 July 2021.
c. General population and Medical workers.
Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 29 December 2023, 9:15 [JST].

Table 18. Japan - Cumulative Number of Monovalent Omi XBB.1.5 Administered Doses

Dose Number → / Age Group ↓	D1	D2	D3	D4	D5	D6	D7
General population[a]	20203	16113	51823	371323	4061643	3539804	14246532
Elderly	4747	3492	11099	61888	421450	2111230	12974812
Child (5 to < 12 years)	2811	2267	9648	38515	62321	497	NA
Infant (6 months – 4 years)	7253	5545	NA	30343	NA	NA	NA

a. Including elderly, children and infants.
Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 29 December 2023, 9:15 [JST].

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 Contractual Party Data – Interval Exposure

MAH Data

Approximately a total of 224,550,280 doses of BNT162b2 (original, bivalent and monovalent) were shipped worldwide during the current reporting interval from 19 June 2023 through 18 December 2023. Out of the shipped doses during the reporting period, 4,010,600 were original vaccine (Tris/Sucrose), 27,952,740 were bivalent vaccines and 192,586,940 were monovalent XBB.1.5 presentations; there were 212,378,080 doses for adult[14] presentations and 12,172,200 doses for paediatric[15] presentations. Overall, 62,659,040 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW.[16]

Table 19. Interval Estimated Number of Shipped Doses by Vaccine Presentation, Region and Age Group

Age Group	Paediatrics				Adults			
Vaccine Presentation → / Region/Country ↓	Original	Bivalents	Monovalent	Total	Original	Bivalents	Monovalent	Total
EU/EEA, US, Japan	0	1254800	7025480	8280280	200	12372500	141238260	153610960
ROW	790200	1592600	1509120	3891920	3220200	12732840	42814080	58767120
Total	790200	2847400	8534600	12172200	3220400	25105340	184052340	212378080

Table 20 and Table 21 show the worldwide estimated interval number of shipped doses by vaccine presentation (original and bivalent Omi BA.4/BA.5)[37] region and countries and by age group.

[37] No doses of bivalent Omi BA.1 were shipped in the reporting period and the number of doses shipped of Monovalent Omi XBB.1.5 overlaps with cumulative number of doses shipped.

Table 20. Interval Estimated Number of 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	**0.5**	**9600**	**9600**	**0**	**19200**
European Union (27)	0	0	0	0	0
European Economic Area Countries (3)	0	0	0	0	0
Switzerland	0.5	9600	9600	0	19200
UK	0	0	0	0	0
Other Countries	0	0	0	0	0
Commonwealth of Independent States	0	0	0	0	0
North America	**0**	**0**	**0**	**200**	**200**
US	0	0	0	200	200
Canada	0	0	0	0	0
Central and South America	**16.1**	**252000**	**374400**	**20160**	**646560**
Asia	**14.8**	**48600**	**52800**	**492480**	**593880**
Japan	0	0	0	0	0
Other Countries	14.8	48600	52800	492480	593880
Oceania	**4.7**	**0**	**43200**	**144000**	**187200**
Australia/New Zealand	1.4	0	43200	14400	57600
Other Countries	3.2	0	0	129600	129600
Africa	**63.9**	**0**	**0**	**2563560**	**2563560**
Total	**100**	**310200**	**480000**	**3220400**	**4010600**

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

Table 21. Interval Estimated Number of Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**11.9**	**0**	**0**	**3336480**	**3336480**
European Union (27)	0.2	0	0	66240	66240
European Economic Area Countries (3)	0	0	0	0	0
Switzerland	0	0	0	0	0
UK	0	0	0	0	0
Other Countries	0.2	0	0	51840	51840
Commonwealth of Independent States	11.5	0	0	3218400	3218400
North America	**53.5**	**1254800**	**1385000**	**12306260**	**14946060**
US	53.5	1254800	1385000	12306260	14946060
Canada	0	0	0	0	0
Central and South America	**9.2**	**39600**	**168000**	**2371980**	**2579580**
Asia	**10.7**	**0**	**0**	**2999580**	**2999580**
Japan	0	0	0	0	0
Other Countries	10.7	0	0	2999580	2999580
Oceania	**9**	**0**	**0**	**2517120**	**2517120**
Australia/New Zealand	8.9	0	0	2499840	2499840

Table 21. Interval Estimated Number of Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years	All
Other Countries	0.1	0	0	17280	17280
Africa	**5.6**	**0**	**0**	**1573920**	**1573920**
Total	**100**	**1294400**	**1553000**	**25105340**	**27952740**

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

CP Data

Interval CP (Fosun) data on the number of BNT162b2 original and bivalent doses administered in Hong Kong, Macau and Taiwan, as well as the monovalent XBB.1.5 doses administered in Macau is provided in Table 22 below.

Table 22. Interval Number of Administered Doses of BNT162b2 Original and BNT162b2 Bivalent and Monovalent Omi XBB.1.5 Vaccine – Contractual Party Data

Region **Country** ***-Vaccine Presentation***	**Number of Administered Doses**
Asia	**67862**
Hong Kong[a]	*17722*
- BNT162b2 (Original), 30 µg	*11422*
- BNT162b2 (Original), 10 µg	*1900*
- BNT162b2 (Original), 3 µg	*4400*
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	*50140*
Macau [b]	5064
- BNT162b2 (Original) + Bivalent (Original + Omicron BA.4/BA.5) total	*1802*
BNT162b2 (Omicron XBB.1.5) (30 mcg/dose)	*3262*
Taiwan[c]	11586
- BNT162b2 (Original), 30 µg	*1084*
- BNT162b2 (Original), 10 µg	*8402*
- BNT162b2 (Original), 3 µg	*21000*
- Bivalent (Original + Omicron BA.4/BA.5)	*0*

a. Interval period: 19 June 2023 through 15 December 2023.
b. Interval period: 12 June 2023 to 17 December 2023, For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. Interval period: 19 June 2023 through 30 August 2023.

5.2.2.2. Health Authority Public Data – Interval Exposure

Estimated interval data (2023 week 25 through 2023 week 40) about the number of COMIRNATY® doses administered are published only for the EU/EEA countries.

Table 23 displays the interval EU/EEA published data with number of doses administered for each age group and by vaccine presentation.

Table 23. EU/EEA – Interval Number of Administered Doses by Age Group and Vaccine Presentation

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi	BNT162b2 Monovalent XBB.1.5[a]	Total
< 18 years	2314	50	505	770	87	3726
0 – 4 years	1494	NA	0[b]	0	0	1494
5 – 9 years	1929	NA	16	0	0	1945
10 – 14 years	682	0	203	260	29	1174
15 – 17 years	361	5	264	506	26	1162
18 – 24 years	2479	112	1734	2469	156	6950
25 – 49 years	26024	563	7589	8798	3321	46295
50 – 59 years	26090	304	3725	5881	2693	38693
60 – 69 years	72538	689	6134	5414	5796	90571
70 – 79 years	97559	813	10293	3010	6664	118339
≥ 80 years	57697	451	7248	1607	4208	71211
Age Unknown	2953	2	7	0	0	2962
All	282973	2907	69565	27179	22838	405462

a. Interval period: 2023 week 25 through 2023 week 40 (05 October 2023).
b. Interval period: 2023 week 31 through 2023 week 40 (05 October 2023).

Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 24 through Table 27 provide the interval total number of administered doses for each vaccine presentations in EU/EEA, by age group and dose number. Individual country data are provided in Appendix 5.1.

Table 24. EU/EEA – Interval Number of Administered Doses of BNT162b2 Original by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	1032	793	282	153	40	7	2	5
18 – 24 years	218	170	498	882	653	51	4	3
25 – 49 years	1065	550	3174	9724	10300	1020	172	19
50 – 59 years	680	93	1512	4906	16242	2336	310	11
60 – 69 years	12086	123	13231	5088	23626	16663	1621	100
70 – 79 years	14442	109	15929	3890	15259	20901	26924	105
≥80 years	7265	87	7945	2111	6857	12001	17637	3794
Age Unknown	37	15	26	2875	0	0	0	0
All	35931	1222	42336	26712	73100	52972	46668	4032

Interval period: 2023 week 25 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 25. EU/EEA – Interval Number of Administered Doses of BNT162b2 Bivalent Omi BA.1 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	283	453	10660	6210	246	0	0	0

Table 25. EU/EEA – Interval Number of Administered Doses of BNT162b2 Bivalent Omi BA.1 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
18 – 24 years	362	484	37035	145740	4100	4	0	39
25 – 49 years	1747	1885	130894	1267615	43116	48	1	180
50 – 59 years	530	570	43262	1080473	54289	72	0	70
60 – 69 years	601	458	49182	1486253	234240	423	3	156
70 – 79 years	584	463	37849	1784089	372312	794	8	370
≥80 years	588	566	26819	657636	788246	966	2	3532
Age Unknown	2	3	5	27	4	0	0	4
All	4408	4423	325023	6421805	1496303	2307	14	4340

Interval period: 2023 week 25 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 26. EU/EEA – Interval Number of Administered Doses of BNT162b2 Bivalent Omi BA.4/BA.5 by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	63	87	243	90	22	0	0	0
18 – 24 years	104	124	855	530	100	8	0	13
25 – 49 years	241	221	1650	3712	1567	146	3	49
50 – 59 years	48	40	254	1565	1581	228	6	3
60 – 69 years	47	41	187	1259	3513	1039	43	5
70 – 79 years	57	33	155	813	5039	3889	304	3
≥80 years	125	87	198	934	3559	2155	188	2
Age Unknown	1	1	0	1	4	0	0	0
All	1193	1127	5075	16621	37464	7465	544	76

Interval period: 2023 week 25 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

Table 27. EU/EEA – Interval Number of Administered Doses of BNT162b2 Bivalent Omi by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5
< 18 years	1	1	694	64	10
18 – 24 years	1	2	1680	754	32
25 – 49 years	5	5	2776	5603	409
50 – 59 years	0	1	607	4759	514
60 – 69 years	1	0	317	4414	682
70 – 79 years	0	0	122	2437	451
≥80 years	0	0	127	1210	270
Age Unknown	0	0	0	0	0
All	7	8	5629	19177	2358

Interval period: 2023 week 25 through 2023 week 40.
Source: European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker.
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 18 December 2023.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 26.1 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, C4591048 and C4591054.

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, and BNT162-17.

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

Appendix 2.2[38] 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 2.2.6 provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type

[38] The interval data are notable for a large bolus of cases from New Zealand consisting of 61,897 cases (of the 107,065 total cases for the reporting period). The vast majority of the 61,897 cases are for BNT162b2 original vaccine (61,784 cases), compared to a much smaller proportion of cases for BNT162b2 Bivalent (Original and Omicron BA.4/BA.5). This bolus of cases originated from the New Zealand Regulatory Authority, MedSafe, which sent to Pfizer during the current reporting interval a listing of all AE reports MedSafe had received for Comirnaty from the time of initial product registration, 03 Feb 2021. The interval bolus of reports does not represent new significant safety information that is material to the safety profile of the BNT162b2 vaccines.

[BNT162b2 original and BNT162b2 bivalent (Omicron, Omi BA.1, Omi BA.4/BA.5, Omi), BNT162b2 multivalent NOS, BNT162b2 monovalent Omi XBB.1.5]. 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 2023 and the interval data are from 19 June 2023 to 18 December 2023. 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 2.2.6 totals, due to the fact that Appendix 2.2 through Appendix 2.2.6 only display 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 2.2.7 displays, for the PM dataset, demographic interval data, including ethnicity and race when available.

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

Table 28 below summarises the study treatments in the clinical studies by original vaccine or the variant-adapted vaccine.

Table 28. Clinical Trials During the Reporting Period: Study Treatments – Original and Variant-Adapted Vaccines

Original	BNT162b2	C4591001, C4591007, C4591015, C4591024, C4591030, C4591031, C4591036[a], BNT162-01[b], BNT162-14, BNT162-17
Other Constructs	BNT162b1	C4591001, BNT162-01,
Variant-Adapted Vaccines	BNT162b2 (B.1.351)	C4591001, BNT162-14[c]
	BNT162b2 (B.1.1.7) BNT162b2 (B.1.1.7 + B.1.617.2) BNT162b2 (B.1.617.2) BNT162b2 (B.1.1.529.1)	BNT162-17
	Original + Omi BA.1	C4591031, C4591036[a], C4591044
	Original + Omi BA.2[d]	C4591044
	Original + Omi BA.4/BA.5	C4591036[a], C4591044, C4591048
	Omi BA.1	C4591031
	Omi BA.4/BA.5	C4591044
	Omi XBB.1.5	C4591048, C4591054

a. Low-Interventional.
b. BNT162a1, BNT162b1, and BNT162c2 were also study vaccines in this trial.
c. BNT162b2 (B.1.351), which is also referred to as BNT162b2s01 and BNT162b2$_{SA}$.
d. BNT162b5.

Appendix 4.2 provides a list of interventional safety studies.

7.1. Completed Clinical Trials

1. Safety Trials

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

2. 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.

3. Remaining Trials

During the reporting interval, there were 3 completed clinical trials (C4591001, C4591030, and BNT162-14) with final CSRs (available upon request). No clinically important new information has emerged from these clinical trials; overall conclusions from the reports of these studies are provided below.

Table 29. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
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 Individual	This study had multiple interim CSRs to report data from prior data cuts. The conclusions from the final CSR: • Additional efficacy data showed that BNT162b2 30 µg likely also provides some protection against asymptomatic SARS-CoV-2 infection in an analysis conducted prior to the emergence of Omicron. • Overall immunogenicity responses were similar for lower booster doses (Dose 3) of BNT162b2 (5 or 10 µg) in the BNT162b2 5- and 10-µg groups, and SARS-CoV-2 neutralizing GMTs substantially increased at 1 month after the lower booster dose. In addition, administration of lower booster dose of BNT162b2 (5 or 10 µg) was safe and tolerable. • The primary 2-dose series for BNT162b1 and BNT162b2 at doses of 10, 20, and 30 µg was safe and tolerable. Administration of booster dose(s) (Dose 3, 4, or 5) of BNT162b2 30 µg to participants who had completed the 2-dose series shows continued safety and tolerability with most AEs consistent with reactogenicity-type events, and no new safety concerns.
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	The study objectives were met, demonstrating noninferiority of BNT162b2 and SIIV immune responses when BNT162b2 was coadministered with SIIV compared with those elicited by either vaccine administered alone. Full-length S-binding IgG GMCs increased from baseline to 1 month after BNT162b2, with slightly lower GMCs in the coadministration group compared with the separate administration group. Strain-specific HAI GMTs increased at 1 month after SIIV vaccination in both the coadministration and separate-administration groups. BNT162b2 was safe and well-tolerated when coadministered with SIIV. The results of this study support the coadministration of BNT162b2 and SIIV.

Table 29. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
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.	Based on the totality of the safety data, the booster dose of 30 μg Comirnaty and BNT162b2s01 were generally well tolerated and had an acceptable safety profile aligned with that known for Comirnaty.

7.2. Ongoing Clinical Trials

During the reporting period, there were 8 ongoing[39] sponsor-initiated clinical trials.

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

   There were 3 ongoing clinical trials.

   a) PASS:

   ➢ ***Original Vaccine***

– 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[40]: *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 new information has emerged from this ongoing PASS.

[39] 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.

[40] 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 authorisation 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 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.

➢ ***Original and Variant-Adapted***

– C4591036: *Low-interventional cohort study of myocarditis/pericarditis associated with COMIRNATY in persons less than 21 years of age*. No clinically important new information has emerged from this ongoing PASS.

b) 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.

2) Other Trials that reported new significant efficacy information

There were 5 ongoing CTs, of which one was with the BNT162b2 original vaccine (C4591007) and 4 were with variant-adapted version(s) of the vaccine (C4591044, C4591048, and C4591054); in the CT C4591031 both original and variant-adapted vaccines were administered.

➢ ***Original vaccine***

– 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.*

➢ ***Original and Variant-Adapted Vaccines***[41]

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

Study C4591031 consists of 6 substudies. All substudies are completed, with final CSRs for substudies C [original] and F [variant-adapted vaccines] available during the reporting interval; no clinically significant safety and/or efficacy information has emerged.

➢ ***Variant-Adapted Vaccines***[41]

– 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.*

[41] Refer to Table 28 for the study treatments.

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

– C4591054: *A phase 2/3 protocol to investigate the safety, tolerability, and immunogenicity of BNT162b2 RNA-based vaccine candidates for SARS-COV-2 new variants in healthy individuals.*

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

During the reporting period, there were no cases reporting serious adverse reactions or fatal outcomes considered possibly related to study vaccine from ongoing studies.

3) Remaining Trials

There was 1 ongoing clinical trial:

➢ ***Original vaccine and Variant Adapted Vaccines***

– BNT162-17: *A phase II trial to evaluate the safety and immunogenicity of SARSCoV2, monovalent and multivalent RNA-based vaccines in healthy subjects*.

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

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 being utilised as study vaccine in other 2 Pfizer-sponsored clinical development programs (C526 and C548) and in another BioNTech-sponsored clinical development program (BNT162b4). See below for details.

7.5. New Safety Data Related to Fixed Combination Therapies

BNT162b2 was also administered as study vaccine in other Pfizer-sponsored clinical development programs of combinations with an investigational mRNA influenza vaccine in Study C5261001 and with QIV and RSV preF vaccines in Study C5481001 and in another BioNTech sponsored clinical development program of co-administration with BNT162b4.

There was no new clinically important safety information identified for this reporting period from these combination programs.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Health Canada: 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 5.3 for the interim report of study C4591021 submitted in the reporting period. No interim reports were submitted for studies C4591010 and C4591022 in the current reporting interval.

Appendix 4.3 and Appendix 4.4 provide a list of non-interventional safety studies completed/terminated or ongoing during the reporting period.

8.1. Completed Non-Interventional Studies

1. Safety studies

The PASSs C4591008[42] and C4591012[43] were completed during the reporting period; the summary of results from these studies is provided in Table 30.

No 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.

Table 30. Summary of Results from Completed Non-Interventional Safety Studies During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591008	Healthcare Worker Exposure Response and Outcomes (HERO)-Together: A Post-Emergency Use Authorization Observational Cohort Study to Evaluate the Safety of the Pfizer-BioNTech COVID-19 Vaccine in US Healthcare Workers, Their Families, and Their Communities	The study population enrolled in HERO-Together was primarily White, female, and had a low comorbidity burden at baseline. The incidence of positively adjudicated safety events of interest, including hospitalizations, was low and most commonly included arthritis/arthralgia and non-severe allergic reaction. Based on age-adjusted SCRI analyses, there was no observed increased risk of either a composite of any AESI or all-cause hospitalization in the post-vaccination period.

[42] 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.

[43] C4591012 and C4591022 are commitments to the US FDA and are Category 3 commitments in the EU RMP v.9.0.

Table 30. Summary of Results from Completed Non-Interventional Safety Studies During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591012	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	Overall, no examined safety events of interest were found to be associated with the Pfizer-BioNTech COVID-19 vaccine based on the analyses conducted in the final report.

2. Other studies

During the reporting period, the study C4591061 was completed. No new safety information emerged from this non-interventional study; the summary of results from this study is provided in Table 31.

Table 31. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591061	Investigating uptake and subsequent health outcomes associated with Pfizer-BioNTech bivalent COVID-19/Influenza vaccine concomitant administration using a claims-based real-world data source in the US.	In this study, coadministration of BNT162b2-biv and SIIV was associated with generally similar effectiveness in the community setting against COVID-19-related and SIIV-related outcomes compared with giving each vaccine alone and may help improve uptake of both vaccines.

8.2. Ongoing Non-Interventional Studies

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

   - PASS[44]: Non-interventional studies C4591009,[45] C4591010,[46] C4591021[45], C4591022,[45] C4591038[45], C4591049[47], and C4591055[48] are PASS. No clinically

[44] During the reporting period, interim CSRs were issued for the studies C4591021 (20 September 2023), and C4591038 (22 September 2023).

[45] Studies C4591009, C4591021, C4591022 and and C4591038 are requirements by the US FDA and are Category 3 commitments in the EU-RMP v.9.0.

[46] Study C4591010 is no longer a Category 3 commitment in the EU-RMP v. 9.0. by request from PRAC (procedure EMEA/H/C/005735/MEA 0.11.8).

[47] C4591049 is a voluntary study designed to provide real-world safety information on a cohort of people receiving the Pfizer-BioNTech COVID-19 vaccine.

[48] C4591055 is a voluntary study addressing risk factors for myocarditis.

important information has emerged from PASS. Summary of the interim report of the NIS C4591021 submitted during the reporting period is available in Appendix 5.3.

- 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.

2. Other Studies

There were 7 ongoing non-interventional studies:

- C4591014,[49] *Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- C4591025,[50] *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.*
- C4591050[51], *Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance.*
- C4591053, *The impact of Pfizer-BioNTech (BNT162b2) vaccination on the long-term effects of COVID among adults in England diagnosed with COVID prior to Omicron dominance.*
- C4591059, *Use and Effectiveness of COVID-19 Vaccines using state vaccine registries and insurance claims data.*

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

[49] PAM-MEA-013.

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

[51] C4591050 is a study requested by Indonesian RA observing safety profile of BNT162b2 in Indonesian population aged 12 years and older.

9.2. Medication Errors

Analysis of the safety database

Cases potentially indicative of medication errors[52] that occurred in the reporting period are summarised below.

Of the 8413 cases, 533 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 477 cases [53];
- 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 56 cases.

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #6.

Post-Authorisation Data

- Number of cases: 7880 cases reporting 20,168 events (7.4% of 107,046 cases, the total PM dataset) indicative of potential medication errors were retrieved compared to 11,362 relevant cases (15.3%) analysed in the PSUR #5.

[52] Medication errors search criteria: MedDRA (version 26.1): *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 programming error; Device use error; Dosage not adjusted; 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.

[53] Among the 533 cases, 49 cases involved children 6 months to 4 years and 123 cases involved children 5 through 11 years.

- The 7880 relevant medication error cases originated (≥2% of cases) from the following countries: US (2334), Japan (2129), Sweden (944), UK (720), Germany (718), France (204) and Canada (183).

- The most frequently reported (≥2%) medication error PTs included Poor quality product administered (3888), Product temperature excursion issue (2559), Inappropriate schedule of product administration (2303), Product administration error (1254), Underdose (475), Wrong product administered (447), Wrong technique in product usage process (379), Incorrect route of product administration (271), Expired product administered (223), Product preparation error (176), Incorrect dose administered (158).

- Clusters of medication errors were reported in two instances. The medication error cases (>400) were identified and coded to the PTs Poor quality product administered and Product temperature excursion issue. No cases demonstrated harm, and none had co-reported events: in 640 cases (US), it was reported that the provider administered BNT162b2 that was not stored properly and in 401 cases (Japan) it was reported that BNT162b2 was incorrectly stored in the temperature range -25 to -15 °C.

9.2.1. Medication Errors Categorisation

Among the medication error cases (7880 cases), compared to 11,362 medication errors in the PSUR #5, 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)]: 303 cases (3.8%) compared to 360 cases (3.2%) in the PSUR #5. The clinically relevant co-reported events (≥10) were coded to the PTs Vaccination site pain (59), Pain in extremity (42), Fatigue (41), Pyrexia (40), Headache (37), Arthralgia (31), Pain (29), Malaise (27), Myalgia (22), Chills (20), Pruritus, Vaccination site erythema (18 each), Vaccination site swelling (16), Dizziness, Nausea (15 each), Swelling, Rash (13 each), Disturbance in attention, Dyspnoea (12 each), Diarrhoea, Back pain (10 each).
- Medication errors without harm [i.e., not resulting in adverse reaction(s)]: 7571 cases (96.1%) compared to 10,995 (96.8%) in the PSUR #5.
- Potential medication errors: 6 cases (0.1%) compared to 6 cases (0.1%) in the PSUR #5.
- Intercepted medication errors: no cases compared to 1 case (0.01%) in the PSUR #5.

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

Cases are clustered in original or bivalent or monovalent Omi XBB.1.5 according to the vaccine formulation administered as last suspect dose.

9.2.2. Medication Errors in Subjects aged 6 Months through <5 Years[54]

- Number of relevant cases: 303.
- Country/region of incidence: US (230), Japan (68), Finland (2), Australia, Canada, UK (1 each).
- Number of relevant events: 521.
- Relevant event seriousness: serious (1), non-serious (520).
- Relevant medication errors PTs most frequently reported (>10): Poor quality product administered (184), Product preparation error (104), Product temperature excursion issue (77), Product administration error (53), Expired product administered (29), Product preparation issue (21), Underdose (15), Inappropriate schedule of product administration (14).

Table 32 describes for each ME category the top 3 medication errors by vaccine presentation in individuals aged 6 months through <5 years.

Table 32. Medication Error Categories: Top 3 Medication Errors in Subjects aged 6 Months through <5 Years by Vaccine Presentations

ME Categories	Vaccine Presentation	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	Poor quality product administered	0	1	1
		Product administration error	0	1	1
	Omi XBB.1.5	Incorrect dose administered	0	1	1
		Accidental overdose	0	1	1
		Product preparation error	0	1	1
	Multivalent NOS	-	0	0	0
Medication Errors without harm	**Original**	Poor quality product administered	0	78	78
		Product temperature excursion issue	0	63	63
		Product administration error	0	14	14
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	Poor quality product administered	0	36	36
		Product administration error	0	19	19
		Product preparation error	0	14	14
	Omi XBB.1.5	Product preparation error	0	84	84
		Poor quality product administered	0	70	70
		Expired product administered	0	23	23
	Multivalent NOS	-	0	0	0

[54] Case where the age was reported as "Infant" (1 case) was evaluated in this age group.

Table 32. Medication Error Categories: Top 3 Medication Errors in Subjects aged 6 Months through <5 Years by Vaccine Presentations

ME Categories	Vaccine Presentation	Medication error PTs	Intended	Administered	Total
Potential Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0
Intercepted Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0

9.2.3. Medication Errors in Subjects aged 5 through <12 Years[55]

- Number of relevant cases: 607.
- Country/region of incidence: Japan (355), US (234), Australia (5), Spain, UK (3 each), Brazil, Germany (2 each), Czech Republic, France, Mexico (1 each).
- Number of relevant events: 1159.
- Relevant event seriousness: non-serious (1159).
- Relevant medication errors PTs most frequently reported (>10): Poor quality product administered (504), Product temperature excursion issue (372), Product administration error (151), Wrong product administered (28), Inappropriate schedule of product administration, Product preparation error (25 each), Expired product administered (15).

Table 33 describes for each ME category the top 3 medication errors that occurred by vaccine presentation in individuals aged 5 through <12 years.

Table 33. Medication Error Categories: Top 3 Medication Errors in Subjects aged 5 through <12 Years by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Original**	Expired product administered	0	1	1
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	Product administered at inappropriate site	0	1	1
	Multivalent NOS	-	0	0	0

[55] Cases where the age was reported as "Child" (422 cases) were evaluated in this age group.

Table 33. Medication Error Categories: Top 3 Medication Errors in Subjects aged 5 through <12 Years by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication Errors without harm	**Original**	Poor quality product administered	0	339	339
		Product temperature excursion issue	0	336	336
		Product administration error	0	26	26
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	Poor quality product administered	0	131	131
		Product administration error	0	108	108
		Wrong product administered	0	24	24
	Omi XBB.1.5	Poor quality product administered	0	34	34
		Wrong product administered	0	18	18
		Product administration error	0	17	17
	Multivalent NOS	-	0	0	0
Potential Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0
Intercepted Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0

9.2.4. Medication Errors in Subjects aged 12 Years and Older[56]

- Number of cases: 4633.
- Country/region of incidence (≥2%): Japan (1434), Sweden (921), Germany (664), US (527), UK (292), France (152), Norway (110), Finland (100), Canada (91).
- Number of relevant events: 6535.
- Relevant event seriousness: non-serious (6492), serious (43).
- Relevant medication errors PTs most frequently reported (>10): Inappropriate schedule of product administration (2202), Poor quality product administered (1701), Product temperature excursion issue (1287), Product administration error (433), Wrong product

[56] Cases where the age was reported as: "Adolescent" (730 cases), "Adult (577 cases) or "Elderly" (110 cases) were evaluated in this age group.

administered (323), Incorrect route of product administration (158), Incorrect dose administered (114), Expired product administered (106), Vaccination error (44), Underdose (38), Medication error, Product administered at inappropriate site (23 each), Product preparation error (13).

Table 34 below describes for each ME category the top 3 medication errors occurred by vaccine presentation in individuals aged 12 years and older age group.

Table 34. Medication Error Categories: Top 3 Medication Errors in Subjects aged 12 Years and Older by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication errors with harm	**Original**	Inappropriate schedule of product administration	1	111	112
		Incorrect route of product administration	0	32	32
		Wrong product administered	11	15	26
	Bivalent Omi BA.1	Wrong product administered	10	2	12
		Incorrect route of product administration	0	1	1
		Product administered at inappropriate site	0	1	1
	Bivalent Omi BA.4/BA.5	Wrong product administered	11	3	14
		Incorrect route of product administration	0	9	9
		Expired product administered	0	8	8
	Omi XBB.1.5	Wrong product administered	11	6	17
		Incorrect route of product administration	0	10	10
		Incorrect dose administered	0	10	10
	Multivalent NOS	Wrong product administered	1	14	15
		Incorrect route of product administration	0	2	2
		Wrong technique in product usage process	0	1	1
Medication Errors without harm	**Original**	Inappropriate schedule of product administration	1	2025	2026
		Poor quality product administered	6	1147	1153
		Product temperature excursion issue	5	1146	1151

Table 34. Medication Error Categories: Top 3 Medication Errors in Subjects aged 12 Years and Older by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication Errors without harm *Cont'd*	**Bivalent Omi BA.1**	Wrong product administered	24	9	33
		Vaccination error	0	3	3
		Inappropriate schedule of product administration	0	2	2
	Bivalent Omi BA.4/BA.5	Poor quality product administered	10	336	346
		Product administration error	8	233	241
		Wrong product administered	136	31	167
	Omi XBB.1.5	Poor quality product administered	4	203	207
		Product administration error	4	175	179
		Wrong product administered	115	42	157
	Multivalent NOS	Wrong product administered	5	19	24
		Vaccination error	0	7	7
		Expired product administered	0	7	7
Potential Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0
Intercepted Error	**Original**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
	Omi XBB.1.5	-	0	0	0
	Multivalent NOS	-	0	0	0

9.2.5. Medication Errors in Subjects with Unknown Age

- Number of cases: 2337.
- Country/region of incidence (≥2%): US (1343), UK (424), Japan (272), Canada (91), Germany (52), France (51).
- Number of relevant events: 4244.
- Relevant event seriousness: non-serious (4240), serious (4).
- Relevant medication errors PTs most frequently reported (>2%): Poor quality product administered (1499), Product temperature excursion issue (823), Product administration error (617), Underdose (413), Wrong technique in product usage process (370), Incorrect route of product administration (108), Wrong product administered (91), Expired product administered (73), Inappropriate schedule of product administration (62).

Table 35 below describes for each ME category the top 3 medication errors occurred by vaccine presentation when the vaccine presentation is unknown age.

Table 35. Medication Error Categories: Top 3 Medication Errors in Unknown Age Group by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Total
Medication errors with harm	**Original**	Wrong product administered	4
		Inappropriate schedule of product administration	3
		Counterfeit product administered	2
	Bivalent Omi BA.1	Wrong product administered	1
	Bivalent Omi BA.4/BA.5	Incorrect route of product administration	2
		Expired product administered	1
		Poor quality product administered	1
	Omi XBB.1.5	Incorrect route of product administration	5
		Poor quality product administered	1
		Product administered at inappropriate site	1
	Multivalent NOS	-	0
Medication Errors without harm	**Original**	Poor quality product administered	132
		Product temperature excursion issue	81
		Product administration error	49
	Bivalent Omi BA.1	Poor quality product administered	48
		Product administration error	48
		Wrong product administered	6
	Bivalent Omi BA.4/BA.5	Poor quality product administered	436
		Product administration error	372
		Underdose	356
	Omi XBB.1.5	Poor quality product administered	876
		Product temperature excursion issue	687
		Product administration error	142
	Multivalent NOS	Underdose	15
		Wrong technique in product usage process	14
		Wrong product administered	6
Potential Error	**Original**	Circumstance or information capable of leading to medication error	3
	Bivalent Omi BA.1	-	0
	Bivalent Omi BA.4/BA.5	Circumstance or information capable of leading to medication error	1
	Omi XBB.1.5	Circumstance or information capable of leading to medication error	5
		Product expiration date issue	1
	Multivalent NOS	-	0
Intercepted Error	**Original**	-	0
	Bivalent Omi BA.1	-	0
	Bivalent Omi BA.4/BA.5	-	0
	Omi XBB.1.5	-	0

Table 35. Medication Error Categories: Top 3 Medication Errors in Unknown Age Group by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Total
	Multivalent NOS	-	0

Conclusion

Overall, among the 7880 relevant PM medication error cases, 303 cases (0.3% of the total interval cases, 3.8% of total relevant medication error cases) were considered harmful because they were accompanied by clinically relevant co-reported events. These co-reported events were consistent with the known safety profile of BNT162b2.

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 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.

Nonclinical investigations into the pathogenesis of mRNA-LNP-associated myocarditis/pericarditis did not identify any validated linear or 3-dimensional molecular mimicry candidates, release of cytokines including TGF-β from iPSC-CM after administration of surrogate mRNA-LNP, nor distribution of mRNA or expression of the encoded protein (GFP or spike) in the heart of mice administered a single IM dose of surrogate mRNA-LNP or BNT162b2.

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.

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.

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 information that presented important new safety findings were identified.

Ad-hoc literature searches for specific safety topic reviews and evaluations, performed on additional databases, did not reveal important new safety findings.

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 in Table 36.

Table 36. List of Periodic Reports submitted in the Reporting Period

Periodic Report Type	No.	Reporting Period
Abbreviated SMSR[a]	18	16 June 2023 through 15 July 2023
	19	16 July 2023 through 15 August 2023
	20	16 August 2023 through 15 September 2023
	21	16 September 2023 through 15 October 2023
	22	16 October 2023 through 15 November 2023

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 DLP,

- The ongoing signals (Postmenopausal haemorrhage and Pulmonary embolism) were closed as no risk on 22 December 2023 and on 10 January 2024, respectively.

- The EU-RMP version 11.2 was submitted, as detailed in the table below.

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
EMEA/H/C/005735/II/0206/G RMP update regarding final CSR of study C4591012 and protocol amendments of study C4591052 and C4591021	22 December 2023	RMP v11.2: 22 December 2023 (Gateway)	On-going

- After DLP, CDS version 25.0 was made effective on 26 January 2024. This version includes information of participants from the paediatric study C4591007 reflecting a larger safety population from the 6-month post dose-3 interim study report. Study C4591007, which was conducted with BNT162b2 original vaccine, included individuals 6 months through <12 years of age receiving the primary series or first booster dose. There were no new safety issues identified from the larger safety population of this study. A footnote in Table 48 (Clinical Trial section of CDS) related to the data from the flu vaccine co administration study C4591030, which was added to the CDS in the November 2023 update, was revised to more clearly define the noninferiority criteria.

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

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made: *The MAH should continue to closely monitor hemophagocytic lymphohistiocytosis (HLH) and report all new (literature) cases of HLH including a WHO-UMC causality assessment per case and age-stratified observed/expected analyses using 21-day and 42-day risk intervals.*

Response

Please refer to Appendix 5.2 Hemophagocytic Lymphohistiocytosis.

Following the review of the COMIRNATY mRNA COVID-19 Vaccines Cumulative Review on Idiopathic Inflammatory Myopathies (control #277008), a communication from Health Canada (MHPD) recommended the following actions:

BioNTech Manufacturing GmbH is requested to commit to the following:

- *To continue to closely monitor idiopathic inflammatory myopathies/myositis, and idiopathic inflammatory myopathies flares through routine pharmacovigilance in the upcoming PSURs/PBERs including (but not restricted to):*
  - *Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms, as appropriate.*

Response

The review of the new cases reporting idiopathic inflammatory myopathies/myositis (including those reporting rechallenge information) and of the scientific literature did not reveal any new safety information. Please refer to the review in the subsection *Other Safety Topics Not Considered Signals*.

Signal Overview

New signals detected, signals with ongoing evaluations, and signals that were closed during the reporting interval are presented below in Table 37. A summary of the signals is in Appendix 3.

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.

Review of safety topics and evaluation of signals take into consideration safety data available for original, bivalent and monovalent Omi XBB.1.5 (2023/2024 formula) BNT162b2.

Table 37. Overview of Signals (at DLP 18 December 2023)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Pulmonary embolism	New and ongoing	Inquiry from a competent authority (Saudi FDA)	Not yet determined	Not applicable
Post-menopausal haemorrhage	New and ongoing	Inquiry from a competent authority (EMA/PRAC)	Not yet determined	EPITT No. 19989

Table 37. Overview of Signals (at DLP 18 December 2023)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Mastitis/Breast swelling	New and closed	Inquiry from a competent authority (Australia TGA)	Not a risk	Not applicable
Sensorineural hearing loss	Closed	Inquiry from a competent authority (Australia TGA)	Not a risk	Not applicable
Retinal vascular occlusion	Closed	Routine PV review of medical literature	Not a risk	Not applicable
Menstrual irregularities	Closed	Routine PV review of spontaneous AE reports	Not a risk	Not applicable

* 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 that were considered in coming to this conclusion 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 etiologies based on clinical and scientific experience, and temporal clustering of events.

The safety topics monitored or reviewed are the following:

- HLH (Appendix 5.2), and
- Idiopathic Inflammatory Myopathies/Myositis (see end of this section)

Product Lots and AE Reports

The most frequently reported lot numbers in PM case reports (>320 cases) are listed in Table 38 below.

Table 38. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases[b]
EK9788	1442
EM0477	969
HD9871	628
EL8723	373
EM6950	370
FH3023	324

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium).
b. Multiple lots were reported in the same case; hence the sum of the cases exceeds the real number of cases.

Out of total 4103 cases (11,109 AEs) with these lot numbers, the clinical AEs most frequently reported (≥ 5%) included Headache (1529), Pain (1474), Myalgia (1193), Pyrexia (1054), Fatigue (571), Arthralgia (569), Malaise (295), Chills (235), Diarrhoea (227), Lymphadenopathy (217) and Nausea (211).

These AEs do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per the RSI.

Of note, out of 4103 cases, there were 331 non-serious cases reporting PTs indicative of potential product quality issues including:

- three hundred and twenty-two (322) cases reported PT Product temperature excursion issue,[57] all involving lot FH3023 and without any co-reported clinical AEs;
- eight (8) cases reported PT Product packaging quantity issue,[58] all involving lot HD9871 without any co-reported clinical AEs;
- a single case reported PT Product substitution issue involving lot HD9871 with a single non serious co-reported event (PT Arthralgia).

There were no safety signals related to product quality defects or issues identified with product complaint investigations.

Lot HG2252

As mentioned in Section 3, following the question from DMA (Denmark) regarding possible bubble formation in the vaccine product after drawing into syringes on 17 October 2023, lot HG2252 was quarantined for a few days.

There were one hundred and eighty-three (183) cases reported with lot number HG2252. The clinical AEs most frequently reported (≥ 3%) were Fatigue (23), Headache and Malaise (22

[57] Originated from a single cluster from Japan.

[58] Originated from a single cluster from Ireland.

each), Pyrexia (20), Vaccination site pain (18), Myalgia (16), Arthralgia, Asthenia, Chills and Nausea (11 each), Pain in extremity and Vaccination site swelling (10 each), Dizziness and Vomiting (9 each), Dyspnoea and Pruritus (8 each), Erythema and Vaccination site inflammation (7 each), Diarrhoea, Rash papular, and Vaccination site erythema (6 each).

There were no cases reporting a PT indicative of a product quality issue nor cases suggesting a suspected association between quality complaints and the AEs. In addition, the cases reviewed made no mention of bubbles in the syringes.

The reported AEs for HG2252 do not differ from those most reported in the overall incremental dataset and are listed or consistent with listed events as per the RSI.

Overall, the most frequently (≥ 22 occurrences) reported events potentially indicative of product issues regardless of lot number included the following PTs: Product temperature excursion issue (2561), Product counterfeit (37), and Product packaging quantity issue (22).

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

- Cases reporting PT Product counterfeit originated from a single cluster of non-serious legal cases from Greece. These cases described a possible administration of counterfeit vaccine as it was not administered in the designated governmental facilities and the vaccination certificate recorded incorrect data on vaccination dates and facility. A PQC investigation cannot be performed due to absence of lot number/sample.

- Cases reporting the PT Product packaging quantity issue described volume overfill in vials.

- 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 original and bivalent primary series/booster doses are adequately described on the product packaging/labelling.

Surveillance for any correlation ("AE/PC alert") between the number of AE reports and the number of product quality complaints received in the review period is performed through review of AE/PC Lot and Lot profile reports and SAE/PC reports, and review of AE-batch/lot trending by Country reports. In support to this process as needed, a review of AE data related to respective PCs may be requested to support Trend Alert analysis and Trend Notifications.

AE/PC alerts are reviewed and evaluated to establish whether there is an association between the reported adverse event and a product quality defect or complaint. Upon safety evaluation, it is determined whether an alert does or does not constitute a potential safety signal and any required further evaluation and escalation as per standard procedures.

Conclusion

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

Idiopathic Inflammatory Myopathies/Myositis

Search criteria – PTs: Anti-melanoma differentiation-associated protein 5 antibody positive; Anti-SRP antibody positive; Antisynthetase syndrome; Autoimmune myositis; Dermatomyositis; Focal myositis; Idiopathic inflammatory myopathy; Immune-mediated myositis; Inclusion body myositis; Juvenile polymyositis; Lupus myositis; Myositis; Necrotising myositis; Orbital myositis; Overlap syndrome; Polymyositis.

In reference to the request from Health Canada (MHPD) and considering the cumulative review done up to 15 January 2023 of all evidence concerning the association between myositis and vaccination with Comirnaty provided to PRAC in the context of the signal evaluation request (EPITT 19883), the Pfizer safety database was searched from 16 January 2023 to the DLP of this PSUR.[59]

Clinical Trial Data

- Number of cases: none.

Post-Authorisation Data

- Number of cases: 156 (original [135]; bivalent Omi BA.1 [7]; bivalent Omi BA.4/BA.5 [10]; multivalent NOS [3], monovalent Omi XBB.1.5 [2]).
- MC cases (78); NMC cases (78).
- Country/region of incidence (≥ 2%): Germany (47); Sweden, UK (14 each); Japan (12); Australia (9); US (8); France (7); Finland, New Zealand (5 each); Denmark, Norway (4 each); Brazil, Italy, Turkey (3 each); Canada, Czech Republic, Greece, Poland, Romania, and Spain (2 each); the remaining 6 cases were distributed among 6 unique countries.
- Subjects' gender: female (101); male (50) and unknown (5).
- Subjects' age in years: n = 151; range: 10 – 85 years; mean: 52.5; median: 53.0.
- Medical history (n = 67); the most frequently (≥ 4) reported medical conditions included Hypertension (14); Depression (10); Anxiety (8); Autoimmune thyroiditis (7); Arthropathy, Hypersensitivity, Immunodeficiency, and Panic attack (4 each).
- COVID-19 Medical history (n = 6): COVID-19 and Suspected COVID-19 (3 each).

[59] Since the search period for this topic overlaps with the reporting period of the previous PSUR (19 December 2022 through 18 June 2023) and the current PSUR reporting period, no comparison between the cases of idiopathic inflammatory myopathies/myositis reported in the reporting periods of PSUR 5 and the current PSUR 6 is possible.

- Co-suspect medications (n = 4): relevant co-suspect medications (⩾2) included elasomeran (2).
- Number of relevant events: 164.
- Relevant event seriousness: serious (118), non-serious (46).
- Reported relevant PTs: Myositis (87), Dermatomyositis (32), Polymyositis (13), Autoimmune myositis (8), Antisynthetase syndrome, Orbital myositis (6 each), Immune-mediated myositis (4), Anti-melanoma differentiation-associated protein 5 antibody positive, Overlap syndrome (2 each), Focal myositis, Idiopathic inflammatory myopathy, Inclusion body myositis, and Necrotising myositis (1 each).
- Time to event onset[60]: n = 51, range: <24 hours to 499 days, median: 4 days.
  - <24 hours: 12 events (1 of which had a fatal outcome),
  - 1 day: 4 events,
  - 2-7 days: 13 events,
  - 8-14 days: 4 events,
  - 15-30 days: 6 events,
  - 31-100 days: 6 events,
  - 101-499 days: 6 days.
- Duration of relevant events[61]: n = 2.
  - 2 days: 1 event,
  - 4 days: 1 event.
- Relevant event outcome: fatal (2), resolved/resolving (37), resolved with sequelae (6), not resolved (65), unknown (54).

  The 2 cases reporting 2 relevant events Dermatomyositis and Necrotising myositis with fatal outcome, involved elderly subjects (67 and 69 years). In one of these 2 cases, influenza vaccine was reported as co-suspect and relevant medical history included malignancies (breast cancer and squamous cell carcinoma of the skin).The reported causes of death were Abdominal distension, Dermatomyositis, Pneumonia aspiration, Acute kidney injury, Autoimmune disorder, Autoimmune hepatitis, Blood pressure systolic decreased, Dyspnoea, Erythema, Hepatic necrosis, Hepatitis, Hypoaesthesia, Hypoxia, Interchange of vaccine products, Intervertebral disc annular tear, Intervertebral disc protrusion, Malaise, Necrotising myositis, Nerve compression, Neuropathy peripheral, Paraneoplastic syndrome, Pleural effusion, Pneumothorax, Pruritus, Respiratory failure, Respiratory tract infection, Rhabdomyolysis, Spinal stenosis, Troponin increased (1 each). Of the 69 cases reporting medical history and/or co-suspect medications, 22 cases reported relevant medical history/risk factors (e.g., autoimmune

[60] This number does not include the events for which administration dates or event onset dates were partially reported.

[61] Provided when reported for events with outcome of resolved and resolved with sequelae.

disorders, infections, malignancies, rheumatoid arthritis, muscular disorders, underlying dermatomyositis) and/or co-suspect vaccines which may have contributed to the development of the events indicative of idiopathic inflammatory myopathies/myositis.

- Among these 156 cases, 5 subjects reported IIM flares. In 2 cases flare of juvenile idiopathic inflammatory myopathy and of dermatomyositis was reported after administration of dose 2 (1 each). Additionally, recurrences of myositis were reported in a subject after dose 3, 4 and 5 of vaccine and in further 2 subjects after 2 doses of vaccines (unspecified dose numbers for the first subject and dose 2 and 3 for the second subject).

Analysis by age group

CT: there are no cases reporting idiopathic inflammatory myopathies/myositis in the CT dataset.

PM: Paediatric (3), Adults (103), Elderly (45) and Unknown (5).

– No notable difference was observed in the reporting proportion of idiopathic inflammatory myopathies/myositis 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.

Literature

Review of the literature did not identify any significant new information regarding the COVID-19 mRNA vaccine and idiopathic inflammatory myopathies/myositis, and no scientific literature on possible pathogenic mechanisms.

Conclusion

No new significant safety information was identified based on the review of the new cases reporting idiopathic inflammatory myopathies/myositis (including those reporting rechallenge information). This topic will continue to be monitored with routine pharmacovigilance activities and presented in future PSURs only if any significant new information is identified.

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

The EU-RMP at the beginning of the reporting period was version 9.0 adopted on 10 November 2022 (Procedure number EMEA/H/C/005735/II/0147).

In the PSUR #4, the MAH, based on clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of VAED/VAERD from the list of the safety concerns.

The PRAC agreed to remove VAED/VAERD from the safety concerns as per the AR of PSUR 4 received during the previous PSUR reporting period. This risk is not included in the safety concerns at the beginning of the reporting period (see Table 39) according to the explanatory note on PSURs, in the EU regional appendix in GVP Module section VII.C.5.3.

Table 39. Safety Concerns at the Beginning of the Reporting Period

Important identified risks	Myocarditis and Pericarditis
Important potential risks	None
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

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

1. Version 9.4 submitted on 19 June 2023 (Eudralink) / 23 August 2023 (Gateway) to update a milestone for study C4591007 following EMA approval of Justification milestone extension (EMEA/H/C/005735/X/0180). Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.

2. Version 9.5 submitted on 21 June 2023 (Eudralink) / 23 August 2023 (Gateway) to consolidate the EU-RMP by merging RMP versions 9.3 (RMP v9.1 for EMEA/H/C/005735/X/0176 and RMP version 9.2 for EMEA/H/C/005735/II/0177) and 9.4 (EMEA/H/C/005735/X/0180) as well as to update the EU-RMP PART I according to the simplified posology implemented in the SmPC. Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.

3. Up-versioned 10.0 (content-wise similar to RMP version 9.5) submitted on 22 June 2023 (Eudralink) / 23 August 2023 (Gateway) covered procedures EMEA/H/C/005735/X/0176, EMEA/H/C/005735/II/0177 and EMEA/H/C/005735/X/0180. Approved CHMP Opinion: 22 June 2023, EC decision: 08 August 2023.

4. Version 10.1 submitted on 09 August 2023 (Gateway) and up-version 11.0 (content-wise similar to version 10.1) submitted on 13 October 2023 (Eudralink) / 21 December 2023 (Gateway) for procedure EMEA/H/C/005735/II/0188/G to update the Product Information with interim 6 months post Dose 2 and final CSR data of study C4591001 including corresponding RMP update to include editorial changes regarding the new strain XBB.1.5 as well as to remove studies/milestone commitments from aPV activities

related to the following completed studies: C4591001, BNT-162-01 and WI235284 (Emory). Approved CHMP Opinion: 26 October 2023, EC decision: 29 November 2023.

Version 11.1 submitted on 11 December 2023 (Gateway) to update the Product Information based on final CSR data of study C4591030 including corresponding RMP update to remove study C4591030 commitment and missing information related to "Interactions with other vaccines" (EMEA/H/C/005735/II/0201).

After DLP, the MAH submitted the following version of the EU-RMP:

5. Version 11.2 submitted on 22 December 2023 (Gateway - EMEA/H/C/005735/II/0206/G) to update the RMP regarding the removal of C4591012 RMP study/milestone commitments following submission of its final CSR, protocol amendments of studies C4591052 (PA #1) and C4591021 (PA #4) as well as the implementation of the following minor RMP changes:

   - C4591022 final CSR milestone update - from 31 December 2024 to 28 February 2026.
   - C4591051 final CSR milestone update from 31 January 2028 to 31 January 2027.
   - C4591024 final CSR milestone change from 30 June 2023 to 31 July 2024 as per PRAC's PAM-MEA-016.5 outcome.
   - C4591011 deletion from the RMP as per PRAC's PAM-MEA-009.1 outcome.
   - C4591009 interim CSR milestone change from 31 Oct 2023 to 30 April 2024 as per PRAC's PAM-MEA-037.5 outcome.
   - C4591044 restriction of RMP commitments to cohorts 2 and 3 only and change of final CSR milestone from 30 September 2023 to 30 June 2024 as per outcome of PRAC's PAM-MEA-059.3.
   - C4591036 final CSR milestone change from 14 November 2029 to 28 February 2031 as per PRAC's PAM-MEA-041.3 outcome.
   - Inclusion of the vaccine presentation COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection in plastic pre-filled syringe based on ongoing procedure EMEA/H/C/005735/II/0205.

16.2. Signal Evaluation

On 27 October 2023, SAHPRA (South Africa) communicated to Pfizer recommending that the MAH include the safety issue Mastitis/Breast swelling in the next BNT162b2 PBRER.

Response

Section 14, *Late-Breaking Information* of the PSUR #5 noted that a new signal "Mastitis/breast swelling" opened after the DLP of PSUR #5 and was ongoing. The signal has been closed in the reporting period of PSUR #6 (Table 37) and a summary of the evaluation of this signal is included in this PSUR #6 in Section 16.2.1 *Evaluation of Closed Signals*.

On 22 November 2023, SAHPRA (South Africa) communicated to Pfizer that the Pharmacovigilance Advisory Committee (PVC) noted that retinal vascular occlusion (RVO) was classified as an ongoing safety signal in PSUR 5 and recommended that *the MAH re-evaluates the signal, include an updated review in their next PSUR and submit the PSUR for evaluation*.

Response

The signal of "Retinal vascular occlusion" was ongoing in the reporting period of PSUR #5. The signal has been closed in the reporting period of PSUR #6 (Table 37) and the summary of the signal evaluation is provided in Section 16.2.1 *Evaluation of Closed Signals*.

Please refer to Table 37 for signals that were ongoing and closed during the reporting interval.

16.2.1. Evaluation of Closed Signals

Table 40 provides summary evaluations of the signals closed during the reporting period. Routine signal detection continues.

Table 40. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined Not to be Risks	
Mastitis/Breast swelling	Following communication from a regulatory authority (Australia TGA) on 05 July 2023 that the TGA's Pharmacovigilance Branch had assessed the risk of mastitis and breast swelling with tozinameran and concluded that there were sufficient safety grounds to request an update to the COMIRNATY PI with mastitis and breast swelling, the MAH evaluated this signal. Evaluation consisted of the review of preclinical toxicity studies that showed no signs of enlarged mammary glands, either clinically or microscopically in rats treated with up to 100 mcg BNT162b2 on Study Days 1, 8 and 15 and DART study data from dams treated with 30 mcg BNT162b2 21 and 14 days prior to mating and on gestation days 9 and 20 that showed no clinical signs of mastitis. The clinical trial database of blinded, placebo-controlled clinical trial data for studies C4591001, C4591031 substudy A and C4591015 was searched for reports of breast swelling, breast

Table 40. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	enlargement, breast oedema and mastitis. Four AE reports of mastitis were retrieved from the 3 studies: 1 from the BNT162b2 group and the remaining 3 from placebo groups. The literature search retrieved few articles apart from case reports (which are included in the post-authorization database review). The 2 most relevant articles described prospective cohort studies of lactating women who had been vaccinated with BNT162b2 or another mRNA COVID-19 vaccine; one focused on solicited AEs of relevance to lactating women (e.g. breast engorgement, mastitis) and found the incidence of mastitis/breast engorgement was not increased compared to published global estimates and axillary lymphadenopathy was not associated with mastitis or breast engorgement. The other prospective cohort study was smaller and focused on determination of Anti-SARS-CoV-2 antibody levels in milk and serum; in this study 1 mother developed mastitis and 1 developed a lump/swelling of the breast on the same side as the vaccination. The global safety database retrieved over 3100 AE reports of reports of breast swelling, breast enlargement, breast oedema and/or mastitis (breast swelling was the most frequently reported of the 4 PTs), the vast majority reported for BNT162b2 (original). Most of the reports were not medically confirmed and were reported by women between 31 and 50 years of age (80 cases in pregnant women) and a minority of cases described any kind of imaging study. The AE reports were examined for co-reported events of local vaccination reactions and lymphadenopathy in an attempt to determine if, for example, there were reports of local swelling severe enough to cause breast swelling or axillary lymphadenopathy contributing to breast swelling. A small minority of the reports (47) described local swelling/oedema that extended to the breast and a minority of reports (154) described ipsilateral lymphadenopathy and breast swelling however the chronology of the events was unclear. Disproportionality analyses did not indicate any statistical signal. Overall, based on the totality of the information available, a causal relationship between vaccination and mastitis/breast swelling in women could not be concluded. Routine pharmacovigilance will continue.
Sensorineural hearing loss	Following communication from a regulatory authority (Australia TGA) on 15 June 2023 that the TGA's MaVIS section was reviewing the signal of sensorineural hearing loss, the MAH evaluated this signal with review of medical literature, AE reports in the global safety database, clinical trial data and O/E analyses. Participants in the placebo-controlled, blinded periods of the pivotal, Pfizer-led clinical studies reported a low number of hearing loss events in the vaccination and placebo groups, with no meaningful difference apparent between the two groups. The literature, consisting of 13 articles, not including case reports, enabled evaluation of population level data. While preliminary disproportionality findings were positive in 2 articles, a 3rd study did not, and the remaining large observational studies were not supportive of an increased occurrence of hearing loss post-vaccination. No signal of disproportionate reporting was observed in the Pfizer safety database for any of the preferred terms included in the safety database search. The O/E analyses on deafness and sensorineural hearing loss supports that the reports of hearing loss and tinnitus in the stratified populations and doses are not greater than would be expected as background occurrences. The spontaneously reported cases received in the safety database are of variable quality. There are individual cases that report events close to the time of vaccination and provide detailed information without alternative explanations for hearing loss, however, due to the nature of sensorineural hearing loss and its myriad etiologies and the sheer number of vaccination doses administered globally, this is not unexpected, and the possibility of coincidental occurrence (of hearing loss and vaccination) cannot be discounted. The number of vaccine doses administered, and the subsequent number of adverse event reports received for the vaccine are unprecedented and raise the importance of population level data. Considering the totality of the data available, a causal association between Comirnaty and sensory neural hearing loss is not supported. Routine pharmacovigilance will continue.

Table 40. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Retinal vascular occlusion	Based on routine pharmacovigilance review of Comirnaty medical literature, retinal vascular occlusion was identified as a safety signal for further evaluation on 22 June 2023. Evaluation consisted of review of the available data from clinical trials, the global safety database, the published literature and an observed versus expected analysis. Two cases of retinal artery occlusion were reported in the blinded placebo-controlled period of the pivotal clinical study C4591001: one in the >23,000 participant placebo group and one in the >23,000 participant BNT162b2 group. The participant in the vaccine group had received BNT162b2 (dose 2) 12 weeks previously and had a medical history of risk factors for retinal artery occlusion; the event was assessed as unrelated to BNT162b2 by the investigator. A critical assessment of published large epidemiological studies was undertaken and one of the 5 studies concluded there may be an increased risk of retinal vascular occlusion after vaccination with a COVID-19 vaccine however, taken together, the literature did not provide strong evidence for an increased risk. The review of post-authorization data revealed the majority of retinal vascular occlusion events occurred in patients aged greater than 50 years, occurring most frequently in the 14 days after dose 1 and dose 2. Many cases were confounded by the presence of known risk factors in the medical history or provided insufficient detail on the clinical work-up to exclude other potential aetiologies. A small number of well-documented cases, with exclusion of the main known aetiologies, occurred with a temporal association to vaccination. Observed versus expected analyses were well below one for retinal arterial and retinal venous occlusion across all age stratifications and both the 21- and 42- day risk windows. Considering the totality of data in the context of global vaccine administration, the MAH did not consider that the currently available information supports a causal association between retinal vascular occlusion and Comirnaty. Routine pharmacovigilance will continue.
Menstrual irregularities	Following signal evaluations and follow-up query responses to EMA/PRAC for the signals heavy menstrual bleeding and amenorrhea in February 2022, the MAH considered that a separate overview of AE reports using a more inclusive MedDRA search strategy indicative of menstrual irregularities was warranted in February 2023. Menstrual irregularities were not widely reported in the clinical trials in adults, and no imbalance between BNT162b2 and placebo groups occurred in the placebo-controlled period of the large pivotal C4591001 study. There were many spontaneously reported cases, and most were non-medically confirmed and non-serious without trends toward events of clinical significance. There were notable differences in regional reporting, with the bulk of reports from the UK and Western European countries and significantly fewer from the US, Australia and Japan, which are countries with robust pharmacovigilance systems and which account for an overall high proportion of ICSRs received in the global safety database. Review of the accumulating literature, supported by epidemiology, focused on studies robustly conducted but also included a look at other studies such as cross-sectional surveys based on convenience samples that generally did not have comparator groups or adjusted analyses. The literature provided reassurance that menstrual abnormalities reported following vaccination do not appear to be clinically consequential. Study observations included: weak/small observations of temporary changes in menstrual cycle length, inconsistent (some point toward, and others do not) changes in the length of reported menses, inconsistent (some point toward, and others do not) observations of heavier than usual menstrual bleeding. The difficulties of discerning causality of menstrual irregularities to the vaccine have been discussed in other reviews and evaluation documents produced by Pfizer and include that menstrual irregularities are common and may be multifactorial in etiology. Based on the totality of information, including the regional reporting differences, lack of signal in the pivotal studies and inconsistencies in the medical literature, the strength and quality of evidence was not

Table 40. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	supportive of a causal association between menstrual irregularities and Comirnaty. Routine pharmacovigilance will continue.
Important Risks	
None	
Risks Not Categorised as Important	
None	

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 41. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Pulmonary embolism	Following a request from a regulatory authority (Saudi FDA) on 27 October 2023, a signal evaluation including review of post-authorization AE reports, medical literature, clinical study data, non-clinical data and O/E analyses was conducted. The signal was closed by the MAH as "not a risk" on 10 January 2024 (after the PSUR #6 DLP).
Post-menopausal haemorrhage	Following a request from a regulatory authority (EMA/PRAC) on 30 October 2023, a signal evaluation including review of post-authorization AE reports, medical literature, clinical study data, non-clinical data and O/E analyses was conducted. The signal was closed by the MAH as "not a risk" on 22 December 2023 (after the PSUR #6 DLP). EPITT No. 19989

16.3. Evaluation of Risks and New Information

Evaluation of new information regarding important identified and 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

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 843 potentially relevant cases of myocarditis and pericarditis: 482 cases reported myocarditis and 432 cases reported pericarditis (in 71 of these 843 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 interval, there were no significant new safety data received from literature sources.

Risk Assessment of New Information

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

This risk and appropriate action to take is communicated in the BNT162b2 CDS, in:

- Section 4.4, Special warnings and precautions for use - Myocarditis and pericarditis: "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".[62]

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

- Appendices A and B.

This risk will continue to be monitored through routine and additional pharmacovigilance activities as per EU-RMP v. 9.0 adopted on 10 November 2022.

16.3.1.1.1. Important Identified Risks – Myocarditis

Search criteria - 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, no cases were retrieved in the PSUR #5.

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

Post-Authorisation Data

- Number of cases: 482 (original [424], bivalent Omi BA.1 [8], bivalent Omi BA.4/BA.5 [15], multivalent NOS [9], monovalent Omi XBB.1.5 [26]; 0.5% of 107,046 cases, the total PM dataset), compared to 711 cases (1.0%) retrieved in the PSUR #5.
- Country/region of incidence (≥10): Germany (103), New Zealand (78), Canada (50), UK (42), Japan (39), Australia (38), France (25), US (22), Austria (17), Italy (10).
- MC cases (259), NMC cases (223).
- Subjects' gender: female (190), male (272) and unknown (20).
- Subjects' age in years: n = 432, range: 1.25 – 97, mean: 39.7, median: 35.5.
- Medical history (n = 154); the most frequently (≥10) reported medical conditions included Hypertension (21), Asthma, Obesity (12 each).
- COVID-19 Medical history (n = 30): COVID-19 (23), Suspected COVID-19 (4), Coronavirus infection (3).
- Co-suspect medications (≥2): COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), elasomeran (3 each).
- Number of relevant events: 491.
- Relevant event seriousness: serious (491).
- Reported relevant PTs: Myocarditis (404), Myopericarditis (77), Carditis (7), Autoimmune myocarditis, Chronic myocarditis, Eosinophilic myocarditis (1 each).
- Relevant event outcome: fatal (23), resolved/resolving (172), resolved with sequelae (31), not resolved (121), unknown (144).
- Risk factors: Of the 482 cases reporting events indicative of myocarditis, 259 cases (53.7%) were MC. Of the 482 cases, in 176 cases (36.5% 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. In 113 cases (23.4%) the cases were confounded by co-reported events indicative of an alternate aetiology, 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. In 323 cases (67.0%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

***Age-stratified data*[63]**

Subjects aged 6 months through <5 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 1; (original [1]; 0.001% of 107,046 cases, the total PM dataset, 0.3% of the 398 subjects aged 6 month to less than 5 years), no cases were retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (1).
- Subjects' age: 15 months
- Medical history: None.
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Co-reported PTs: Pulmonary oedema, infant irritability, Respiratory depression, Hypertension, Dehydration, Ejection fraction decreased (1 each).

Myocarditis relevant data in this subgroup of subjects are summarised in the Table 42 below.

Table 42. Myocarditis in Subjects Aged 6 months through <5 years (N = 1)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	0	1	0
	No	0	0	0
Relevant PT[a]	Myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	0	1	0
	No	0	0	0
Relevant suspect dose	Dose unknown	0	1	0
Vaccine Presentation	Original	0	1	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	0
	Multivalent NOS	0	0	0
	Monovalent Omi XBB.1.5	0	0	0

[63] Cases where the age was reported only as:

- "Adolescent" (7 cases) were evaluated in the overall and in the 16-17 years age groups, and

- "Adult" (12 cases) were evaluated in the overall and in the Age Unknown age group;

Table 42. Myocarditis in Subjects Aged 6 months through <5 years (N = 1)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 1	≤ 24 hours	0	0	0
	1-5 days	0	0	0
	6-13 days	0	0	0
	14-21 days	0	1	0
Event Outcome	Fatal	0	0	0
	Not resolved	0	1	0
	Resolved	0	0	0
	Resolving	0	0	0
	Resolved with sequelae	0	0	0
	Unknown	0	0	0
Duration of event[b]	Unknown	0	1	0

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

Fatal cases: None

Subjects aged 5 through <12 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 4 (original [3], monovalent Omi XBB.1.5 [1]; 0.004% of 107,046 cases, the total PM dataset, 0.2% of the 1701 subjects aged 5-11 years), compared to 2 cases (0.003 %) retrieved in the PSUR #5.
- Country/region of incidence: Canada, Japan, New Zealand, and US (1 each).
- Subjects' age in years: n = 4, range: 5 – 8, mean: 6.5, median: 6.5.
- Medical history (n = 1): Abdominal pain, Arrhythmia, Atrioventricular block, Cardiac failure, Ejection fraction decreased, Hospitalisation, Keloid scar, Lung assist device therapy, Myocarditis, Rash, Somnolence, and Vomiting (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs (2 cases): Arthralgia, Atrioventricular block, Bradycardia, Bundle branch block, Chest discomfort, Inappropriate schedule of product administration, Nasal disorder, Oropharyngeal pain, Palpitations, Pyrexia (1 each).

Myocarditis relevant data in this subgroup of subjects are summarised in the Table 43 below.

Table 43. Myocarditis in Subjects Aged 5 through <12 years (N = 4)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	1	0
	No	0	1	0
Relevant PT[a]	Myocarditis	2	1	0
	Myopericarditis	0	1	0
Hospitalisation required/prolonged	Yes	1	1	0
	No	1	1	0
Relevant suspect dose	Dose 1	0	1	0
	Dose 2	1	1	0
	Dose unknown	1	0	0
Vaccine Presentation	Original	1	2	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	0
	Multivalent NOS	0	0	0
	Monovalent Omi XBB.1.5	1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 2	≤ 24 hours	0	0	0
	1-5 days	1	0	0
	6-13 days	1	0	0
Event Outcome	Fatal	0	0	0
	Not resolved	0	0	0
	Resolved	1	2	0
	Resolving	1	0	0
	Resolved with sequelae	0	0	0
	Unknown	0	0	0
Duration of event[b] n = 1	0-7 days	0	0	0
	8-21 days	1	0	0
	21-60 days	0	0	0

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

Fatal cases: None

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 36 (original [34], bivalent Omi BA.4/BA.5 [1], multivalent NOS [1]; 0.03% of 107,046 cases, the total PM dataset, 1.5% of the 2452 subjects aged 12-15 years), compared to 26 cases (0.04%) retrieved in the PSUR #5.
- Country/region of incidence (≥3): Canada (17), Japan (6), New Zealand (5), Brazil (3). The remaining 5 cases were distributed among 5 countries.
- Subjects' age in years: n = 36, range: 12 – 15, mean: 14.4, median: 15.0.

- Medical history (n = 11); the most frequently (≥2) reported medical conditions included Asthma (4), Attention deficit hyperactivity disorder (3), and Obesity (2).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥3): Chest pain (14), Dyspnoea, Pyrexia (8 each), Fatigue (6), Abdominal pain, Vomiting (4 each), Chest discomfort, Headache, Hyperhidrosis, Inappropriate schedule of product administration, Myalgia, Palpitations, Pleuritic pain (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 44 below.

Table 44. Myocarditis in Subjects Aged 12 – 15 years (N = 36)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	12	1
	No	3	17	0
Relevant PT[a]	Myocarditis	6	21	1
	Myopericarditis	0	8	0
Hospitalisation required/prolonged	Yes	3	14	0
	No	3	15	1
Relevant suspect dose	Dose 1	0	10	0
	Dose 2	4	12	0
	Dose 3	1	1	0
	Dose 4	0	1	0
	Dose unknown	1	5	1
Vaccine Presentation	Original	6	27	1
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	1	0
	Multivalent NOS	0	1	0
	Monovalent Omi XBB.1.5	0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 22	≤ 24 hours	0	6	0
	1-5 days	2	8	0
	6-13 days	0	2	0
	14-21 days	0	1	0
	22-31 days	0	1	0
	32-60 days	0	1	0
	61-180 days	0	0	0
	181-365 days	1	0	0
	> 365 days	0	0	0
Event Outcome	Fatal	0	0	0
	Not resolved	1	7	0
	Resolved	2	11	0
	Resolving	0	5	0
	Resolved with sequelae	1	1	0
	Unknown	2	5	1
Duration of event[b] n = 2, median: NA	0-7 days	0	2	0

Table 44. Myocarditis in Subjects Aged 12 – 15 years (N = 36)

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

Fatal cases: None

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 37 (original [37]; 0.03% of 107,046 cases, the total PM dataset, 1.7% of the 2237 subjects aged 16-17 years), compared to 38 cases (0.05%) retrieved in the PSUR #5.
- Country/region of incidence (≥2): Australia (12), Japan (5), China, Germany (4 each), New Zealand (3), Austria (2). The remaining 7 cases were distributed among 7 countries.
- Subjects' age in years: n = 30, range: 16 – 17, mean: 16.6, median: 17.0.
- Medical history (n = 8); Attention deficit hyperactivity disorder, Childhood asthma, Delayed puberty, Developmental delay, Epstein-Barr virus antibody, Food allergy, Hospitalisation, Immunodeficiency common variable, Migraine, Non-tobacco user, Obesity, Orthostatic hypotension (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: elasomeran (1).
- Most frequently co-reported PTs (≥2): Chest pain, Electrocardiogram ST segment elevation, Electrocardiogram T wave inversion, Headache, Tachycardia, Troponin increased (4 each), Fatigue, Magnetic resonance imaging heart, Nausea, Pyrexia (3 each), Dyspnoea, Palpitations, Pericardial effusion, and Tricuspid valve incompetence, Vomiting (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 45 below.

Table 45. Myocarditis in Subjects Aged 16 – 17 years (N = 37)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	25	5
	No	4	1	0
Relevant PT[a]	Myocarditis	6	25	4
	Myopericarditis	0	2	1
Hospitalisation required/prolonged	Yes	2	13	1
	No	4	14	4

Table 45. Myocarditis in Subjects Aged 16 – 17 years (N = 37)

Relevant suspect dose	Dose 1	0	5	0
	Dose 2	2	11	1
	Dose 3	1	5	4
	Dose unknown	3	5	0
Vaccine Presentation	Original	6	26	5
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 15	≤ 24 hours	1	2	0
	1-5 days	2	6	0
	6-13 days	0	0	0
	14-21 days	0	1	0
	22-31 days	1	0	0
	32-60 days	0	0	0
	61-180 days	1	0	0
	181-365 days	1	0	0
	> 365 days	0	0	0
Event Outcome	Fatal	0	0	0
	Not resolved	1	0	0
	Resolved	1	16	0
	Resolving	0	4	0
	Resolved with sequelae	0	0	0
	Unknown	4	5	5
Duration of event[b] n = 4, median: 11 days	0-7 days	0	0	0
	8-60 days	1	2	0
	61-90 days	0	0	0
	91-180 days	0	1	0

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

Fatal cases: None[64]

Subjects aged 18 – 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 62 (original [60], monovalent Omi XBB.1.5 [2]; 0.06% of 107,046 cases, the total PM dataset, 0.7% of the 8288 subjects aged 18-24 years), compared to 89 cases (0.12%) retrieved in the PSUR #5.
- Country/region of incidence (≥3): Germany (22), New Zealand (12), France (9), Austria (3). The remaining 16 cases were distributed among 10 countries.

[64] Duplicate cases were removed.

- Subjects' age in years: n = 62, range: 18 – 24, mean: 20.8, median: 20.5.
- Medical history (n = 16): the most frequently (≥2) reported medical conditions included Influenza, Non-tobacco user, Seasonal allergy (2 each).
- COVID-19 Medical history (n = 5): COVID-19 (5).
- Co-suspect medications: cocaine, elasomeran, influenza vaccine inact split 4V (1 each).
- Most frequently co-reported PTs (≥3): Fatigue (9), Pyrexia (7), Dyspnoea (6), Angina pectoris, Arrhythmia, Chest pain, Headache, Interchange of vaccine products, Tachycardia (4 each), Chest discomfort, Chills, Inappropriate schedule of product administration, Performance status decreased, Pulmonary embolism, Vaccination site pain (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 46 below.

Table 46. Myocarditis in Subjects Aged 18 – 24 years (N = 62)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	6	23	0
	No	13	20	0
Relevant PT[a]	Carditis	2	0	0
	Myocarditis	15	36	0
	Myopericarditis	2	8	0
Hospitalisation required/prolonged	Yes	9	25	0
	No	10	18	0
Relevant suspect dose	Dose 1	1	6	0
	Dose 2	9	15	0
	Dose 3	4	7	0
	Dose unknown	5	15	0
Vaccine Presentation	Original	19	41	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	0
	Multivalent NOS	0	0	0
	Monovalent Omi XBB.1.5	0	2	0

Table 46. Myocarditis in Subjects Aged 18 – 24 years (N = 62)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 35	≤ 24 hours	3	7	0
	1-5 days	1	12	0
	6-13 days	1	1	0
	14-21 days	0	1	0
	22-31 days	0	0	0
	32-60 days	0	1	0
	61-180 days	2	2	0
	181-365 days	1	0	0
	> 365 days	0	3	0
Event Outcome	Fatal	2	1	0
	Not resolved	5	8	0
	Resolved	4	9	0
	Resolving	5	8	0
	Resolved with sequelae	0	1	0
	Unknown	3	17	0
Duration of event[b] n = 4, median: 63 days	0-7 days	0	1	0
	8-60 days	0	0	0
	61-90 days	0	1	0
	91-180 days	1	1	0

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

Fatal cases (3):

An 18-year-old female subject, dose 2 (original), NMC, US:

- Medical history: COVID-19.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myocarditis, Dilated cardiomyopathy, Multiple organ dysfunction syndrome, Encephalopathy, Blood loss anaemia, Embolism venous, Necrosis, Interstitial lung disease, Pulmonary alveolar haemorrhage, Pulmonary artery thrombosis, Acute respiratory failure, Acute pulmonary oedema, Aspiration, Acute kidney injury, Pulmonary embolism, Right ventricular failure, Shock, Acidosis, Intestinal ischaemia, Hypokalaemia, Myocardial infarction, Brain oedema, Gastrointestinal haemorrhage, Multisystem inflammatory syndrome in children, Cardiomegaly, Eosinophilia, Oedema, Neutrophil count abnormal, Pulmonary septal thickening, Bronchial wall thickening, Coagulopathy, Blood thyroid stimulating hormone increased, Hypoproteinaemia, Hypernatraemia, Hypertransaminasaemia, Hyperglycaemia, Dyspnoea, Hypersomnia, Fatigue, Nausea, Pain, Orthostatic hypotension, Weight decreased, Haemorrhage, Brain injury, Circulatory collapse, Myocardial ischaemia.
- Time to onset (myocarditis): Not reported.
- Autopsy: The autopsy reported that the ventricular myocardium showed patchy hypereosinophilia, myocyte contraction band necrosis, and interstitial edema with a mild

acute and chronic inflammatory infiltrate. The right ventricular myocardium shows ional scattered interstitial and perivascular neutrophil aggregates.

- Comment: There were multiple events (not associated with myocarditis) that resulted in a fatal outcome. Additionally, limited information was provided regarding the subject's medical history and clinical course of fatal events limits a meaningful causality assessment in this case.

A 19-year-old male subject, dose 2 (original), NMC, US:

- Medical history: Not reported.
- Co-suspect medications: none.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Myocarditis, Pericarditis.
- Time to onset (myocarditis): Not reported.
- Causes of death: As mentioned above, the events coded to the PTs Myocarditis, Pericarditis. It was not reported if an autopsy was performed.
- Comment: Limited information was available on the diagnosis of myocarditis, clinical course of the fatal events, subjects' medical history and concomitant medications, precluding a meaningful causality assessment.

A 23-year-old female subject, dose 2 (original), NMC, Australia:

- Medical history: Asthma, Influenza
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Asthma, Myocarditis, Cardiac arrest, Swelling face, Generalised oedema.
- Time to onset (myocarditis): Not reported.
- Autopsy: The reporter stated the following: "vaccine induced myocarditis in her heart tissue, her heart was almost double its normal size, the oral steroids, and high doses of inhaled steroids, were enough to trigger her cardiac arrest".
- Comment: The subject with a medical history of ongoing asthma, received two doses of vaccine. Almost one and a half months after the second dose, the patient developed shortness of breath. She received inhaler, oral steroids, a preventer and reliever (details not provided) for treatment. The patient visited emergency services for the asthma aggravation with no cardiac or other investigations performed. It was reported that patient administered high doses of Ventolin (albuterol), experienced swollen face and oedema and 3 days later the patient died due to the above-mentioned events during an asthma attack which could not be resuscitated. The cause of death was considered asthma. The autopsy as per the reporter showed vaccine induced myocarditis in her heart tissue, and "her heart was almost double it's normal size, the oral steroids, and high doses of inhaled steroids, were enough to trigger her cardiac arrest". In consideration to long period of

time post-vaccination, and the asthma as the trigger of the clinical course and fatal outcome, a role of the vaccine is not supported.

Subjects aged 25 – 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 32 (original [29], bivalent Omi BA.4/BA.5 [1], multivalent NOS [1], monovalent Omi XBB.1.5 [1]; 0.03% of 107,046 cases, the total PM dataset, 0.4% of the 8625 subjects aged 25-29 years), compared to 61 cases (0.08%) retrieved in the PSUR #5.
- Country/region of incidence (≥2): Germany (10), New Zealand (5), Canada (3), Austria, France, Japan, US (2 each). The remaining 6 cases were distributed among 6 countries.
- Subjects' age in years: n = 32, range: 25 – 29, mean: 26.6, median: 26.0.
- Medical history (n = 8); the most frequently (≥2) reported medical condition included Seasonal allergy (2).
- COVID-19 Medical history (n = 1): Coronavirus infection (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥3): Dyspnoea (5), Fatigue, Pyrexia (4 each), Chest pain, Dizziness, Paraesthesia, Pericardial effusion, Tachycardia (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 47 below.

Table 47. Myocarditis in Subjects Aged 25 – 29 years (N = 32)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	5	10	1
	No	7	9	0
Relevant PT[a]	Carditis	1	0	0
	Myocarditis	8	13	1
	Myopericarditis	3	6	0
Hospitalisation required/prolonged	Yes	5	8	1
	No	7	11	0
Relevant suspect dose	Dose 1	2	5	1
	Dose 2	3	7	0
	Dose 3	3	1	0
	Dose 4	0	1	0
	Dose unknown	4	5	0
Vaccine Presentation	Original	12	17	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	1	0
	Multivalent NOS	0	1	0
	Monovalent Omi XBB.1.5	0	0	1

Table 47. Myocarditis in Subjects Aged 25 – 29 years (N = 32)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 14	≤ 24 hours	4	1	0
	1-5 days	0	2	0
	6-13 days	2	0	0
	14-21 days	0	1	0
	22-31 days	0	1	0
	32-60 days	0	2	0
	61-180 days	0	1	0
	181-365 days	0	0	0
	> 365 days	0	0	0
Event Outcome	Fatal	0	0	0
	Not resolved	7	5	0
	Resolved	1	6	1
	Resolving	1	2	0
	Resolved with sequelae	1	2	0
	Unknown	2	4	0
Duration of event[b] n = 1	0-7 days	0	1	0

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

Fatal cases: None

Subjects aged 30 – 39 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 75 (original [73], bivalent Omi BA.4/BA.5 [1], monovalent Omi XBB.1.5 [1]; 0.07% of 107,046 cases, the total PM dataset, 0.4% of the 19,265 subjects aged 30-39), compared to 112 cases (0.2%) retrieved in the PSUR #5.
- Country/region of incidence (≥2): Germany, New Zealand (18 each), Canada (8), Australia, Austria, UK (5 each), France (4), Belgium, Finland (2 each). The remaining 8 cases were distributed among 8 countries.
- Subjects' age in years: n = 75, range: 30 – 39, mean: 34.3, median: 34.0.
- Medical history (n = 17); the most frequently (≥2) reported medical conditions included Seasonal allergy (3), Asthma, Migraine, Obesity (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: elasomeran, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), sodium chloride (1 each).

- Most frequently co-reported PTs (≥5): Chest pain (16), Dyspnoea, Fatigue (15 each), Palpitations (13), Chest discomfort (12), Dizziness, Tachycardia (6 each), Pyrexia (5).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 48 below.

Table 48. Myocarditis in Subjects Aged 30 – 39 years (N = 75)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	14	25	0
	No	17	19	0
Relevant PT[a]	Carditis	0	2	0
	Myocarditis	28	33	0
	Myopericarditis	5	11	0
Hospitalisation required/prolonged	Yes	11	21	0
	No	21	23	0
Relevant suspect dose	Dose 1	6	10	0
	Dose 2	11	15	0
	Dose 3	4	2	0
	Dose 4	1	0	0
	Dose unknown	9	17	0
Vaccine Presentation	Original	30	43	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	1	0	0
	Multivalent NOS	0	0	0
	Monovalent Omi XBB.1.5	0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 43	≤ 24 hours	7	10	0
	1-5 days	3	7	0
	6-13 days	2	2	0
	14-21 days	0	3	0
	22-31 days	0	1	0
	32-60 days	0	2	0
	61-180 days	1	2	0
	181-365 days	0	1	0
	> 365 days	1	1	0
Event Outcome	Fatal	0	2	0
	Not resolved	12	13	0
	Resolved	9	17	0
	Resolving	1	5	0
	Resolved with sequelae	3	3	0
	Unknown	8	6	0
Duration of event[b] n = 4, median: 159 days	0-60 days	1	0	0
	61-120 days	0	0	0
	121-180 days	1	0	0
	181-240 days	0	1	0
	>240 days	1	0	0

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

Fatal cases (2):

A 34-year-old male subject, dose 2 (original), NMC, Canada:

- Medical history: Not reported.
- Co-suspect medications: None.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Myocarditis, Arrhythmia (1 each).
- Time to onset (myocarditis): Not reported; fatal outcome occurred 4 months after the last dose.
- Causes of death: Clinical autopsy showed malignant cardiac dysrhythmia due to lymphohistiocytic myocarditis.
- Comment: Cause of death was attributed to cardiac arrhythmia secondary to the chronic effects of myocarditis "which would have likely been present for many weeks to months" as per the reporter. Absent any complaints or symptoms during the 4 months since the last vaccine dose, and in view of the fibrotic changes in the myocardium, it is not possible to determine fully the role of the vaccine in inducing this outcome.

A 37-year-old male subject, dose 2 (original), NMC, Germany:

- Medical history: Not reported.
- Co-suspect medications: Not reported.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): Not reported.
- Causes of death: Myocarditis. It was not reported if an autopsy was performed.
- Comment: Due to limited information on concomitant medications, medical history, clinical course of event, the role of vaccine in inducing myocarditis is un-assessable.

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 192 (original [151], bivalent Omi BA.1 [7], bivalent Omi BA.4/BA.5 [8], multivalent NOS [6], monovalent Omi XBB.1.5 [20]; 0.2% of 107,046 cases, the total PM dataset, 0.3% of the 57,136 subjects ⩾ 40 years), compared to 303 cases (0.4%) retrieved in the PSUR #5.
- Country/region of incidence (≥5): Germany (42), New Zealand (30), UK (28), Japan (21), Canada (15), US (12), Australia (11), France (10), and Sweden (5). The remaining 18 cases were distributed among 10 countries.
- Subjects' age in years: n = 192, range: 40 – 97, mean: 59.4, median: 57.0.

- Medical history (n = 85); the most frequently (≥3) reported medical conditions included Hypertension (19), Obesity (6), Arthritis, Fibromyalgia, Tobacco user (5 each), Asthma, Diabetes mellitus, Rheumatoid arthritis, Type 2 diabetes mellitus (4 each), Arrhythmia, Benign prostatic hyperplasia, Cardiac failure, Coronary artery disease, Drug hypersensitivity, Dyslipidaemia, Gastrooesophageal reflux disease, Immunodeficiency, Myocardial ischaemia, Non-tobacco user, Pain (3 each).
- COVID-19 Medical history (n = 19): COVID-19 (14), Suspected COVID-19 (3), Coronavirus infection (2).
- Co-suspect medications (≥1): andusomeran, bisoprolol, codeine, COVID-19 vaccine inact (VERO) CZ02, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), elasomeran, imelasomeran, hydromorphone, influenza vaccine, influenza vaccine inact SAG 3V, nivolumab, pregabalin, sumatriptan (1 each).
- Most frequently co-reported PTs (≥10): Dyspnoea (50), Fatigue (42), Chest pain (40), Palpitations (33), Pyrexia (23), Chest discomfort, Tachycardia (21 each), Cardiac failure (18), Arrhythmia (15), Interchange of vaccine products (13), Dizziness (12), Headache, Malaise, Myalgia (10 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 49 below.

Table 49. Myocarditis in Subjects Aged ≥40 years (N = 192)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	50	54	0
	No	51	36	1
Relevant PT[a]	Autoimmune myocarditis	1	0	0
	Chronic myocarditis	0	1	0
	Eosinophilic myocarditis	1	0	0
	Myocarditis	90	74	1
	Myopericarditis	10	16	0
Hospitalisation required/prolonged	Yes	35	41	1
	No	66	49	0
Relevant suspect dose	Dose 1	29	21	0
	Dose 2	12	22	0
	Dose 3	18	9	0
	Dose 4	7	12	0
	Dose 5	3	7	0
	Dose 6	3	0	0
	Dose unknown	29	19	1
Vaccine Presentation	Original	80	70	1
	Bivalent Omi BA.1	2	5	0
	Bivalent Omi BA.4/BA.5	3	5	0
	Multivalent NOS	3	3	0
	Monovalent Omi XBB.1.5	13	7	0

Table 49. Myocarditis in Subjects Aged ≥40 years (N = 192)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 109	≤ 24 hours	12	11	0
	1-5 days	19	14	0
	6-13 days	8	6	0
	14-21 days	3	7	0
	22-31 days	3	2	0
	32-60 days	6	2	0
	61-180 days	5	3	0
	181-365 days	2	1	0
	> 365 days	0	5	0
Event Outcome	Fatal	4	10	0
	Not resolved	27	24	0
	Resolved	15	12	0
	Resolving	16	12	0
	Resolved with sequelae	7	10	1
	Unknown	33	23	0
Duration of event[b] n = 8, median: 57 days	0-7 days	2	1	0
	8-21 days	0	0	0
	21-60 days	2	0	0
	61-180 days	0	1	0
	181-365 days	1	0	0
	>365 days	0	1	0

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

Fatal cases (14 cases):

Of the 14 cases, there were 13 MC cases and 1 NMC case.

A 60-year-old male subject, dose 3 (original), MC, Slovenia:

- Medical history: Smoking.
- Co-suspect medications: None.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Cardiac failure, Chronic myocarditis (1 each).
- Time to onset (myocarditis): 438 days.
- Causes of death: Clinical autopsy showed immediate cause of death was failure of a chronically diseased, hypertrophic and moderately dilated heart. The primary cause of heart failure and death was chronic granulomatous myocarditis, with consequent disseminated fibrosis in the myocardium of the left ventricle.
- Comment: Cause of death was attributed to cardiac failure secondary to the chronic effects of myocarditis. In view of the chronic cardiac conditions and the long period of time post-vaccination, the causal role of the vaccine is not supported.

A 64-year-old male subject, dose 4 (original, Bivalent Omi BA.4/BA.5), MC, Germany:

- Medical history: Arteriosclerosis, Cardiac failure, and Hypertension.

- Co-suspect medications: None.
- Concomitant medications: None.
- PTs with fatal outcome: Myopericarditis, Myocardial infarction, Arteriosclerosis coronary artery, Arteriosclerosis, Hypertension, Acute myocardial infarction.
- Time to onset (myocarditis): 295 days.
- Causes of death: Autopsy diagnoses showed stenosed coronary artery sclerosis with myocardial infarction scar in the presence of general arteriosclerosis and hypertension, lvmphohistiocytic myopericarditis with diffuse fine reticular myocardial fibrosis, interstitial edema, myocytolysis and Z-band damage, and interstitial and pericapillary lymphohistiocytic infiltration (including in the pericardium). Detection of SARS-CoV-2 spike protein subunit in endothelial cells of interstitial capillaries in myo- and pericardium.
- Comment: The long latency period and the presence of co-reported cardiac ischaemic events, make the myocarditis diagnosis unlikely related to the vaccine.

A 41-year-old male subject, dose 1 (original), MC, Netherlands:

- Medical history: Not reported
- Co-suspect medications: None
- Concomitant medications: None.
- PTs with fatal outcome: Myocarditis
- Time to onset (myocarditis): 24 months
- Causes of death: It was not reported if an autopsy was performed.
- Comment: The long latency period makes the myocarditis diagnosis unlikely related to the vaccine.

A 76-year-old male subject, dose 3 (original), MC, Spain:

- Medical history: Parkinson's disease.
- Co-suspect medications: None.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Encephalitis post immunization, Parkinson's disease, Pneumonia aspiration, Myocarditis, Vasculitis (1 each).
- Time to onset (myocarditis): Not reported.
- Causes of death: Clinical autopsy showed recurrent aspiration pneumonia. In addition, necrotizing encephalitis and vasculitis were considered to be major contributors to death. Furthermore, there was mild lympho-histiocytic myocarditis with fine-spotted myocardial fibrosis as well as systemic arteriosclerosis, which will have also contributed to the deterioration of the physical condition.
- Comment: Based on the current available limited information provided in the case, the reported events appear to be a more likely consequence of the aspiration pneumonia in this patient.

A 68-year-old female subject, dose 3 (original), MC, Japan:

- Medical history: None.
- Co-suspect medications: None.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Arrhythmia, Myocarditis (1 each).
- Time to onset (myocarditis): 9 days.
- Causes of death: Clinical autopsy revealed no inflammatory findings of myocardial tissue. Softening of the left and right ventricles was noted with reduced muscle tension.
- Comment: In view of the autopsy showing absence of inflammatory findings, a diagnosis of myocarditis is not supported in this case.

A 41-year-old female subject, dose 2 (original), MC, Malaysia:

- Medical history: Hypertension, Gastritis.
- Co-suspect medications: None.
- Concomitant medications: Amlodipine.
- PTs with fatal outcome: Chest pain, Loss of consciousness, Ventricular fibrillation, Eosinophilic myocarditis (1 each).
- Time to onset (myocarditis): 41 days.
- Causes of death: Clinical autopsy revealed cause of death was eosinophilic myocarditis.
- Comment: Although the patient had a relevant cardiovascular condition (hypertension) and the latency from vaccination is long, a causal role of the vaccine cannot be excluded.

An 82-year-old male subject, dose 2 (original), MC, Japan:

- Medical history: Benign prostatic hyperplasia, Diabetes mellitus, Gastrooesophageal reflux disease.
- Co-suspect medications: None.
- Concomitant medications: Famotidine, metformin, mitiglinide/voglibose, sitagliptin, tamsulosin.
- PTs with fatal outcome: Myocarditis, Cardio-respiratory arrest, Acute myocardial infarction, Cardiac arrest (1 each).
- Time to onset (myocarditis): 15 days.
- Causes of death: Clinical autopsy was not performed. The above-mentioned events were reported as the cause of death.
- Comment: The individual role of vaccine in the development of fatal events was confounded by patient's medical history and elderly age.

A 77-year-old male subject, dose 4 (original), MC, Japan:

- Medical history: Dyslipidaemia, Hypertension, Hyperuricaemia.
- Co-suspect medications: None.
- Concomitant medications: None.
- PTs with fatal outcome: Cardio-respiratory arrest, Ventricular fibrillation, Kounis syndrome, Allergy to vaccine, Arteriospasm coronary, Sudden cardiac death, Prostate

cancer, Pulmonary congestion, Liver disorder, Aortic arteriosclerosis, Arrhythmia, Endocarditis, Myocarditis, Cardiac arrest (1 each).
- Time to onset (myocarditis): 1 day.
- Causes of death: Clinical autopsy showed brown tone colour variation in the endocardium side, linearly in some parts. Minor congestion was observed in the tissue. Infiltration of allergic mast cells was present. The above-mentioned events were reported as the cause of death.
- Comment: This patient reports a complex medical history and clinical course, and importantly, the occurrence of an ischemic cardiomyopathy, which is a criterion of exclusion for myocarditis.

A 49-year-old female subject, dose 1 (original), MC, Australia:

- Medical history: Not reported.
- Co-suspect medications: Codeine, hydromorphone, pregabalin.
- Concomitant medications: None.
- PTs with fatal outcome: COVID-19 pneumonia, Accidental overdose, Cardiac failure, Hypotension, Myocarditis, Sepsis, Toxicity to various agents, Troponin increased.
- Time to onset (myocarditis): Not reported.
- Causes of death: It was not reported if autopsy was performed.
- Comment: Based on the limited information provided, the patient's fatal outcome is more likely the result of the opioid overdose.

A 79-year-old male subject, dose 1 (Monovalent Omi XBB.1.5), MC, Japan:

- Medical history: Atrial fibrillation, Myocardial infarction.
- Co-suspect medications: Influenza vaccine.
- Concomitant medications: None.
- PTs with fatal outcome: Anaphylactic reaction, Cardiac arrest, Myocarditis, Febrile convulsion (1 each).
- Time to onset (myocarditis): Same day.
- Causes of death: Autopsy was not performed.
- Comment: The patient primarily experienced anaphylaxis and febrile convulsions after administration of influenza vaccine, which occurred over 9 hours from the administration of the COVID-19 vaccine. Myocarditis was reported due to suspicion of occurrence given the patient's history of myocardial infarction, but there were no investigations conducted to confirm a myocarditis occurred. In view of limited information offered in the case, and temporal association of the anaphylaxis with the influenza vaccination, the role of the COVID-19 vaccine is unassessable..

A 72-year-old male subject, dose 3 (original), MC, Japan:

- Medical history: Gastric cancer.
- Co-suspect medications: Nivolumab.
- Concomitant medications: None.
- PTs with fatal outcome: Myocarditis (1).

- Time to onset (myocarditis): 3 days.
- Causes of death: Myocarditis. Autopsy was not performed.
- Comment: The event myocarditis was confounded by the presence of co-suspect medication (nivolumab), which is known to increase the risk of myocarditis.

A 67-year-old female subject, no data, MC, Japan:

- Medical history: Not reported.
- Co-suspect medications: None.
- Concomitant medications: None.
- PTs with fatal outcome: Intestinal ischaemia; Myocarditis (1 each).
- Time to onset (myocarditis): 22 days.
- Causes of death: It was not reported if autopsy was performed.
- Comment: Due to limited information on concomitant medications, clinical course of the events, and autopsy details, the role of vaccine in inducing myocarditis is unassessable.

A 97-year-old male subject, dose 5 (original), MC, Japan:

- Medical history: Heart rate abnormal, Myelodysplastic syndrome, Neoplasm malignant, Supraventricular tachycardia.
- Co-suspect medications: None.
- Concomitant medications: Pilsicainide, verapamil.
- PTs with fatal outcome: Bradyarrhythmia, Bradycardia, Cardiac arrest, Cardiac failure, Cardio-respiratory arrest, Circulatory collapse, Multiple organ dysfunction syndrome, Myocarditis, Right ventricular failure, Thrombosis with thrombocytopenia syndrome, Sinus node dysfunction, Intracardiac thrombus (1 each).
- Time to onset (myocarditis): 7 days.
- Causes of death: It was not reported if autopsy was performed. The above mentioned events were cause of death.
- Comment: The individual role of vaccine in the development of fatal events was confounded by patient's medical history (heart rate abnormal, supraventricular tachycardia), and elderly age.

A 69-year-old male subject, dose 2 (original), NMC, Germany:

- Medical history: Non-tobacco user.
- Co-suspect medications: None.
- Concomitant medications: None.
- PTs with fatal outcome: Multiple organ dysfunction syndrome, Arrhythmia, Myocarditis, Lymphoma (1 each).
- Time to onset (myocarditis): 103 days.
- Causes of death: It was not reported if autopsy was performed. The above mentioned events were reported as cause of death.

– Comment: The events developed more than 100 days after the second dose vaccination; and the patient had a malignant condition, which was more likely to lead to the fatal outcome.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 43 (original [36], bivalent Omi BA.1 [1], bivalent Omi BA.4/BA.5 [4], multivalent NOS [1], monovalent Omi XBB.1.5 [1]; 0.04% of 107,046 cases, the total PM dataset; 0.6% of the 6846 subjects with unknown age), compared to 80 cases (0.1%) retrieved in the PSUR #5.
- Country/region of incidence (≥2): UK (8), Australia, Germany (6 each), Canada (5), New Zealand, US, Austria, Italy (2 each). The remaining 8 cases were distributed among 8 countries.
- Medical history (n = 8); the most frequently (≥2) reported medical conditions included Anaemia, Immunodeficiency, Gastroesophageal reflux disease (2 each).
- COVID-19 Medical history (n = 2): COVID-19, Suspected COVID-19 (1 each).
- Co-suspect medications: COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19), tocilizumab (1 each).
- Most frequently co-reported PTs (≥3) included Dyspnoea (9), Chest pain, Fatigue (8 each), Palpitations (7), Malaise (5), Chest discomfort, Pyrexia, Tachycardia (4 each), Cough, Dizziness, Interchange of vaccine products, Pulmonary oedema, Supraventricular tachycardia, Thrombosis (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 50 below.

Table 50. Myocarditis in Subjects Aged Unknown (N = 43)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	8	7	4
	No	5	11	8
Relevant PT[a]	Carditis	1	0	1
	Myocarditis	10	17	11
	Myopericarditis	2	1	1
Hospitalisation required/prolonged	Yes	4	5	1
	No	9	13	11
Relevant suspect dose	Dose 1	3	2	4
	Dose 2	1	5	0
	Dose 3	4	1	3
	Dose 4	3	1	0
	Dose 5	0	0	1
	Dose unknown	2	9	4
Vaccine Presentation	Original	10	16	10
	Bivalent Omi BA.1	0	0	1
	Bivalent Omi BA.4/BA.5	3	1	0
	Multivalent NOS	0	1	0
	Monovalent Omi XBB.1.5	0	0	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 5	≤ 24 hours	0	0	0
	1-5 days	2	0	1
	6-13 days	0	1	0
	14-21 days	0	0	0
	22-31 days	0	0	0
	32-60 days	1	0	0
	61-180 days	0	0	0
	181-365 days	0	0	0
	> 365 days	0	0	0
Event Outcome	Fatal	0	0	2
	Not resolved	3	5	2
	Resolved	1	3	0
	Resolving	0	1	0
	Resolved with sequelae	0	0	1
	Unknown	9	9	8
Duration of event[b] n = 1, median: NA	1-60 days	1	0	0

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

Fatal cases (1):

A subject of unknown age and gender (original), medically confirmed, Brazil:

- Medical history: Not reported.
- Co-suspect medications: Not reported.
- Concomitant medications: Not reported.
- PTs with fatal outcome: Myocarditis, and Myopericarditis.

- Time to onset (myocarditis): Not reported.
- Causes of death: Myocarditis, and Myopericarditis.Comment: This case offers no information regarding medical history, concomitant/co-suspect medications, clinical course of the events thus precluding a meaningful causality assessment.

16.3.1.1.2. Important Identified Risks – Pericarditis

Search criteria - 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 #5.

Post-Authorisation Data

- Number of cases: 432 (original [373], bivalent Omi BA.1 [13], bivalent Omi BA.4/BA.5 [16], multivalent NOS [4], monovalent Omi XBB.1.5 [26]; 0.4% of 107,046 cases, the total PM dataset), compared to 379 cases (0.5%) retrieved in the PSUR #5.

- Country/region of incidence (⩾10): New Zealand (166), Canada (58), France (32), Germany, UK (31 each), Australia (19), Japan, US (16 each), and Italy (11). The remaining 52 cases were distributed among 17 countries.

- MC cases (206), NMC cases (226).

- Subjects' gender: female (201), male (221) and unknown (10).

- Subjects' age in years: n = 402, range: 12 – 88, mean: 42.7, median: 40.0.

- Medical history (n = 118); the most frequently (⩾5) reported relevant medical history included Hypertension (18), Hypothyroidism (9), Breast cancer (8), Asthma, Diabetes mellitus, Pericarditis (7 each), Rheumatoid arthritis, Seasonal allergy (6 each), Dyslipidaemia, and Non-tobacco user (5 each).

- COVID-19 Medical history (n = 18): COVID-19 (14), Suspected COVID-19 (3), Post-acute COVID-19 syndrome (1).

- Co-suspect medications (n = 8); relevant co-suspect medications included elasomeran, influenza vaccine inact SAG 4V, influenza vaccine inact split 4V (2 each), influenza vaccine, and influenza vaccine inact SAG 3V (1 each).

- Number of relevant events: 432.

- Relevant event seriousness: serious (432).

- Reported relevant PTs: Pericarditis (424), Pericarditis constrictive (5), Pleuropericarditis (3).

- Relevant event outcome: fatal (6), resolved/resolving (169), resolved with sequelae (11), not resolved (148), unknown (98).

Cumulatively, there were 11,572 cases of pericarditis which constitute 0.6% of the overall PM dataset (1,946,152). During the current reporting period, there were 432 cases that reported pericarditis which constitute 0.4% of 107,046 cases of the total PM dataset, and majority (97.7%) of these cases were spontaneously reported. Of these 432 cases, the majority of the cases (313 cases; 72.5%) were reported from adult population with the ages ranging from 18 to 64 years of age. Of these 432 cases, the female subjects (201 cases; 46.5%) and the male subjects (221 cases; 51.2%) were reported in similar proportion. In the majority (373 cases; 86.3%) 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), multivalent NOS, or monovalent Omi XBB.1.5 (13.7%).

Of the 432 cases reporting events indicative of pericarditis, 206 cases (47.7%) were medically confirmed. Of the 432 cases, in 70 cases (16.2% of the cases reporting pericarditis related events) the events were confounded by subjects' relevant medical history such as cardiac disorders, neoplasms, COVID-19, immune disorders, embolic disorders etc and/or relevant co-suspect medications. Of the total 432 cases, in 113 cases (23.6%) the cases were confounded by co-reported events indicative of an alternate aetiology, such as neoplasms, ischaemic cardiomyopathy/coronary artery disease, infections, or the long time to onset of the pericarditis event post-vaccination (>21 days) was less consistent with a vaccine induced event. Of the 432 cases, in 344 cases (79.6%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

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[65]

Subjects aged 6 months through <5 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

[65] Cases where the age was reported only as:
- "Child" (1 case) was evaluated in the overall and in the 5 through <12 years age groups,
- "Adolescent" (3 cases) were evaluated in the overall and in the 16-17 years age groups,
- "Adult" (8 cases) were evaluated in the overall and in the Age Unknown group.

Post-Authorisation Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Subjects aged 5 through <12 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 1 (original [1]; 0.001% of 107,046 cases, the total PM dataset; 0.06% of the 1701 subjects aged 5-11 years), compared to 3 cases (0.004%) retrieved in the PSUR #5.
- Country/region of incidence: Canada (1).
- Subjects' age in year: Not reported.[65]
- Medical history: none.
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs: none.

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 51 below.

Table 51. Pericarditis in Subjects Aged 5 through <12 years (N = 1)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	0	1	0
Relevant PT[a]	Pericarditis	0	1	0
Hospitalisation required/prolonged	No	0	1	0
Relevant suspect dose	Dose 1	0	1	0
Vaccine Presentation	Original	0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 1	6-13 days	0	1	0
Event Outcome	Resolved	0	1	0
Duration of event[b] n = 1, median: N/A	None	0	1	0

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

Fatal cases: None

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 11 (original [11]; 0.01% of 107,046 cases, the total PM dataset; 0.4% of the 2452 subjects aged 12-15 years), compared to 10 cases (0.01% of the total PM dataset) retrieved in the PSUR #5.
- Country/region of incidence: Canada (4), New Zealand (3), Spain (2), Australia and Japan (1 each).
- Subjects' age in years: n = 11, range: 12.0 – 15.0, mean: 14.0, median: 15.0.
- Medical history (n = 4): Attention deficit hyperactivity disorder, Crohn's disease, Immunodeficiency, Nephrotic syndrome, and Seasonal allergy (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain, Myocarditis (3 each), Palpitations, Pyrexia, Vaccination site pain (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 52 below.

Table 52. Pericarditis in Subjects Aged 12-15 (N = 11)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	6	0
	No	0	2	0
Relevant PT[a]	Pericarditis	3	8	0
Hospitalisation required/prolonged	Yes	0	3	0
	No	3	5	0
Relevant suspect dose	Dose 1	2	1	0
	Dose 2	0	5	0
	Dose unknown	1	2	0
Vaccine Presentation	Original	3	8	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 11	≤ 24 hours	0	2	0
	1-5 days	1	3	0
	6-13 days	0	1	0
	Unknown	2	2	0
Event Outcome	Fatal	0	0	0
	Not resolved	3	1	0
	Resolved	0	2	0
	Resolving	0	5	0

Table 52. Pericarditis in Subjects Aged 12-15 (N = 11)

	Resolved with sequelae	0	0	0
	Unknown	0	0	0
Duration of event[b] n = 2, median: N/A	None	0	2	0

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

Fatal cases: None

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 16 (original [15], bivalent Omi BA.4/BA.5 [1]; 0.01% of 107,046 cases, the total PM dataset; 0.7% of the 2237 subjects aged 16-17 years), compared to 5 cases (0.007% of the total PM dataset) retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (6), Japan (4), Austria, China (2 each), Brazil, Canada (1 each).
- Subjects' age in years: n = 13, range: 16 – 17, mean: 16.5, median: 16.0.
- Medical history: Food allergy (2), Childhood asthma, Giardiasis, Milk allergy, Upper respiratory tract infection, Urticaria (1 each)
- COVID-19 Medical history: none
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Myocarditis (6), Pyrexia (5), Chest pain (4), Fatigue, Nausea (3 each), Dizziness, Dyspnoea, Headache, Pericardial effusion, and Vaccination site pain (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 53 below.

Table 53. Pericarditis in Subjects Aged 16-17 (N = 16)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	8	2
	No	1	3	0
Relevant PT[a]	Pericarditis	3	11	2
Hospitalisation required/prolonged	Yes	0	6	0
	No	3	5	2
Relevant suspect dose	Dose 1	0	1	0
	Dose 2	0	2	0
	Dose 3	0	3	2

Table 53. Pericarditis in Subjects Aged 16-17 (N = 16)

	Dose 4	0	1	0
	Dose unknown	3	4	0
Vaccine Presentation	Original	3	10	2
	Bivalent Omi BA.4/BA.5	0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 16	≤ 24 hours	1	3	0
	1-5 days	0	4	0
	14-21 days	1	2	0
	32-60 days	0	1	0
	Unknown	1	1	2
Event Outcome	Fatal	0	0	0
	Not resolved	3	0	0
	Resolved	0	7	0
	Resolving	0	3	0
	Resolved with sequelae	0	0	0
	Unknown	0	1	2
Duration of event[b] n = 7, median: 8	Up to 3 days	0	1	0
	7 to 10 days	0	2	0
	58 to 180 days	0	1	0
	None	0	3	0

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

Fatal cases: None

Subjects aged 18 – 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 40 (original [39]; monovalent Omi XBB.1.5 [1]; 0.04% of 107,046 cases, the total PM dataset; 0.5% of the 8288 subjects aged 18-24 years), compared to 38 cases (0.05% of the total dataset) retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (29), France (3), Australia, US (2 each), Austria, Germany, Norway, UK (1 each).
- Subjects' age in years: n = 40, range: 18 – 24, mean: 21.4, median: 21.5.
- Medical history: none.
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications: none.

- Most frequently co-reported PTs (≥2): Myocarditis (10), Chest discomfort, Chest pain, Headache (3 each), Angina pectoris, Dyspnoea, Musculoskeletal pain, and Pyrexia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 54 below.

Table 54. Pericarditis in Subjects Aged 18-24 (N = 40)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	4	15	0
	No	5	16	0
Relevant PT[a]	Pericarditis	9	30	0
	Pericarditis constrictive	0	1	0
Hospitalisation required/prolonged	Yes	2	4	0
	No	7	27	0
Relevant suspect dose	Dose 1	2	4	0
	Dose 2	0	2	0
	Dose 3	1	0	0
	Unknown	6	25	0
Vaccine Presentation	Original	9	30	0
	Monovalent Omi XBB.1.5	0	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 40	≤ 24 hours	5	12	0
	1-5 days	0	6	0
	6-13 days	1	3	0
	14-21 days	1	1	0
	32-60 days	0	2	0
	61-180 days	1	1	0
	181-365 days	1	1	0
	Unknown	0	5	0
Event Outcome	Fatal	0	1	0
	Not resolved	4	11	0
	Resolved	0	5	0
	Resolving	2	7	0
	Resolved with sequelae	0	2	0
	Unknown	3	5	0
Duration of event[b] n = 7, median: N/A	None	0	7	0

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

Fatal cases (1):

This NMC case involved a 19-year-old male subject who received the 2nd dose of BNT162b2 for COVID-19 immunisation, and presented with pericarditis and myocarditis that had a fatal outcome. This case has been reviewed under the Section Important identified risks – *Myocarditis*.

Subjects aged 25 – 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 56 (original [52], bivalent Omi BA.4/BA.5 [3], monovalent Omi XBB.1.5 [1]) 0.05% of 107,046 cases, the total PM dataset; 0.6% of the 8625 subjects aged 25-29 years), compared to 32 cases (0.04% of the total PM dataset) retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (26), Canada (12), France, Germany, Norway (3 each), Japan, UK, US (2 each), Australia, Tunisia, Turkey (1 each).
- Subjects' age in years: n = 56, range: 25 – 29, mean: 26.3, median: 26.0.
- Medical history (n = 14): the medical conditions reported more than once included Pericarditis (3), Mental disorder (2).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain (14), Dyspnoea (9), Chest discomfort (8), Palpitations (5), Myocarditis (4), Fatigue, Pericardial effusion (3 each), Angina pectoris, Dizziness, Lymphadenopathy, Mental disorder, and Pyrexia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 55 below.

Table 55. Pericarditis in Subjects Aged 25-29 (N = 56)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	4	11	0
	No	14	27	0
Relevant PT[a]	Pericarditis	18	38	0
Hospitalisation required/prolonged	Yes	1	5	0
	No	17	33	0
Relevant suspect dose	Dose 1	2	9	0
	Dose 2	4	6	0
	Dose 3	3	4	0
	Dose 4	1	0	0
	Unknown	8	19	0
Vaccine Presentation	Original	16	36	0
	Bivalent Omi BA.4/BA.5	1	2	0
	Monovalent Omi XBB.1.5	1	0	0

Table 55. Pericarditis in Subjects Aged 25-29 (N = 56)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 56	≤ 24 hours	5	16	0
	1-5 days	3	7	0
	6-13 days	5	2	0
	14-21 days	2	4	0
	32-60 days	0	3	0
	181-365 days	0	1	0
	Unknown	3	5	0
Event Outcome	Fatal	0	0	0
	Not resolved	5	14	0
	Resolved	5	7	0
	Resolving	3	4	0
	Resolved with sequelae	2	0	0
	Unknown	3	13	0
Duration of event[b] n = 14, median: 67.5	58-180 days	0	2	0
	None	7	5	0

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

Fatal cases: None

Subjects aged 30 – 39 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 77 (original [76]; monovalent Omi XBB.1.5 [1]) 0.07% of 107,046 cases, the total PM dataset; 0.4% of the 19265 subjects aged 30-39 years), compared to 67 cases (0.09% of the total PM dataset) retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (49), Germany (7), Canada (6), France (5), UK (3), Australia, Japan (2 each), Greece, Hong Kong, Sweden (1 each).
- Subjects' age in years: n = 77, range: 30 – 39, mean: 34.9, median: 35.0.
- Medical history (n = 11): the medical conditions reported more than once included Hypothyroidism, Non-tobacco user (2 each).
- COVID-19 Medical history (n = 2): COVID-19, Post-acute COVID-19 syndrome (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥3): Chest pain (13), Dyspnoea (12), Chest discomfort, Fatigue (10 each), Myocarditis (9), Dizziness, Headache, Palpitations, Pyrexia (6 each), Arthralgia, Pericardial effusion (5 each), Anxiety, Influenza like illness, Tachycardia (4

each), Asthenia, Cough, Disturbance in attention, Lethargy, Nausea, Pain, and Pain in extremity (3 each).

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

Table 56. Pericarditis in Subjects Aged 30-39 (N = 77)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	21	21	0
	No	14	21	0
Relevant PT[a]	Pericarditis	34	42	0
	Pleuropericarditis	1	0	0
Hospitalisation required/prolonged	Yes	6	7	0
	No	29	35	0
Relevant suspect dose	Dose 1	7	5	0
	Dose 2	6	2	0
	Dose 3	1	3	0
	Dose 4	0	2	0
	Unknown	21	30	0
Vaccine Presentation	Original	34	42	0
	Monovalent Omi XBB.1.5	1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 77	≤ 24 hours	12	15	0
	1-5 days	8	8	0
	6-13 days	3	3	0
	14-21 days	0	3	0
	32-60 days	2	1	0
	61-180 days	2	3	0
	181-365 days	0	1	0
	>365 days	1	2	0
	Unknown	7	6	0
Event Outcome	Fatal	0	0	0
	Not resolved	11	11	0
	Resolved	4	8	0
	Resolving	9	14	0
	Resolved with sequelae	0	0	0
	Unknown	11	9	0
Duration of event[b] n = 12, median: 84.5	4-6 days	0	1	0
	58-180 days	0	1	0
	None	4	6	0

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

Fatal cases: None

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 205 (original [160], bivalent Omi BA.1 [12], bivalent Omi BA.4/BA.5 [10], multivalent NOS [4], monovalent Omi XBB.1.5 [19]; 0.2 % of 107,046 cases, the total PM dataset; 0.4% of the 57,136 subjects ≥ 40 years), compared to 189 cases (0.3%) retrieved in the PSUR #5.
- Country/region of incidence: New Zealand (50), Canada (30), UK (21), Germany (20), France (15), Australia, Italy (11 Each), US (10), Netherlands (9), Japan (7), Sweden (5), Austria (4), Portugal (3), Belgium, Brazil, Greece, Norway, Slovakia, Slovenia, Spain, Switzerland, And Turkey (1 Each).
- Subjects' age in years: n = 205, range: 40 – 88, mean: 57.5, median: 55.0.
- Medical history (n = 80): the medical conditions reported more than 3 times included PTs Hypertension (17), Breast cancer (8), Hypothyroidism (7), Asthma, Diabetes mellitus (6 each), Rheumatoid arthritis (5), Arrhythmia, Autoimmune thyroiditis, Chemotherapy, Dyslipidaemia, Pericarditis, Radiotherapy, Seasonal allergy, and Type 2 diabetes mellitus (4 each).
- COVID-19 Medical history (n = 13): COVID-19 (10), Suspected COVID-19 (3)
- Co-suspect medications (n= 8): elasomeran, influenza vaccine inact SAG 4V, influenza vaccine inact split 4V (2 each), influenza vaccine, and influenza vaccine inact SAG 3V (1 each).
- Most frequently co-reported PTs (≥10): Dyspnoea (54), Chest pain (44), Fatigue (36), Pericardial effusion (33), Myocarditis (28), Palpitations (27), Tachycardia (24), Chest discomfort (20), Dizziness (17), Pyrexia (16), Headache (14), Nausea (12), Pleural effusion (11), and Pain in extremity (10).

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

Table 57. Pericarditis in Subjects Aged ≥40 years (N = 205)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	62	33	0
	No	60	50	0
Relevant PT[a]	Pericarditis	120	80	0
	Pericarditis constrictive	2	2	0
	Pleuropericarditis	0	1	0
Hospitalisation required/prolonged	Yes	43	27	0
	No	79	56	0
Relevant suspect dose	Dose 1	37	14	0
	Dose 2	17	17	0
	Dose 3	13	9	0
	Dose 4	12	2	0
	Dose 5	1	6	0
	Dose 6	2	1	0
	Unknown	40	34	0
Vaccine Presentation	Original	95	65	0
	Bivalent Omi BA.1	6	6	0
	Bivalent Omi BA.4/BA.5	6	4	0
	Multivalent NOS	3	1	0
	Monovalent Omi XBB.1.5	12	7	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 205	≤ 24 hours	21	16	0
	1-5 days	16	13	0
	6-13 days	13	9	0
	14-21 days	5	9	0
	22-31 days	4	0	0
	32-60 days	6	5	0
	61-180 days	8	5	0
	181-365 days	4	2	0
	>365 days	4	3	0
	Unknown	41	21	0
Event Outcome	Fatal	2	3	0
	Not resolved	50	29	0
	Resolved	21	18	0
	Resolving	21	15	0
	Resolved with sequelae	5	1	0
	Unknown	23	17	0
Duration of event[b] n = 45, median: 31	Up to 3 days	2	1	0
	4 to 6 days	0	1	0
	27 to 57 days	1	2	0
	58 to 180 days	2	1	0
	None	21	14	0

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

Fatal cases (5 [1 adult and 4 elderly patients]):

Adult:

A 63-year-old female subject,[66] dose 3 (original), MC, Turkey:

- Medical history: Arteriosclerosis, chronic obstructive pulmonary disease, and tobacco user.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Arterial occlusive disease, Cerebrovascular accident, Deep vein thrombosis, Pericarditis, Pleural effusion, and Pulmonary embolism.
- Time to onset (pericarditis): not reported.
- Causes of death: All the above PTs were reported with fatal outcome.

Comment: The subject with a medical history of tobacco use (smoking), COPD, and arteriosclerosis received the 3rd dose of BNT162b2 for COVID-19 immunisation. On the same day evening, her SARS-CoV-2 (RT-PCR) test showed positive. On the 8th day of vaccination, the subject underwent percutaneous transluminal angioplasty due to left anterior tibial posterior occlusion. However, due to thrombosis and necrosis, both the lower extremities were amputated. She was discharged home but was readmitted to another hospital and died on the 13th day of vaccination. In this case, many thrombotic complications (stroke, pulmonary embolism, deep vein thrombosis in the upper and lower extremities, acute arterial occlusion in both lower extremities) and non-thrombotic complications (pleural effusion, pericarditis) developed simultaneously, which might be attributed to the patient's co-morbidities and an individual role of BNT162b2 vaccine cannot be established in isolation.

Elderly:

A 67-year-old male subject, dose 3 (original), NMC, Greece:

- Medical history: Tobacco user.
- Co-suspect medications: none.
- Concomitant medications: none.
- PT with fatal outcome: Pericarditis.
- Time to onset (pericarditis): >365 days.
- Causes of death: Cardiac arrest, lung neoplasm malignant, oesophagitis, pericarditis
- Comment: The subject with a medical history of tobacco use (smoking) received the 3rd dose of BNT162b2 for COVID-19 immunisation on 04 December 2021. On 23 March 2023, the subject was diagnosed with pericarditis and he died on 01 June 2023 due to cardiac arrest, lung neoplasm malignant, oesophagitis, and pericarditis. No autopsy

[66] Bayrak V. A case report overlapped vaccine and COVID-19 in disseminated atherosclerosis. Clinical and Experimental Vaccine Research. 2023;12(2):172-175.

was performed. Based on a long latency and other concurrent illness (lung neoplasm malignant), an individual contributory role of the suspect medication (BNT162b2 vaccine) cannot be established in isolation.

A 72-year-old female subject, dose 4 (original), MC, Japan:

- Medical history: Angina pectoris, dyslipidaemia, hypertension, joint dislocation, and peripheral arterial occlusive disease.
- Co-suspect medications: none.
- Concomitant medications: atorvastatin, sacubitril/valsartan.
- PT with fatal outcome: Anti-neutrophil cytoplasmic antibody positive vasculitis, Blood pressure decreased, Cerebral infarction, Interchange of vaccine products, Large intestine perforation, and Pericarditis.
- Time to onset (pericarditis): not reported.
- Causes of death: All the above PTs reported with fatal outcome.
- Comment: The subject with a medical history of angina pectoris, dyslipidaemia, hypertension, joint dislocation, and peripheral arterial occlusive disease, received Moderna vaccine as the 3rd dose on 19 February 2022 and BNT162b2 as the 4th dose on 29 August 2022 for COVID-19 immunisation. The details on 1st and 2nd dose were not reported. Earlier, on 19 August 2022, the subject had mild oedema of the lower limb that remained during the 4th dose of COVID-19 immunisation. For the same, treatment with candesartan and amlodipine was switched to sacubitril/valsartan. On 6 October 2022, the subject was diagnosed with cystitis and anti-neutrophil cytoplasmic antibody positive vasculitis. Later, the subject also had multiple events such as blood pressure decreased, feeding disorder, large intestine perforation, and pericarditis. The subject was hospitalized on 10 November 2022 due to exacerbation of oedema (end stage renal disease) and was diagnosed with cerebral infarction. Despite providing intensive treatment, she died in the hospital on 09 January 2023. In this case, patient's multiple co-morbidities and patient's age factor might be contributing to the fatal outcome and an individual contributory role of BNT162b2 vaccine cannot be established in isolation.

A 79-year-old male subject, dose 6 (BNT162b2 Omi BA.1), MC, Japan:

- Medical history: Diabetes mellitus.
- Co-suspect medications: BNT162b2.
- Concomitant medications: none.
- PT with fatal outcome: Cardio-respiratory arrest. Interchange of vaccine products. Pericarditis. Pleurisy.
- Time to onset (pericarditis): not reported.
- Causes of death: All the above PTs reported with fatal outcome.
- Comment: The subject with a medical history of diabetes mellitus received BNT162b2 Omi BA.1 as the 6th dose on 17 May 2023. Earlier the subject had BNT162b2 (Comirnaty) for Dose 1 to 3, Moderna Spikevax for dose 4, and BNT162b2 Omi

BA.4/BA.5 for dose 5 of COVID-19 immunisation. On 27 May 2023, the patient developed dyspnoea, and was noted with pleural effusion. Despite treatment with antibiotics and diuretics, the symptoms did not improve, and he was hospitalized on 20 June 2023 and was discharged on 28 June 2023, as the pericardial and pleural effusion disappeared. However, within 2 days (on 30 June 2023), he had cardio-respiratory arrest in his home toilet and was brought to emergency centre. On the same day, he died due to cardio-respiratory arrest, pericarditis and pleurisy. In this case, the patient's medical history (diabetes), age factor and the infection reported might be contributing to the fatal events, and an individual contributory role of BNT162B2 Omi BA.1 cannot be established in isolation.

An 85-year-old male subject, unspecified dose (BNT162b2 Omi BA.1), NMC, UK:

- Medical history: none.
- Co-suspect medications: BNT162b2.
- Concomitant medications: none.
- PT with fatal outcome: Angina pectoris. Coronary artery thrombosis. Decreased appetite. Fatigue. Myocardial infarction. Pericarditis.
- Time to onset (pericarditis): not reported.
- Causes of death: All the above PTs reported with fatal outcome.
- Comment: The subject with an unspecified medical history who completed primary COVID-19 immunisation series, received BNT162b2 Omi BA.1 on 20 September 2023. Two (2) days after the vaccination, the subject developed chest pain, fatigue and poor appetite (PTs: Angina pectoris, Fatigue, and Decreased appetite). On 27 September 2023, he was found dead at home. His autopsy showed pericarditis and a large myocardial infarction caused by a right coronary thrombosis (PTs Pericarditis, Myocardial infarction, Coronary artery thrombosis). It was reported that the subject did not test positive for COVID-19 and the reaction occurred co-reported with an inadvertent administration of the vaccine (PT Medication error). In this elderly case, there was limited information regarding the role of the medication error, and the autopsy pathological findings indicate that patient had a complicated severe ischaemic cardiac condition, which in conjunction with patient's advanced age were more likely drivers of the clinical course, thus an individual contributory role of the vaccine cannot be assessed in isolation.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 26 (original [19], bivalent Omi BA.1 [1], bivalent Omi BA.4/BA.5 [2], monovalent Omi XBB.1.5 [4]; 0.02% of 107,046 cases, the total PM dataset; 0.4% of the

6846 subjects with unknown age), compared to 35 (0.05% of the total PM dataset) cases retrieved in the PSUR #5.

- Country/region of incidence: France (6), Canada, UK (4 each), New Zealand (3), Australia, US, US minor outlying islands (2 each), Austria, Spain, and Sweden (1 each).
- Medical history (n = 4): the medical conditions reported more than once included the PT Fibromyalgia (2).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥3): Palpitations (6), Fatigue (5), Chest pain, Dyspnoea, Myocarditis (4 each), and Pleuritic pain (3).

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

Table 58. Pericarditis in Subjects with unknown age (N = 26)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	4	6
	No	8	3	2
Relevant PT[a]	Pericarditis	10	7	8
	Pleuropericarditis	1	0	0
Hospitalisation required/prolonged	Yes	1	2	1
	No	10	5	7
Relevant suspect dose	Dose 1	4	1	2
	Dose 2	3	2	0
	Dose 3	0	1	0
	Dose 4	1	0	0
	Dose 5	0	0	1
	Unknown	3	3	5
Vaccine Presentation	Original	9	5	5
	Bivalent Omi BA.1	0	0	1
	Bivalent Omi BA.4/BA.5	1	1	0
	Monovalent Omi XBB.1.5	1	1	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n = 26	≤ 24 hours	0	1	0
	1-5 days	4	1	1
	32-60 days	1	0	0
	181-365 days	1	0	0
	Unknown	5	5	7
Event Outcome	Fatal	0	0	0
	Not resolved	5	1	0
	Resolved	0	0	5
	Resolving	2	0	1
	Resolved with sequelae	0	0	1
	Unknown	4	6	1
Duration of event[b] n = 6, median: N/A	None	0	0	6

Table 58. Pericarditis in Subjects with unknown age (N = 26)

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

Fatal cases: None

O/E Analysis

O/E analysis was performed for Myocarditis and Pericarditis (see Appendix 5.4 *Observed versus Expected Analyses for Myocarditis and Pericarditis).*

Conclusion

Evaluation of Myocarditis and Pericarditis did not reveal any significant new safety information for this interval.

16.3.2. Evaluation of Important Potential Risks

During the reporting period there were no important potential risks for BNT162b2.[17]

16.3.3. Evaluation of Other Risks (not categorised as important)

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made: *for future PSURs, in 'Adverse Events of Special Interest (AESIs)' of section 'Evaluation of Other Risks (not categorised as important)', the AESIs 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 in cases potentially reflective of AESIs, no new safety issues/signals or reporting pattern changes were detected. Section 16.3.3.1 Adverse Events of Special Interest has been removed from this document.
O/E analyses were conducted by the MAH for all AESIs that were previously included in the PSUR 5. Current analyses were restricted to the EEA countries only due to lack of availability of up-to-date exposure data from other regions. No new safety issue was identified; therefore, the MAH has included O/E results in the Appendix 5.4 for Myocarditis and Pericarditis only, as part of continuous monitoring.

As part of the approval letter for the emergency use of Tozinameran – COVID-19 mRNA vaccine (nucleoside modified) – COMIRNATY® on 26 January 2021, 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.*

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: 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.

Response

Upon review of the incremental data in cases evaluated for these topics, no new safety issues/signals or reporting pattern changes were detected. These topics will continue to be monitored with routine pharmacovigilance activities and presented in future PSURs only if any significant information is identified. These topics have been removed from this Section of the PSUR.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

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 this Section of the PSUR.

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.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

Response

Upon review of the incremental data of cases indicative of death, no new safety issues/signals or reporting pattern changes were detected. This topic has been removed from the evaluation of special situations discussed in Section 16.3.4 *Evaluation of Special Situations* of the PSUR.

In the PRAC AR of the PSUR #5 (EMEA/H/C/PSUSA/00010898/202306), the following request was made: *For future PSURs, in 'Evaluation of special situations' of section 'Evaluation of Other Risks (not categorised as important)', lack of therapeutic efficacy 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 indicative of lack of therapeutic efficacy, no new safety issues/signals or reporting pattern changes were detected. This topic has been removed from the evaluation of special situations discussed in Section 16.3.4. *Evaluation of Special Situations* of the PSUR.

16.3.5. Update on Special Patient Populations

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 '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 co-morbidities 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 Section 16.3.5 *Update on Special Patient Populations* of the PSUR.

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 16.3.5.2 *Use in Pregnant/Lactating Women* for a general overview of the use of all BNT162b2 vaccine presentations in this population.

In the AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *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.*

Response

Upon review of the incremental data of cases reported in elderly population, no new safety issues/signals or reporting pattern changes were detected. This population has been removed from the populations discussed in Section 16.3.5 *Update on Special Patient Populations* of the PSUR.

The populations of immunocompromised patients and of patients with autoimmune or inflammatory disorders are summarised in Section 16.4.2 *Description of Missing information.*

16.3.5.1. 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.

16.3.5.1.1. Paediatric Subjects <5 Years of Age

Clinical Trial Data

- Number of cases: 5 (original [2] and bivalent Omi BA.4/BA.5 [3] originated from clinical studies C4591007-OPENLABEL, C4591048-SSB [2 each], and C4591048-SSA [1]; 26.3% of 19 cases, the total CT dataset), compared to 41 cases (50.0%) retrieved in the PSUR #5.
- Country/region of incidence: US (3) and Brazil (2).
- Subjects' gender: female (2), male (3).
- Subjects' age in years: n = 5, range: 2-3 years, mean: 2.5, median: 2.7.
- Medical history (n = 2): Dermatitis atopic and Vesicoureteric reflux (1 each).
- COVID-19 Medical history: none
- Co-suspect medications: none.
- Reported PTs in participants with ages of 2-3 years (n = 5):
  - Following dose 1
    - Formulation 3 mcg (Maroon cap): none.
    - Formulation other/unknown (n = 1): PT Cellulitis
  - Following dose 2
    - Formulation 3 mcg (Maroon cap): none.
    - Formulation other/unknown (n = 1): PT Asthma
  - Following dose 3
    - Formulation 3 mcg (Maroon cap): none.
    - Formulation other/unknown (n = 2): PT Cellulitis, Adenoidal hypertrophy
  - Following dose 4
    - Formulation 3 mcg (Maroon cap): none.
    - Formulation other/unknown (n = 1): PT Urinary tract infection
- All events were assessed as unrelated to BNT162b2 or bivalent Omi BA.4/BA.5.
- Time to event onset: n = 5, range: from 7 to 365 days, median: 52 days.
  - 7 days, 34 days, 52 days, 121 days, and 365 days (1 each).
- Duration of relevant events: n = 5, range: 4 to 125 days, median: 6 days.
  - 4 days, 5 days, 6 days, 13 days, and 125 days (1 each).

- Event outcome: resolved (5).

Post-Authorisation Data

- Number of cases: 395 (original [136], bivalent Omi XBB.1.5 [194], and bivalent Omi BA.4/BA.5 [72]; 0.4% of 107,046 cases, the total PM dataset), compared to 396 cases (0.5%) retrieved in the PSUR #5.
- MC cases (344), NMC cases (51).
- Country/region of incidence: US (275), Japan (78), Brazil, New Zealand (8 each), Australia, Canada (6 each), UK (4), Germany (3), Finland (2). The remaining 5 cases were distributed among 5 countries.
- Subjects' gender: female (145), male (122), and unknown (128).
- Subjects' age in years: n = 308, range: 5 months – 4 years, mean: 2.1, median: 2.0.
- Medical history (n = 43); the most frequently (≥2) reported medical conditions included Constipation, Gastrooesophageal reflux disease (4 each), Autism spectrum disorder, Drug hypersensitivity, Eczema, Food allergy, Hydronephrosis, Hypersensitivity (3 each), Atrial septal defect, Cardiac murmur, Dermatitis atopic, Developmental hip dysplasia, Epilepsy, Haemangioma, Hypoxia, Lactose intolerance, Patent ductus arteriosus, and Speech disorder developmental (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect medications (n = 45); the most frequently (≥2) reported included sodium chloride, (17), influenza vaccine (10), sodium chloride bacteriostatic (9), influenza vaccine inact SAG 3V, influenza vaccine inact split 3V, pneumococcal 13-val conj vac (dipht CRM197 protein), and pneumococcal vaccine conj 15V (CRM197) (2 each).
- Number of events: 847.
- Most frequently reported PTs (≥ 2) in subjects with ages of 5 months through 4 years (n = 847):
  - Following dose 1
    - Formulation 3 mcg (Maroon cap) (n = 30): Poor quality product administered (10), Overdose (6), Product administration error, Product temperature excursion issue (5 each), Product preparation error, Pyrexia (3 each), Concomitant disease aggravated, Expired product administered, Product preparation issue, Seizure, and Urticaria (2 each).
    - Formulation other/unknown (n = 87): Overdose (47), Product preparation error (38), Poor quality product administered (29), Product administered to patient of inappropriate age (20), Product administration error, Product preparation issue (9 each), Expired product administered (7), Underdose (6), Accidental overdose, Product administered inappropriate site, and Vaccination error (2 each).
  - Following dose 2
    - Formulation 3 mcg (Maroon cap) (n = 24): Poor quality product administered (9), Inappropriate schedule of product administration (8), Product administration

error (6), Overdose (4), Product preparation error, Product temperature excursion issue, Pyrexia (3 each), COVID-19, and Vaccination failure (2 each).
  - Formulation other/unknown (n = 17): Overdose (8), Inappropriate schedule of product administration, Product administered to patient of inappropriate age (4 each), Incorrect dose administered, Product preparation error (3 each), Accidental overdose, Fatigue, Interchange of vaccine products, Off label use, Pain, Poor quality product administered, and Wrong product administered (2 each).
- Following dose 3
  - Formulation 3 mcg (Maroon cap) (n = 16): Poor quality product administered (11), Product administration error (10), COVID-19, Inappropriate schedule of product administration, Overdose, Vaccination failure, and Wrong product administered (2 each).
  - Formulation other/unknown (n = 13): Overdose (7), Product administered to patient of inappropriate age, Product preparation error (4 each), Incorrect dose administered (3), Accidental overdose, Fatigue, Interchange of vaccine products, Pain, Poor quality product administered, and Pyrexia (2 each).
- Following dose other/unknown
  - Formulation 3 mcg (Maroon cap) (n = 83): Poor quality product administered (77), Product temperature excursion issue (65), Product administration error (12), Overdose, and Product preparation error (4 each).
  - Formulation other/unknown (n = 135): Overdose (54), Product preparation error (50), Poor quality product administered (48), Product administered to patient of inappropriate age (21), Expired product administered (17), Product administration error (13), Product preparation issue (9), Underdose (8), Pyrexia (6), Off label use (5), Infant irritability, Product use issue (4 each), Rash, Wrong product administered (3 each), Accidental overdose, Decreased appetite, Incorrect dose administered, Infantile diarrhoea, Interchange of vaccine products, Musculoskeletal pain, Product administered at inappropriate site, Product packaging quantity issue, Product temperature excursion issue, and Sleep disorder (2 each).

Please refer to Section 9.2, *Medication Errors* for the categorisation of the PTs indicative of medication errors reported in this population.

- Event seriousness: serious (42), non-serious (805).
- Time to event onset: n = 486, range: from <24 hours to 354 days, median: 12.5 days.
  - <24 hours: 454 events;
  - 1 day: 7 events;
  - 2-7 days: 12 events;
  - 8-14 days: 6 events;
  - 15-60 days: 3 events.
- Duration of relevant events: n = 14, range: from <24 hours to 3 days, median: 1 day.

- <24 hours: 11 events;
- 1 day: 1 event;
- 3 days: 2 events.

- Event outcome: fatal (1), resolved/resolving (69), not resolved (12), unknown (765).

Fatal case (1)

- Age: 14 months (1).
- NMC case (1).
- Gender: unknown (1).
- Country/region of incidence: US (1).
- Fatal PT: Death (1).
- Medical history: none.

This case reported PT Death only as the fatal AE. Neither cause of death nor information on autopsy was provided in this case involving a 14-month-old subject (unspecified gender) who died after getting the vaccine bivalent Omi BA.4/BA.5. Timing of vaccination and date of death was not reported. Limited information was provided, precluding any meaningful assessment.

16.3.5.1.2. Paediatric Subjects ≥5 Years and ≤ 11 Years of Age

Clinical Trial Data

- Number of cases: 4 (blinded therapy [2],[67] original, and bivalent Omi BA.4/BA.5 [1 each], originated from clinical studies C4591007 [2], C4591007-OPENLABEL, and C4591048-SSB [1 each]; 21.1% of 19 cases, the total CT dataset), compared to 7 cases (8.5%) retrieved in the PSUR #5.
- Country/region of incidence: Poland, and US (2 each).
- Subjects' gender: male (4).
- Subjects' age in years: n = 4, range: 5 – 11 years, mean: 9, median: 10.0.
- Medical history (n = 2); the reported medical conditions included Seasonal allergy (2), Constipation, Eczema, Behaviour disorder, Congenital umbilical hernia, Epilepsy with myoclonic-atonic seizures, Gastrooesophageal reflux disease, Gluten sensitivity, Irritable bowel syndrome, Lactose intolerance, Psychomotor hyperactivity, and Speech disorder developmental (1 each).
- COVID-19 Medical history: none.

[67] After DLP, due to end of study unblinding, the blinded treatment was broken and the administered treatment was original vaccine.

- Co-suspect medications: none.
- Reported PTs (4): Tonsillitis bacterial (2), Faecaloma, and Syncope (1 each). All events were assessed as unrelated to BNT162b2, bivalent Omi BA.4/BA.5, or blinded therapy.
- Time to event onset: n = 4, range: 125 days to 325 days, median: 240.5 days.
  - 125 days, 158 days, 323 days, and 325 days (1 each).
- Duration of relevant events: n = 4, range: from <24 hours to 11 days, median: 6.5 days.
  - < 24 hours, 3 days, 10 days, and 11 days (1 each).
- Event outcome: resolved (4).

Post-Authorisation Data

- Number of cases: 1697 (original [1345], bivalent Omi BA.4/BA.5 [201], bivalent Omi XBB.1.5 [174], bivalent Omi BA.1 [3], and BNT162b2 Multivalent NOS [2]; 1.6% of 107,046 cases, the total PM dataset), compared to 1225 cases (1.7%) retrieved in the PSUR #5.
- MC cases (1418), NMC cases (279).
- Country/region of incidence (≥2%): New Zealand (828), Japan (381), and US (311).
- Subjects' gender: female (611), male (576), and unknown (510).
- Subjects' age in years: n = 1221, range: 5-11 years, mean: 8.5, median: 9.0.
- Medical history (n = 45); the most frequently (≥2) reported medical conditions included Asthma (10), Chronic sinusitis, Rhinitis allergic (3 each), Abdominal pain, Attention deficit hyperactivity disorder, Cardiac disorder, Food allergy, Granulomatosis with polyangiitis, Mycotic allergy, Pyrexia, Renal disorder, Rhinitis, and Tonsillectomy (2 each).
- COVID-19 Medical history (n = 7): COVID-19 (7).
- Co-suspect medications (n = 18); the most frequently (≥2) reported included influenza vaccine (3), COVID-19 vaccine, influenza vaccine inact split 4V (2 each).
- Number of events: 3622.
- Event seriousness: serious (296), non-serious (3326).
- Most frequently reported PTs (≥3% of cases): Poor quality product administered (507), Product temperature excursion issue (372), Dizziness (208), Nausea (175), Product administration error (154), Overdose (123), Product administered to patient of inappropriate age (122), Vomiting (121), Headache (114), Chest discomfort (98), Pyrexia (91), Abdominal pain, Vaccination site pain (82 each), Pallor (81), Syncope (75), Presyncope (66), Drug ineffective (51), and COVID-19 (50).
- Time to event onset: n = 2425, range: from <24 hours to 609 days, median: 64 days.

- <24 hours: 2100 events;
- 1 day: 79 events;
- 2-7 days: 136 events;
- 8-14 days: 24 events;
- 15-40 days: 24 events;
- 41-100 days: 12 events;
- 101-180 days: 5 events;
- 181-240 days: 10 events;
- 241-360 days: 33 events;
- 361-609 days: 2 events.

- Duration of relevant events: n = 47, range: from <24 hours to 28 days, median: 14 days.
  - <24 hours: 28 events;
  - 1 day: 2 events;
  - 2-7 days: 6 events;
  - 8-28 days: 11 events.

- Relevant event outcome: resolved/resolving (347), resolved with sequelae (3), not resolved (152), unknown (3120).

16.3.5.1.3. Paediatric Subjects ≥12 to ≤ 17 Years of Age

Clinical Trial Data

- Number of cases: none, compared to 5 cases (6.1%) retrieved in the PSUR #5.

Post-Authorisation Data

- Number of cases: 4690 (original [4502], bivalent Omi BA.4/BA.5 [114], bivalent Omi XBB.1.5 [77], BNT162b2 Multivalent NOS [7], bivalent Omi BA.1 [5]; 4.4% of 107,046 cases, the total PM dataset), compared to 1287 cases (1.7%) retrieved in the PSUR #5.
- MC cases (3511), NMC cases (1179).
- Country/region of incidence (>2%): New Zealand (3254), Japan (813), and US (129).
- Subjects' gender: female (2062), male (1818), and unknown (810).
- Subjects' age in years: n = 3899, range: 12 – 17 years, mean: 14.6, median: 15.0.
- Medical history (n = 160); the most frequently (>5) reported medical conditions included Asthma (24), Food allergy (18), Attention deficit hyperactivity disorder (16), Seasonal allergy (11), Migraine, Mite allergy, Obesity (9 each), Solid organ transplant (8), Drug hypersensitivity (7), Anxiety, Crohn's disease, and Urticaria (6 each).

- COVID-19 Medical history (n = 33): COVID-19 (31), COVID-19 immunisation, Exposure to SARS-CoV-2, and Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (n = 28); the most frequently (>1) reported included COVID-19 vaccine (9), influenza vaccine (8), and elasomeran (4).
- Number of events: 12,918.
- Relevant event seriousness: serious (1723), non-serious (11,196).
- Most frequently reported PTs (≥3%): Dizziness (1466), Nausea (838), Poor quality product administered (768), Headache (738), Product temperature excursion issue (736), Syncope (538), Pyrexia (450), Vaccination site pain (424), Lethargy (421), Chest discomfort (398), Vomiting (316), Anxiety (255), Abdominal pain (254), Pallor (229), Dyspnoea (226), Presyncope (218), Influenza like illness (213), Lymphadenopathy (177), Feeling of body temperature change (153), and Vision blurred (143).
- Time to event onset: n = 10,255, range: from <24 hours to 720 days, median: 85.5 days.
  - <24 hours: 8416 events;
  - 1 day: 501 events;
  - 2-7 days: 622 events;
  - 8-14 days: 186 events;
  - 15-40 days: 256 events;
  - 41-100 days: 117 events;
  - 101-180 days: 34 events;
  - 181-240 days: 14 events;
  - 241-360 days: 55 events;
  - 361-720 days: 54 events.
- Duration of relevant events: n = 165, range: <24 hours to 732 days, median: 22 days.
  - <24 hours: 46 events;
  - 1 day: 32 events;
  - 2-7 days: 30 events;
  - 8-14 days: 26 events;
  - 15-40 days: 10 events;
  - 41-100 days: 5 events;
  - 101-732 days: 16 events.
- Relevant event outcome: fatal (20), resolved/resolving (1572), not resolved (1479), resolved with sequelae (69), unknown (9778).

Fatal cases (8)

- Age: 13 years (3), unknown (2), 12 years, 14 years, and 15 years (1 each).

- MC cases (3), NMC cases (5).
- Gender: female (1) and males (7).
- Country/region of incidence: Spain (3), Germany (2), Austria, Hong Kong, and Philippines (1 each).
- Fatal PTs (20): reported AEs included Myocarditis, Pyrexia, Hypertrophic cardiomyopathy (2 each), Brain oedema, Brain herniation, Chest pain, Circulatory collapse, Drug ineffective, COVID-19, Muscular weakness, Dyspnoea, Use of accessory respiratory muscles, Guillain-Barre syndrome, Acute respiratory failure, Hypoxia, Asphyxia, and Arrhythmia (1 each).
- Medical history (n = 2): Obesity and Attention deficit hyperactivity disorder (1 each).

The 8 fatal cases are summarised below:

In 1 MC and 1 NMC case, limited information was provided, precluding any meaningful assessment. The subjects' medical history/underlying conditions, concomitant medications, or date of death were not reported. Lab data are limited (body temperature: 38-39 centigrade), and information on autopsy was not provided in these 2 cases.

In 6 cases, potential explanations other than vaccination for death are not evident in the reports:

- In 1 NMC case, a 13-year-old female subject experienced pyrexia, chest pain, and circulatory collapse 51 days after receiving BNT162b2 as dose 2, single for COVID-19 immunisation and died on the 52nd day. The subject's medical history, concomitant medications, and information on autopsy were not reported.
- In 3 NMC cases, 3 separate parents reported their children (12, 13, and 14 years of age) died suddenly while playing sports after receiving BNT162b2 (unknown dose number, lot number FG9428 [2] and FG7898 [1]) for COVID-19 immunisation. Fatal events in these 3 cases were Hypertrophic cardiomyopathy (2), Asphyxia, and Arrhythmia (1 each). All subjects had no relevant medical history. Concomitant medications and information on autopsy were not provided and date of death was unknown. No related quality issues were identified on this lot during the investigation.
- In the remaining 2 MC cases originated from 1 literature[68], the 2 adolescent male subjects experienced myocarditis after receiving BNT162b2 vaccination dose 2, single (lot number: unknown) for COVID-19 immunisation (see Section 16.3.1.1.1 *Important Identified Risks - Myocarditis*). The latency time were 3 days and 4 days, respectively. One subject had the medical history of obesity, and another had attention deficit hyperactivity disorder. Concomitant medications were not reported in both cases. The autopsy results included microscopic myocardial findings (myocardial fibrosis in boy A

[68] Gill JR, Tashjian R & Duncanson E. Autopsy histopathologic cardiac findings in 2 adolescents following the second COVID-19 vaccine dose. Archives of Pathology & Laboratory Medicine 2022, 146(8): 925-9.

and cardiac hypertrophy in boy B) and the subjects died suddenly and unexpectedly without resuscitation within the first week after receiving the second dose.

Analysis of confounders and risk factors

Among the 6791 cases involving paediatric subjects, 385 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (185 cases) and/or underlying medical history (282 cases).

Literature

During the reporting period, the review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

Conclusion

Upon review, the most frequently reported AEs indicative of vaccination errors had a higher reporting proportion in paediatric groups < 5 years and ⩾5 Years and ⩽ 11 Years of Ages compared to the ⩾ 12 years of age; while the most frequent AEs indicative of reactogenicity type had a higher reporting proportion in paediatric group ⩾ 12 years of age compared to groups of < 5 years and ⩾5 Years and ⩽ 11 Years of Ages. Of the frequently reported AEs (⩾2%) in the paediatric dataset, no clinical AEs had a higher reporting proportion compared to the non-paediatric dataset. The medication errors reported in this population were in large majority not associated with harm.

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[68] were consistent with the known reactogenicity and safety profile 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 RSI.

16.3.5.2. Use in Pregnant/Lactating Women[69,70]

Clinical Trial Data

There was no pregnancy or lactation cases in the clinical trial dataset for this reporting period compared to 2 cases (2.4%) retrieved in the PSUR #5.

Post-Authorisation Data

- Number of pregnancy cases: 232 (original [160], bivalent Omi BA.1 [10], bivalent Omi BA.4/BA.5 [24], monovalent Omi XBB.1.5 [38]; 0.2% of 107,046 cases, the total PM dataset), compared to 464 cases (0.6%) retrieved in the PSUR #5. These 232 cases represent 201 unique pregnancies (2 cases [a mother case and a foetus/baby case] were created for 31 pregnancies).
- Country/region of incidence (>10 occurrences): UK (38), US (31), New Zealand (24), Germany (19), Netherlands (16), Australia (15), France (12), Slovakia (11).
- Of the 196 mother cases, 34 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 (19), Maternal exposure timing unspecified (12), Maternal exposure before pregnancy (2), Exposure during pregnancy (1).
- There were 162 mother cases of which 97 were serious and 65 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. The pregnancy exposure events (>10 occurrences) were coded to the PTs Maternal exposure during pregnancy (71), Maternal exposure timing unspecified (20), Maternal exposure before pregnancy (12). Additional pregnancy related events reported in these cases (>10 occurrences) were coded to the PTs Abortion spontaneous (34). Other frequently reported clinical events (≥10 occurrences) were coded to PTs Fatigue (23), Headache (22), Vaccination site pain (17), Malaise (14), Nausea (13), COVID-19, Myalgia, Pyrexia (10 each).

---

[69] Exposure *in utero* cases are included.

[70] Search criteria - "Selects Pregnancy cases from the data set. 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.

- Thirty-six (36) baby/foetal cases, 35 serious and 1 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: 18 of these cases reported 26 congenital anomalies that coded to the PTs Syndactyly, Ventricular septal defect (2 each), Accessory auricle, Aorta hypoplasia, Aplasia cutis congenita, Bicuspid aortic valve, Cardiac septal defect, Cerebellar hypoplasia, Cerebral palsy, Cleft lip, Cleft palate, Congenital anomaly, Congenital tracheomalacia, Congenital umbilical hernia, Cytogenetic abnormality, Dysmorphism, Foetal malformation, Foetal vascular malperfusion, Gnathoschisis, Laryngomalacia, Respiratory tract malformation, Rib deformity, Sensory level abnormal, Vascular compression (1 each). Of these 18 cases, information regarding trimester of exposure was available in 3 cases. Of these 3 cases, in 2 cases foetus was exposed during 1st trimester and remaining 1 case, foetus was exposed during 3rd trimester. Of these 18 cases, in 1 case mother of the baby was on multiple co-suspect/concomitant medications (i.e., acetylsalicylic acid, DTP vaccine, tetanus toxoid vaccine, levothyroxine etc.) which might have contributed to the reported event i.e., supraventricular tachycardia. In the remaining 17 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
    - Pregnancy outcome: Spontaneous abortion: 2 cases reported spontaneous abortion. In both these cases information regarding trimester of exposure was unknown. The clinical events in these 2 cases other than exposure related events were coded to PTs Foetal death, Foetal malformation (2 each). In these 2 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.
    - Pregnancy outcome: Elective termination: 1 case reported elective termination of pregnancy due to foetal defects. In this case information regarding trimester of exposure was unknown. The events reported in case other than exposure related events were coded to PTs Multiple congenital abnormalities, Chromosomal deletion, Hydrops foetalis, Congenital foot malformation, Heart disease congenital, Congenital hand malformation, Amniotic fluid volume increased, Dysphagia (1 each). In this case there was limited information regarding mothers' obstetric history which precluded meaningful causality assessment.
    - Pregnancy outcome: Stillbirth: 5 cases reported foetal death/ neonatal death. Of these 5 cases, 2 cases reported stillbirth with foetal defect and 3 cases reported stillbirth without foetal defect. The information regarding trimester of exposure was available in 2 cases and in these cases, foetus was exposed during 2nd and 3rd trimester. The events reported in these cases other than exposure related events were coded to PTs Foetal growth restriction (2), Congenital anomaly, Foetal cystic hygroma, Foetal death, Premature baby death (1 each). Of these 5 cases, in 1 case mother of the baby had underlying urinary tract infection, which might have contributed to the reported event. In the remaining 4 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Live birth without congenital anomaly: 10 cases reported live birth babies without congenital anomaly. Of these 10 cases, information regarding trimester of exposure was available in 3 cases. In these 3 cases, foetus was exposed during the 1st, 2nd and 3rd trimester each. The events reported in these 10 cases other than exposure related events were coded to PTs Foetal hypokinesia (4), Premature baby (2), Foetal growth restriction, Ischaemic stroke, Sebaceous naevus (1 each). In all these 10 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 232 cases, 172 cases provided pregnancy outcomes which are provided in Table 59 below. Pregnancy outcome was pending or not provided in the remaining 60 cases.

Table 59. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a,b]

Pregnancy outcome	Prospective cases 87 (37.5% of pregnancy cases)				Retrospective cases 85 (36.6% 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	0	0	0	0	0
Spontaneous abortion	0	0	0	3	2	0	0	21
Elective termination (foetal defects)	0	0	0	0	0	0	0	2
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	2	0	1
Stillbirth without foetal defects	0	0	0	0	0	1	0	6
Live birth with congenital anomaly	0	0	0	2	4	4	0	17
Live birth without congenital anomaly	10	12	0	60	3	9	0	13
Total	***10***	***12***	***0***	***65***	***9***	***16***	***0***	***60***

a. 19 June 2023 through 18 December 2023.
b. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception.

Lactation cases

- Number of lactation cases: 94 (original [81], bivalent Omi BA.1 [2], bivalent Omi BA.4/BA.5 [8], monovalent Omi XBB.1.5 [3]; 0.1% of 107,046 cases, the total PM dataset), compared to 119 cases (0.2%) retrieved in the PSUR #5.

- Breast feeding baby cases: 80, of which:
- Sixty-eight (68) cases reported exposure to vaccine during breastfeeding Exposure via breast milk) without the occurrence of any clinical events.
- Twelve (12) cases, 1 serious and 11 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 (>1 occurrence) other than exposure related events were coded to PTs Infantile diarrhoea, Pyrexia (3 each), Infant irritability, Anxiety, Abdominal pain, Urticaria (2 each).
- Breast feeding mother cases: 14, of which
- Six (6) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
    - Eight (8) cases, 2 serious and 6 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (≥2 occurrences) other than exposure related events were coded to PTs Dizziness (3), Mastitis, Pyrexia, Vomiting, Arthralgia (2 each).

Literature

Review of the literature did not identify any new safety information regarding the use of BNT162b2 in pregnant/lactating women.

Conclusion

There were no safety signals regarding use in pregnant/lactating women that emerged from the review of these cases or the medical literature.

16.4. Characterisation of Risks

In the PSUR #4, the MAH, based on the review of clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of VAED/VAERD from the list of the safety concerns.

The PRAC agreed to remove the VAED/VAERD from the safety concerns as per the AR of PSUR 4 received during the previous PSUR 5 reporting period. This risk is not included in the safety concerns at the beginning of the reporting period according to the explanatory note on PSURs, in the EU regional appendix in GVP Module section VII.C.5.3.

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[71] of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 11.0 approved on 26 October 2023.

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 2023 is provided in Section 16.4.1.1 and Section 16.4.1.2.

[71] None.

16.4.1.1. Cumulative Characterisation of Important Identified Risks

Table 60. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
Myocarditis and Pericarditis	Cumulatively, there were 6[a] cases of Myocarditis and Pericarditis: 4 cases reported myocarditis and 2 cases reported pericarditis (none of these 6 cases reported developing both the events- myocarditis and pericarditis). *Myocarditis* • No. of cases: 4 [original]. • No. of SAEs: 4. • Relevant PTs: Myocarditis, Myopericarditis (2 each). • Related SAEs: Myopericarditis (2), Myocarditis (1). *Pericarditis* • No. of cases: 2[a] [original]. • No. of SAEs: 2. • Relevant PTs: Pericarditis (2). • Related SAEs: none. Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.	Cumulatively, there were 24,103 cases of Myocarditis and Pericarditis: 14,842 cases reported myocarditis and 11,572 cases reported pericarditis (in 2311 of these 24,103 cases, the subjects developed both myocarditis and pericarditis). *Myocarditis* • No. of cases: 14,842 (original [14,659], bivalent Omi BA.1 [75], bivalent Omi BA.4/BA.5 [83]), multivalent NOS [9], monovalent Omi XBB.1.5 [26]. • Relevant PTs: Myocarditis (12,480), Myopericarditis (2278), Carditis (196), Eosinophilic myocarditis (19), Autoimmune myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis (7 each), Immune-mediated myocarditis (6), Chronic myocarditis (5). • Frequently co-reported PTs (≥200): Chest pain (4,868), Dyspnoea (3,225), Fatigue (2,587), Palpitations (2,367), Pericarditis (2,304), Pyrexia (2,176), Tachycardia (1,616), Chest discomfort (1,583), Headache (1,280), Dizziness (953), Off label use (923), Immunisation (898), Troponin increased (895), Interchange of vaccine products (845), Malaise (726), Inappropriate schedule of product administration (698), Asthenia (689), Arrhythmia (682), Nausea (615), Myalgia (586), Pain (571), Pain in extremity (551), Pericardial effusion (497), Chills (494), Angina pectoris (464), Syncope (450), Arthralgia (436), Vomiting (385), Heart rate increased (372), Cough (348), Cardiac failure (332), Paraesthesia (327), Dyspnoea exertional (326), Hyperhidrosis (310), Diarrhoea (291), Influenza like illness (273), C-reactive protein increased (261), Hypertension (260), Vaccination site pain (249), COVID-19 (245), Hypoaesthesia (244), Lymphadenopathy (243), Back pain (234), Myocardial infarction (220), Atrial fibrillation (215), Lethargy (203), Electrocardiogram ST segment elevation (202). • Subjects' gender: female (5094), male (9216) and unknown (532).

Table 60. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		• Subjects' age in years (n = 13,381), range: 1.25 – 102 years, mean: 35.7 years, median: 32.0 years. • Age group: Paediatric (2165), Adults (10,180), Elderly (1158) and Unknown (1339). • Case source: Spontaneous (14,279), Literature (496), Clinical study (32), Other Solicited (35). • Event seriousness: serious (15,005) • Event outcome: fatal (293), resolved/resolving (5717), resolved with sequelae (452), not resolved (4232), unknown (4324). *Pericarditis* • No. of cases: 11,572 (original [11,429], bivalent Omi BA.1 [56], bivalent Omi BA.4/BA.5 [57], multivalent NOS [4], monovalent Omi XBB.1.5 [26]). • Relevant PTs: Pericarditis (11,478), Pleuropericarditis (86), Pericarditis constrictive (30), Autoimmune pericarditis, Pericarditis adhesive (1 each). • Frequently co-reported PTs (≥2%): Chest pain (4736), Dyspnoea (2961), Myocarditis (2149), Fatigue (2063), Palpitations (1893), Pyrexia (1328), Tachycardia (1260), Chest discomfort (1252), Pericardial effusion (969), Headache (911), Dizziness (699), Immunisation (686), Off label use (648), Interchange of vaccine products (595), Malaise (522), Nausea (484), Myalgia (471), Pain (464), Asthenia (450), Arthralgia (444), Pain in extremity (436), Inappropriate schedule of product administration (395), Paraesthesia (333), Syncope (312), Cough (285), Angina pectoris (275), Chills (273), Heart rate increased (264), Electrocardiogram abnormal (254), Lethargy (246), Arrhythmia (227), Back pain (223), Pleural effusion (217), Dyspnoea exertional (214), Lymphadenopathy (211), Hyperhidrosis (210), Influenza like illness, Vaccination site pain (208 each), Vomiting (206), Hypoaesthesia (195), Myopericarditis (193), C-reactive protein increased (191), Diarrhoea (185),

Table 60. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Hypertension (184), and Troponin increased (173). • Subjects' gender: female (5453), male (5860) and unknown (259). • Subjects' age in years (n = 10689), range: 2-98 years, mean: 40.1 years, median: 37.0 years. • Age group: Paediatric (765), Adults (8859), Elderly (1133), and Unknown (815). • Case source: Spontaneous (11389), Literature (120), Clinical study (46), Other solicited sources (17). • Event seriousness[b]: serious (11,596). • Event outcome[c]: fatal (52), resolved/resolving (4277), resolved with sequelae (214), not resolved (3924), unknown (3139). Based on the cumulative PM data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.

a. During the current reporting period, one CT case reporting the event - pericarditis was unblinded and was found to have been received placebo, hence excluded from the analysis in the current dataset.
b. Multiple episodes of the same event were reported with a different seriousness in some cases hence the sum of the events seriousness exceeds the total number of events.
c. 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.

16.4.1.2. Cumulative Characterisation of Important Potential Risks

None.[17]

16.4.2. Description of Missing Information

Table 61 describes missing information associated with the use of BNT162b2.

Table 61. Description of Missing Information

Topic	Description	
Use in pregnancy and while breast feeding	The safety profile of the vaccine is not yet fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated. It is important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy are not yet fully understood but some data have suggested that pregnant women have an increased risk of severe disease and complications when affected by COVID-19. This information should be considered in the benefit-risk consideration for vaccination in pregnancy. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.2 *Use in Pregnant/Lactating Women.*	
Use in immunocompromised patients[72]	The vaccine has not been studied in individuals with overt immunocompromised conditions. Therefore, further safety data will be sought in this population.	
	Clinical Study Data	**Post-Marketing Data**
	• No. of cases: 2 (monovalent Omi XBB.1.5; 10.5% of 19 cases, the total CT dataset) compared to 3 cases (3.7%) retrieved in the PSUR #5. • Subjects' gender: female (2). • Subjects' age: 64 years and 82 years, mean: 73.0, median: 73.0. • Reported clinical PTs: Invasive lobular breast carcinoma and Pulmonary embolism (1 each). • Related SAEs: none. • Reported event outcome: not resolved (2).	• No. of cases: 1653 (original [936], bivalent Omi BA.1 [84], bivalent Omi BA.4/BA.5 [267], monovalent Omi XBB.1.5 [366]; 1.5% of 107,046 cases, the total PM dataset) compared to 2628 cases (2.5%) retrieved in the PSUR #5. • Subjects' gender: female (1054), male (531) and unknown (68). • Subjects' age in years: n = 1515, range: 1.5 years – 100 years, mean: 61.6, median: 63.0. • Most frequently reported clinical PTs (≥3%): COVID-19 (294), Fatigue (203), Headache (178), Pyrexia (152), Malaise (105), Chills, Nausea (104 each), Arthralgia (99), Pain in extremity (96),

[72] Search criteria: Patients with Medical history of PTs included in
SMQ Narrow: Malignancy related conditions, Malignancy related therapeutic and diagnostic procedures, Malignant or unspecified tumours;
HLGT (Primary Path): Immunodeficiency syndromes;
HLT (Primary Path): Retroviral infections;
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.

Table 61. Description of Missing Information

Topic	Description	
Use in immunocompromised patients *Cont'd*	• Relevant medical history: Breast cancer and Radioactive iodine therapy (1 each).	Myalgia (93), Pain (90), Dyspnoea (87), Dizziness (84), Vaccination failure, Vomiting (78 each), Asthenia (75), Palpitations (64), Chest pain, Vaccination site pain (56 each), Diarrhoea (52). • Event seriousness: serious (4070), non-serious (2857). • Event outcome: fatal (196), resolved/resolving (1803), resolved with sequelae (122), not resolved (1680), unknown (3134). • Relevant medical history (>50): Immunodeficiency (316), Breast cancer (181), Thyroidectomy (93), Neoplasm malignant (81), Hysterectomy (78), Chemotherapy (76), Prostate cancer (72), Neoplasm (60), Chronic lymphocytic leukaemia (56), Radiotherapy (55).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)[73]	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.	
	Clinical Study Data • Number of cases: 2 [BNT162b2 B.1.1.7, BNT162b2 B.1.617.2 (1), bivalent Omi BA.4/BA.5 (1)]; 10.5% of 19 cases, the total CT dataset) compared to 19 cases (23.2%) retrieved in the PSUR #5. • Subjects' gender: female (1), male (1). • Subjects' age in years: n = 2, range: 5 – 64 years, mean: 34.5 years, median: 34.5 years. • Reported PTs: Faecaloma and Pneumonia bacterial (1 each). • Related SAEs: 0.	**Post-Marketing Data** • No. of cases: 3170 [original (1753), Omi XBB.1.5 (733), bivalent Omi BA.4/BA.5 (390), bivalent Omi BA.1 (120), original with bivalent Omi BA.4/BA.5 (83), unspecified bivalent (73), Omi XBB.1.5 with bivalent Omi BA.4/BA.5 (6), original with bivalent Omi BA.1 (4), original with unspecified bivalent (3), Omi XBB.1.5 with bivalent Omi BA.1 (2), original with Omi XBB.1.5, Omi XBB.1.5 with unspecified bivalent, and original with both bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (1 each)]; 3% of 107,046 cases, the total PM dataset) compared to 5738 cases (7.7%) retrieved in the PSUR #5 No. of cases: 3170

[73] 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 61. 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*	• Relevant event outcomes: resolved (2).	[original (1753), Omi XBB.1.5 (733), bivalent Omi BA.4/BA.5 (390), bivalent Omi BA.1 (120), original with bivalent Omi BA.4/BA.5 (83), unspecified bivalent (73), Omi XBB.1.5 with bivalent Omi BA.4/BA.5 (6), original with bivalent Omi BA.1 (4), original with unspecified bivalent (3), Omi XBB.1.5 with bivalent Omi BA.1 (2), original with Omi XBB.1.5, Omi XBB.1.5 with unspecified bivalent, and original with both bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (1 each)]; 3% of 107,046 cases, the total PM dataset) compared to 5738 cases (7.7%) retrieved in the PSUR #5. • Subjects' gender: female (1930), male (1184), and unknown (56). • Subjects' age in years: n = 3039, range: 1.25 – 101 years, mean: 59.2, median: 62 years. • Relevant PTs most frequently reported (≥2%): COVID-19 (510), Drug ineffective (426), Fatigue (393), Headache (320), Pyrexia (274), Interchange of vaccine products (266), Inappropriate schedule of product administration (224), Arthralgia (215), Malaise (197), Dizziness (187), Dyspnoea (185), Myalgia (184), Pain in extremity (177), Vaccination site pain (157), Pain (150), Nausea (148), Chills (143), Vaccination failure (134), Asthenia (130), Vomiting (96), Palpitations (91), Cough and Pruritus (78 each), Chest pain and Diarrhoea (75 each), Paraesthesia (72), Lymphadenopathy (71), Disturbance in attention and Gait disturbance (70 each), Condition aggravated (67). • Event seriousness: serious (6787), non-serious (6208). • Relevant event outcome: unknown (5499), resolved/resolving (3441), not resolved (3328), resolved with sequelae (400), fatal (366).

Table 61. Description of Missing Information

<table>
<tr><th>Topic</th><th colspan="2">Description</th></tr>
<tr><td rowspan="3">Use in patients with autoimmune or inflammatory disorders[74]</td><td colspan="2">There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.</td></tr>
<tr><td>Clinical Study Data</td><td>Post-Marketing Data</td></tr>
<tr><td>• Number of cases: 2 (monovalent Omi XBB.1.5 [2], 10.5%), compared to 3 cases (3.7%) retrieved in the PSUR #5.
• Subjects' gender: female (2).
• Subjects' age in years: 61 and 64 (n = 2).
• Reported PTs: Acute kidney injury, Condition aggravated, Hyponatraemia, Invasive lobular breast carcinoma, Paroxysmal nocturnal haemoglobinuria (1 each).
None of these events were assessed as related to monovalent Omi XBB.1.5 by the investigator or Sponsor.
• Event outcome: resolved (4), not resolved (1).</td><td>• Number of cases: 3392 (original [2083], bivalent B.1.1.7/B.1.617.2 [1], bivalent Omi BA.1 [133], bivalent Omi BA.4/BA.5 [477], multivalent NOS [109], monovalent Omi XBB.1.5 [708]; 3.2% of 107,046 cases in the total PM dataset), compared to 5856 cases (7.9%) retrieved in the PSUR #5.
• MC cases (1191), NMC cases (2201).
• Subjects' gender: female (2413), male (903), unknown (76).
• Subjects' age in years: n = 3199, range: 3 – 102, mean: 57.5, median: 59.
• PTs most frequently reported (≥300): COVID-19 (560), Drug ineffective (464), Fatigue (458), Headache (384), Pyrexia (273), Arthralgia, Interchange of vaccine products (251 each), Inappropriate schedule of product administration (240), Pain in extremity (225), Myalgia (219), Dizziness, Malaise (206 each).
• Event seriousness: serious (6909), nonserious (6905).
• Event outcome: fatal (152), resolved/resolving (3582), resolved with sequelae (447), not resolved (3653), unknown (5997).</td></tr>
<tr><td colspan="2">Of the 162 cases (1 CT, 161 PM) that reported PTs indicative of exacerbation or flare, 84 cases were determined to be non-contributory and were not included in the discussion for the following reason:
– The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (eg, pain, migraine, menstruation, COVID-19/long COVID).
Therefore, 78 cases (1 CT, 77 PM) are included in the analysis below.</td></tr>
</table>

[74] 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.

Table 61. Description of Missing Information

Topic	Description	
	Exacerbation or flare-up • Number of cases: 1 case (5.3%) compared to no. cases retrieved in the PSUR #5. • Country of incidence: US (1). • Subject's gender: female (1). • Subject's age in years: 61 (n = 1). • Relevant medical history: Paroxysmal nocturnal haemoglobinuria (1). • Number of events: 4 (of which 1 was an event of interest ie, exacerbation/flare AEs). • Relevant PT: Condition aggravated (1; assessed as unrelated to monovalent Omi XBB.1.5 by the investigator and Sponsor). • Relevant event outcome: resolved (1).	***Exacerbation or flare-up*** • Number of cases: 77 cases (0.1%) compared to 200 cases (0.3%) retrieved in the PSUR #5. • MC cases (47), NMC cases (30). • Country of incidence (≥3): Germany (17), France (13), Japan, UK (7 each), Netherlands, US (6 each), Norway (4), Italy (3); the remaining 14 cases were distributed among 10 countries. • Subjects' gender: female (40), male (34), unknown (3). • Subjects' age in years: n = 72, range: 6 – 90, mean: 55.5, median: 55.0. • Relevant medical history: the most frequently (≥3) reported medical conditions included: Pemphigoid, Hypothyroidism (5 each), Sjogren's syndrome, Rheumatic disorder (4 each), Autoimmune thyroiditis, Graves' disease, Rheumatoid arthritis, Type 1 diabetes mellitus, Chronic inflammatory demyelinating polyradiculoneuropathy, IgA nephropathy, Immune thrombocytopenia (3 each). • Number of events: 339 (of which 77 were events of interest ie, exacerbation/flare AEs). • Relevant event seriousness: serious (61), nonserious (16). • Most frequently reported relevant PTs: Condition aggravated (45), Disease recurrence (24), Concomitant disease aggravated (5), Disease progression (3). • Relevant event outcome: resolved/resolving (30), resolved with sequelae (4), not resolved (20), unknown (23); there were no relevant events with a fatal outcome.
Interaction with other vaccines *Search criteria: HLT Interactions (All Paths)*	During the reporting interval, 2 non-serious PM cases reported interaction with other vaccine. The first case reported an interaction with the influenza vaccine inact split 4V whose co-reported events were cough, malaise, and fever. The remaining case reported an interaction with RSV 2v preF protein subunit vaccine and an unspecified influenza vaccine a patient of unspecified age. The co-reported events were Flu/slight flu-like symptoms. In both cases the information is limited.	
Long term safety data	At this time, 6-month post dose 2 safety data are available for all patients who have received COVID-19 mRNA vaccine in Study C4591001.	

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.[75]

17.1.1. Clinical Study Data in Individuals ≥12 Years of Age

Study C4591001 was a multicenter, placebo-controlled- efficacy study in participants 12 years of age and older. Randomisation 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.[76] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[75] 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,[77] were included as were participants with known stable infection with HIV, HCV, or HBV.[75]

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. As shown in the table below, the difference in vaccine efficacy percentages is similar between the without evidence of prior SARS-CoV-2 infection participants and the with or without evidence of prior SARS-CoV-2 infection participants.

[75] As per information reported in the CDS version 24.0 dated 24 November 2023, in effect at the end of the reporting period.

[76] Ref#12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2.

[77] Ref#21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

Table 62. 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*,[78]			
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[79]			
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).

[78] 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.

[79] 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 62. 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).

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 63) 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 63. 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[80,81]			
	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)

[80] 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.

[81] 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.

Table 63. 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 CDC Definition[82,83]			
	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).

* 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:[84]

- 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:[84]

- 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.[85]

---

[82] 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.

[83] 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.

[84] 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.

[85] Ref#62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 63. 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

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.[85]

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 64.

Table 64. 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*,[86]			
	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[87]			
	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

[86] 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.

[87] 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.

TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 through 25 years of age (n = 170), based on results for 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.[88]

Efficacy and immunogenicity in participants ≥ 16 years of age after booster dose

Study C4591031 Substudy A was 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 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.

An interim efficacy analysis evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of a 30 mcg BNT162b2 booster dose after the primary series relative to the placebo booster group was assessed. The relative vaccine efficacy for participants 16 years of age and older was 63.9% (2-sided 95% CI: 51.1:73.5) in the without evidence of SARS-CoV-2 infection population, (63 cases in the BNT162b2 group and 148 cases in the placebo group), with a similar efficacy in the with or without evidence of SARS-CoV-2 infection population.

Clinical Study Data for Omicron BA.1-Adapted Vaccines in Individuals ⩾18 Years of Age

Substudy D of C4591031 is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 Omi, and as a booster (third, fourth, or fifth) dose. Participants ⩾18 years of age to ⩽55 years of age were enrolled. The study consists of 3 cohorts:

[88] 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.

Participants in Cohort 1 completed a 2-dose primary series of BNT162b2 (30-µg doses), with their last dose 90 to 240 days prior to enrollment. Participants were randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 Omi (Group 1), 2 doses (third and fourth) of BNT162b2 Omi, 4 weeks apart (Group 2), or 1 dose (third) of BNT162b2 (Group 2b). Randomization was stratified by age (stratified as 18-30 and 31-55 years of age).

Participants in Cohort 2, enrolled from Study C4591001 and C4591031 Substudy A, completed a 2-dose primary series and received a single booster (third) dose of BNT162b2, with their last dose 90 to 180 days prior to randomization. Participants were randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 Omi (Group 3) or BNT162b2 (Group 4). Participants in both groups were offered a dose of BNT162b2 Omi at the 3-month follow-up visit. Randomization was stratified by age (stratified as 18-30 and 31-55 years of age).

In Cohort 3, participants 18 through 55 years of age who were COVID-19 vaccine–naïve and had not experienced COVID-19 were enrolled to receive 2 doses (primary series) of BNT162b2 Omi, 3 weeks apart, with a dose of BNT162b2 approximately 5 months later (Group 5).

Analyses of the primary immunogenicity endpoints in the 640 participants 18-≤ 55 years of age who received either BNT162b2 Omi 30 µg or BNT162b2 30 µg, at 1 month post vaccination in Cohort 2:

In participants without prior evidence of infection up to 1 month after Dose 4, for the Omicron (BA.1) variant:

- The ratio of GMTs for the BNT162b2 Omi group to BNT162b2 group (GMR) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was >1, the simple superiority of BNT162b2 Omi to BNT162b2 for the Omicron variant was achieved based on GMR at 1 month after Dose 4.
- Seroresponse rates to the Omicron variant were 62.3% in the BNT162b2 Omi group and 39.3% in the BNT162b2 group, and the difference in proportions of participants who achieved seroresponse to Omicron variant between the BNT162b2 Omi and BNT162b2 groups was 23.0% (2-sided 95% CI: 11.1%, 34.3%). As the lower bound of the 2-sided 95% CI for GMR was greater than the prespecified margin of -5%, noninferiority of BNT162b2 Omi to BNT162b2 for the Omicron variant was achieved based on seroresponse rates at 1 month after Dose 4. The lower bound of the 2-sided 95% CI was greater than 0%, suggesting higher seroresponse to Omicron variant in BNT162b2 Omi recipients than BNT162b2 recipients.

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)

Analyses of the primary immunogenicity endpoints in the 610 participants >55 years of age who received either BNT162b2 +BNT162b2 Omi 30 µg or BNT162b2 30 µg, at 1 month post vaccination:

- 'Simple' superiority of bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg was met, as the lower bound of the 2-sided 95% CI for GMR was >1 (GMR of 1.56 [2 sided 95% CI: 1.17, 2.08]).
- Noninferiority based on seroresponse for bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg was met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5% with a point estimate of 14.6% (2-sided 95% CI: 4.0, 24.9).

Clinical Study Data for Original/BA.4/BA.5-Adapted Vaccines in Individuals ⩾12 Years of Age

Analysis of immunogenicity data at 1 month post study vaccination from Study C4591044 Cohort 2 and Cohort 2 and 3 combined for BNT162b2-experienced participants >12 years of age who received a booster (dose 4) of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg or 60 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 or 60 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.

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 higher titers observed in participants with prior infection. Within baseline positive or baseline negative groups, anti-Omicron BA.4/BA.5 and anti-reference strain neutralizing titers were higher in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg compared with other age and vaccine groups at both prevaccination and 1 month after vaccination.

Superiority of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E was met with respect to anti-Omicron BA.4/BA.5 neutralizing titers. Noninferiority based on Omi BA.4/BA.5 seroresponse and anti-reference strain immune response based on GMR was also met in the >55 years of age group.

Noninferiority of the anti-Omicron BA.4/BA.5 response based on GMR and seroresponse for BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg participants 18 through 55 years of age to participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg were also met.

Immune response against Omicron BA.4/BA.5 was higher in all age groups (18 through 55 and >55 years) when compared to control groups from Study C4591031 Substudy E who received BNT162b2 Bivalent (WT/Omi BA.1) vaccine, with a substantially larger increase in baseline negative participants. Immune responses against the Omicron BA.1 and the reference strain were comparable for both bivalent vaccines in baseline positive participants, and a trend of higher increases for baseline negative participants was observed in participants who received BNT162b2 Bivalent (WT/Omi BA.4/BA.5). Immune responses against Omicron sublineages (BA.4.6, BA.2.75.2 and BQ.1.1) were also higher compared to BNT162b2 vaccine. Immune responses against Omicron XBB were limited.

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.

17.1.2. 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.

An initial descriptive efficacy analysis of Study C4591007 was 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[89] with an observed efficacy point estimate of 90.7% (2 sided 95% CI: 67.7, 98.3).

Prespecified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population. In the efficacy analysis in children 5 to 11

[89] 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.

years of age without evidence of prior infection, there were 10 cases out of 2,703 participants who received the vaccine and 42 cases out of 1,348 participants who received placebo. The point estimate for efficacy is 88.2% (95% CI: 76.2, 94.7). In participants with or without evidence of prior infection there were 12 cases in the 3,018 who received vaccine and 42 cases in 1,511 participants who received placebo. The point estimate for efficacy is 85.7% (95% CI: 72.4, 93.2).

An analysis of SARS-CoV-2 50% neutralising titers (NT50) 1 month after dose 2 in a randomly selected subset of participants, demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study C4591007 to participants 16 through 25 years of age in the Phase 2/3 part of Study C4591007 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before dose 1). The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18).[90]

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%).[89]

Immunogenicity after booster (3rd) dose

Effectiveness of a booster dose was based on an assessment of NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose (Dose 3) demonstrated a substantial increase in GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. At 1-month post-dose 3, GMTs 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) and 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 neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed

[90] 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.

neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively.

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Immunogenicity of 4th Dose of Bivalent BNT162b2 (Original/Omi BA.4/BA.5)

Analysis of immunogenicity data from C4591048 Group 2 for BNT162b2-experienced (i.e., they had 3 prior doses of 10 µg original BNT162b2, with the last dose being 90 to 240 days before enrollment) participants ≥5 years to <12 years of age who received a booster (Dose 4) with BNT162b2 Bivalent (Original/Omi BA.4/BA.5) 10 µg indicated a robust immune response against Omicron BA.4/BA.5. Immune responses against Omicron BA.4/BA.5 were generally similar to that of the comparator group, Study C4591007 participants of the same age who received a third dose of the original BNT162b2 vaccine. Immune responses against the reference strain were also comparable for the bivalent BNT162b2 (Original/Omi BA.4/BA.5) and BNT162b2 groups.

The relative magnitude of the Omicron BA.4/BA.5 immune response after Dose 3 of original BNT162b2 is unexpected and may reflect differences in natural exposure and dose intervals between the 2 groups (5.5 months [range 3.5-8.5 months] vs 6.5 months [range 6.3-7.6 months] for BNT162b2 (Original/Omi BA.4/BA.5) dose interval between Dose 3 and Dose 4 and BNT162b2 dose interval between Dose 2 and Dose 3, respectively). As this analysis did not compare 2 contemporaneous randomized groups, there may have been an imbalance between the 2 groups in some measurable or non-measurable factors.

Based on the descriptive immunogenicity and safety data up to 1 month after vaccination with bivalent BNT162b2 (Original/Omi BA.4/BA.5) in Study C4591048 participants ≥5 years to <12 years of age, the 10-µg bivalent booster (Dose 4) with the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine has a favourable benefit-risk profile in this population.

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 paediatric study in healthy children from 6 months to <12 years of age.

Immunobridging success criteria were met for both age groups (6 months to <2 years and 2 to <5 years), 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.

Efficacy in Children 6 Months to <5 Years

The efficacy analysis for Phase 2/3 Study C4591007 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the BNT162b2 (Original) group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded

follow up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of June 17, 2022).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.

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.

17.1.4. Real World Data for Omicron Variant

Omicron-specific VE for the time period 19 June 2023 to 18 December 2023

During the reporting period, a systematic review and meta-analysis by Guo et al., published in the September 2023 issue of American Journal of Infection Control, reported on the real-world effectiveness of original mRNA vaccines (BNT162b2 or mRNA-1273) against Omicron-related infection, symptomatic infection, and severe disease.[91] The systematic review included a total of 34 peer-reviewed publications and preprints published through June 20, 2022 reporting on studies conducted in 8 countries (US, Canada, Denmark, UK, Finland, Malaysia, Norway, and Qatar). The authors found that mRNA booster vaccination provided additional protection against Omicron-related infections, particularly severe infections.

Two-dose mRNA VE against any Omicron infection was 39.43% (95% CI: 35.17 to 43.69), 36.40% (95% CI: 29.59 to 43.20), and 33.14% (95% CI: 21.11 to 45.17) at 3, 3-6 and more than 6 months following 2-dose vaccination, respectively. The mRNA VE against symptomatic infection was 46.22% (95% CI: 37.04 to 55.40), 18.10% (95% CI: 13.72 to 22.47), and 16.79% (95% CI: 4.76- to 28.82) at 3, 3-6 and more than 6 months following 2-dose vaccination, respectively. The mRNA VE against severe infection was 64.23% (95% CI: 54.43 to 74.04), 65.91% (95% CI: 60.26 to 71.55), and 60.43% (95% CI: 50.93 to 69.94) at 3, 3-6 and more than 6 months following 2-dose vaccination, respectively. In summary, the authors found that two-dose mRNA vaccine effectiveness against Omicron-related symptomatic infections significantly decreased by 3-6 months post-dose 2, but did not observe significant waning for any infection or severe infection.

In contrast to 2-dose mRNA vaccine effectiveness, 3-dose mRNA vaccine effectiveness still provided additional protection against all evaluated Omicron-related endpoints after at least 3 months. The 3-dose mRNA vaccine effectiveness against any Omicron infection was 62.31% (95% CI: 58.97 to 65.64), and 55.39% (95% CI: 49.63 to 61.15) at 3 and more than 3 months

[91] Guo K, Ni P, Chang S, et al. Effectiveness of mRNA vaccine against Omicron-related infections in the real world: A systematic review and meta-analysis. Am J Infect Control 2023; 51(9): 1049-55.

following 3-dose vaccination, respectively. The VE against severe infection was 89.86% (95% CI: 87.96 to 91.77), and 73.39% (95% CI: 66.88 to 79.90) at 3 and more than 3 months following 3-dose vaccination, respectively. Relative effectiveness (3 doses versus 2 doses) of BNT162b2 vaccine against Omicron infection, symptomatic infection and severe infection was 33.20% (95% CI: 11.41 to 54.99), 52.48% (95% CI: 39.23 to 65.73) and 70.24% (95% CI: 53.89 to 86.59).

17.2. Newly Identified Information on Efficacy and Effectiveness

17.2.1. Clinical Study Data in Individuals ≥12 Years of Age

There was no new data in the reporting period.

17.2.2. Clinical Study Data in Children 5 Through <12 Years of Age

There was no new immunogenicity data in the reporting period.

17.2.3. Clinical Study Data in Children 6 Months Through <5 Years of Age

Analysis of immunogenicity data at 1 month after vaccination in the evaluable immunogenicity population with or without evidence of infection up to 1 month post dose for participants ⩾6 months to <5 years of age who received a booster (Dose 4) with bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg demonstrated a robust vaccine-elicited immune response to both Omicron BA.4/BA.5 and reference strain compared to participants who received 3 doses of BNT162b2 3 µg.

Primary Immunogenicity Analyses- Per-Protocol Subset

- Superiority of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg to BNT162b2 3 µg with respect to anti-Omicron BA.4/BA.5-neutralizing titers was met.
- Noninferiority of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg to BNT162b2 3 µg with respect to seroresponse rate to Omicron BA.4/BA.5 was met.

Secondary Immunogenicity Analyses- Per-Protocol Subset

- Noninferiority of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg to BNT162b2 3 µg with respect to anti-reference-strain-neutralizing titers was met.
- Noninferiority of bivalent BNT162b2 (Original/Omi BA.4/BA.5) 3 µg to BNT162b2 3 µg with respect to seroresponse rate to reference-strain was met.

Overall, the collective data reinforce the importance of a variant-adapted vaccine in this pediatric age group that is closely matched to current circulating strains.

17.2.4. Real World Data for Omicron-Adapted Vaccines

During the current reporting period, two pre-prints were made available estimating vaccine effectiveness for XBB.1.5-adapted mRNA vaccines and are summarized below.

On 22 November 2023, Hansen et al. posted a pre-print describing XBB.1.5-adapted vaccine effectiveness against COVID-19 hospitalization in a national study of adults older than 65

years of age in Denmark.[92] XBB.1.5-adapted mRNA vaccines were first available in Denmark on 1 October 2023 and the study was conducted from 8 October 2023 until 26 October 2023. The cohort study used nation-wide registry data and followed 442,164 vaccinated and 867,548 unvaccinated individuals older than 65 years of age who had previously received a 2022/23 seasonal COVID-19 booster vaccine dose. Among vaccinated individuals, 90.4% received the Pfizer-BioNTech vaccine and individuals were followed-up for an average of 9.9 days (starting from 7 days after dose receipt to a maximum of 25 days after dose). After adjustment for age, sex, residency region, and number of comorbidities, the XBB.1.5-adapted mRNA vaccine was 75.3% (95% CI: 61.1 to 84.3) effective against COVID-19 hospitalization. A negative control outcome analysis using non-COVID-19 hospitalizations suggested that despite adjustment for potential biases and confounding, the unvaccinated group might have had somewhat poorer health than the vaccinated group.

A study of BNT162b2 XBB.1.5-adapted vaccine effectiveness against COVID-19 hospitalization and ICU admission conducted in the Netherlands was submitted as a pre-print on 13 December 2023 by van Werkhoven et al.[93] This screening method study included adults aged ⩾60 years who had previously received at least one COVID-19 vaccination. The study period included vaccinations on or after 25 September 2023 and hospitalizations between 9 October 2023 and 5 December 2023, and captured approximately 55% of all COVID-19 hospitalizations during the period in the Netherlands. A total of 2,050 hospitalized individuals were included, of whom 295 were vaccinated and 1,755 unvaccinated. Vaccinated individuals were followed starting at 7 days post-dose up to a maximum of 71 days post-dose. After adjustment for calendar date, region, sex, and age, the XBB.1.5-adapted vaccine was 70.7% (95% CI: 66.6 to 74.3) effective against COVID-19 hospitalization and 73.3% (95% CI: 42.2 to 87.6) effective against COVID-19 ICU admission among individuals aged ⩾60 years.

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 in the pre-Omicron era. 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 booster dose(s). Efficacy has also been demonstrated in the 5 to <12 years of age and 6 months to <5 years of age groups.

---

[92] Hansen CH, Moustsen-Helms IR, Rasmussen M, et al. Effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation: a nation-wide cohort study in Denmark, October 2023. (November 8, 2023). Available at SSRN: http://dx.doi.org/10.2139/ssrn.4627268.

[93] van Werkhoven CH, Valk AW, Smagge B, et al. Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023. medRxiv 2023.12.12.23299855; https://doi.org/10.1101/2023.12.12.23299855.

Section 17.2 describes the newly identified information on immunogenicity of a booster dose of Omicron-modified vaccines in individuals ≥12 years of age, 5 to <12 years of age, and 6 months through <5 years of age, and effectiveness of a booster dose of Omicron XBB-adapted vaccine in individuals ≥60 years or >65 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.[94] 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.[95]

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.[96]

As of 23 January 2024, the overall number of SARS-CoV-2 cases was over 702 million worldwide.[96]

Table 65 shows the cumulative number of cases and deaths as of 23 January 2024 for the US, UK, and EU-27 countries. In the EU and the UK, by 23 January 2024, the total number of confirmed cases had accumulated to almost 211 million people, or 419,667 per 1,000,000 population. Across countries in the EU, the cumulative number of confirmed cases ranged from 176,227 to 670,727 cases per 1,000,000 population. Poland, Bulgaria, and Hungary reported the lowest cumulative case rates while Austria, Slovenia, and France reported the highest.

In the US, the number of confirmed cases had reached over 110 million (330,523 per 1,000,000 population) by 23 January 2024.

[94] Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.

[95] World Health Organization. (2020). Novel Coronavirus (2019-nCoV): situation report, 11. World Health Organization. https://iris.who.int/handle/10665/330776.

[96] Worldometer. Reported Cases and Deaths by Country or Territory. https://www.worldometers.info/coronavirus/ Accessed on 23 January 2024.

Table 65. Incidence, Prevalence, and Mortality of COVID-19 as of 23 January 2024[a]

	Total Cases	Total Cases / 1,000,000 pop	Active Cases	Active Cases / 1,000,000 pop	Total Deaths	Deaths / 1,000,000 pop	Population
Global	702181714	90083	22092183	2834	6972220	895	7794830479
EU-27	186346294	428576	712053	1638	1208592	2780	434802948
UK	24872653	363116	17803	260	232112	3389	68497907
EU-27+UK	211218947	419667	729856	1450	1440704	2863	503300855
USA	110660955	330523	1133710	3386	1193042	3563	334805269
EU-27 Countries							
Austria	6081287	670727	3811	420	22542	2486	9066710
Belgium	4853153	415927	7547	647	34376	2946	11668278
Bulgaria	1337834	195458	7404	1082	38719	5657	6844597
Croatia	1309728	322650	32609	8033	18687	4604	4059286
Cyprus	662962	541907	0	0	1364	1115	1223387
Czechia	4755357	442903	4728	440	43468	4049	10736784
Denmark	3183756	545636	0	0	8814	1511	5834950
Estonia	627269	474517	N/A[b]	N/A[b]	3001	2270	1321910
Finland	1513998	272549	1587	286	11242	2024	5554960
France	40138560	612013	0	0	167642	2556	65584518
Germany	38800361	462550	378284	4510	181477	2163	83883596
Greece	6101379	591412	N/A[b]	N/A[b]	37869	3671	10316637
Hungary	2228206	231954	27075	2818	48976	5098	9606259
Ireland	1731136	344834	2754	549	9470	1886	5020199
Italy	26701924	443092	193385	3209	195752	3248	60262770
Latvia	981883	531081	3868	2092	6609	3575	1848837
Lithuania	1392545	523177	5265	1978	9880	3712	2661708
Luxembourg	390465	607850	N/A	N/A[b]	1232	1918	642371
Malta	121295	273167	533	1200	880	1982	444033
Netherlands	8631646	501506	3537	206	22992	1336	17211447
Poland	6650782	176227	N/A	N/A[b]	120439	3191	37739785
Portugal	5640496	556231	2213	218	27976	2759	10140570
Romania	2612206	301884	2242	259	18057	2087	8653016
Slovakia	1875864	343553	0	0	21205	3884	5460193
Slovenia	1355918	652500	419	202	7100	3417	2078034
Spain	13914811	297840	30634	656	121760	2606	46719142
Sweden	2751473	269251	4158	407	27063	2648	10218971

a. World population based on https://www.worldometers.info/coronavirus/ . Accessed 23 January 2024.
b. N/A – not available

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. Further, as at-home rapid testing kits have become more readily available 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[97] where JN.1 was responsible for 85.7%, and HV.1 was responsible for 5.3% of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 20 January 2024.

The main existing treatment options:

Through 18 December 2023, other COVID-19 vaccines are currently authorised[98] in the European Union including:

- COVID-19 Vaccine (recombinant, adjuvanted) - Bimervax (EU/1/22/1709);
- COVID-19 Vaccine (recombinant, adjuvanted) - Nuvaxovid (EU/1/21/1618);
- COVID-19 Vaccine (recombinant, adjuvanted) - VidPrevtyn Beta (EU/1/21/1580);
- COVID-19 vaccine (Ad26.COV2-S [recombinant]) Jcovden previously Janssen vaccine (EU/1/20/1525);
- COVID-19 Vaccine (CHADOX1-S [recombinant]) Vaxzevria previously AstraZeneca vaccine (EU/1/21/1529);
- elasomeran - Spikevax previously COVID-19 vaccine Moderna (EU/1/20/1507).

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[99,100,101,102] 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.[102] A meta-analysis has estimated that 46.7% of infections in children are asymptomatic.[102] The most common symptoms of COVID-19 are

[97] CDC. Variant Proportions. https://covid.cdc.gov/covid-data-tracker/#variantproportions Accessed on 23 January 2024.

[98] Union Register of Medicinal Products. https://ec.europa.eu/health/documents/community-register/html Accessed on 28 January 2024.

[99] Pollock AM, Lancaster J. Asymptomatic transmission of covid-19. BMJ. 2020;371:m4851.

[100] Toba N, Gupta S, Ali AY, et al. COVID-19 under 19: A meta-analysis. Pediatr Pulmonol. 2021;56(6):1332-41.

[101] Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review. Ann Intern Med. 2021;174(5):655-62.

[102] Sah P, Fitzpatrick MC, Zimmer CF, Abdollahi E, Juden-Kelly L, Moghadas SM, et al. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proc Natl Acad Sci U S A. 2021;118(34).

fever, cough, and shortness of breath for both children and adults.[103,104] 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%.[105]

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.[106,107] 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.[107] 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.[107,108]

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 13 January 2024, there were 6,727,160 total hospital admissions for patients with confirmed COVID-19 in the US.[109]

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

[103] Team CC-R. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.

[104] Yasuhara J, Watanabe K, Takagi H, et al. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(5):837-48.

[105] Kumar B, Scheffler P. Ear, Nose, and Throat Manifestations of COVID-19 in Children. Pediatr Ann. 2021;50(7):e277-e81.

[106] CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) | CDC Archive. Last updated on 16 February 2021. Accessed on 30 January 2024.

[107] Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020;383(18):1757-66.

[108] Khan K, Karim F, Cele S, et al. Omicron infection of vaccinated individuals enhances neutralizing immunity against the Delta variant. medRxiv.[Preprint] 2022 January 28. doi: 10.1101/2021.12.27.21268439.

[109] CDC. COVID Data Tracker: New Hospital Admissions. https://covid.cdc.gov/coviddata-tracker/#new-hospital-admissions. Accessed on 23 January 2024.

diarrhoea (33%)[110,111,112,113] COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[114] 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.[112] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[111,115,116] 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.[117] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[118]

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 10–12 days.[106] 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.[100] A study of 82 cases in three paediatric hospitals noted that older children and those with higher body mass index or multiple comorbidities were more likely to receive respiratory support.[119]

[110] Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep. 2020b;69(18):545-50.

[111] Hur K, Price CPE, Gray EL, et al. Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170-8.

[112] Burke RM, Killerby ME, Newton S, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 - United States, January-April 2020. MMWR Morb Mortal Wkly Rep. 2020;69(28):904-8.

[113] Nowak B, Szymański P, Pańkowski I, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med. 2020;130(5):407-11.

[114] Tong JY, Wong A, Zhu D, et al. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2020;163(1):3-11.

[115] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763-70.

[116] Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities In Outcomes Among COVID-19 Patients In A Large Health Care System In California. Health Aff (Millwood). 2020;39(7):1253-62.

[117] Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA Netw Open. 2021;4(4):e215298.

[118] Iaccarino G, Grassi G, Borghi C, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension. 2020;76(2):366-72.

[119] Rubenstein S, Grew E, Clouser K, et al. COVID-19 in Pediatric Inpatients: A Multi-Center Observational Study of Factors Associated with Negative Short-Term Outcomes. Children (Basel). 2021;8(11).

Mortality

As of 13 January 2024, there were 1,169,666 deaths reported in the US by the CDC for all age groups.[109]

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 23 January 2024, the overall SARS-CoV-2 mortality for the EU + UK was 1,440,704 deaths, or 2,863 per 1,000,000 population. Reported mortality among EU countries and the UK ranged from 1,115 to 5,657 deaths per 1,000,000 population. Cyprus, Netherlands, and Denmark reported the lowest mortality; Bulgaria, Hungary, and Croatia reported the highest.[97]

In the US, as of 23 January 2024, the mortality was 1,193,042 deaths (3,563 per 1,000,000 population). Mortality in the US was higher than that of the UK (3,389 per 1,000,000).[97]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK and US.[116,120,121, 122]

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

[120] Gold JAW, Rossen LM, Ahmad FB, et al. Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 - United States, May-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69(42):1517-21.

[121] Jones S, Mason N, Palser T, et al. Trends in Risk-Adjusted 28-Day Mortality Rates for Patients Hospitalized with COVID-19 in England. J Hosp Med. 2021;16(5):290-3.

[122] Gopal Rao G, Allen A, Papineni P, et al. Cross-sectional observational study of epidemiology of COVID-19 and clinical outcomes of hospitalised patients in North West London during March and April 2020. BMJ Open.2021;11(2):e044384.

show that a substantial proportion of people who have had COVID-19 may develop long COVID.[123]

Assuming at least 10% of COVID-19 survivors develop long COVID, it is estimated that 5 million people are facing long COVID globally.[124]

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., elevated D-dimer and CRP values, and low lymphocyte count), although more research is required to substantiate such risk factors.[124]

Studies that have evaluated a potential impact of SARS-CoV-2 vaccination on long COVID include:

Ayoubkhani et al.[125] 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.

[123] Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. Bmj. 2021;374:n1648.

[124] Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53(10):737-54.

[125] Ayoubkhani D, Bermingham C, Pouwels KB, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. Bmj. 2022;377:e069676.

Although causality cannot be inferred from this observational evidence, vaccination may contribute to a reduction in the population health burden of long COVID.[125]

Furthermore, Kuodi et al.[126] 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.[127]

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.[128,129]

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.[128,129]

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.

---

[126] Kuodi P, Gorelik Y, Zayyad H, et al. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. medRxiv. 2022:2022.01.05.22268800.

[127] Office for National Statistics (ONS), released 30 March 2023, ONS website, statistical bulletin, Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 30 March 2023.

[128] Simon MA, Luginbuhl RD, Parker R. Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After. medRxiv. 2021:2021.11.17.21263608.

[129] Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections. Brain Behav Immun. 2022;103:154-62.

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 identified risks 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 66.

Based on pharmacovigilance monitoring activities, there has been no significant new safety information contributing importantly to the risks of BNT162b2.

No actions have been taken upon review of safety topics:

- Hemophagocytic Lymphohistiocytosis,
- Idiopathic Inflammatory Myopathies/Myositis.

Both topics will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Table 66. 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 interval, there were no new significant data received from literature sources.	The risk is communicated through the CDS in Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects and Appendix A and Appendix B and in the EU SmPC in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects. It is also included as an Important identified 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.
Important Potential Risks				
None				

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 all BNT162b2 vaccine presentations, the overall benefit-risk profile of BNT162b2 remains favourable for all age groups in which it is authorised.

Table 67. 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 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, bivalent vaccines Omi BA.1 and BA.4/BA.5 and monovalent Omi XBB.1.5), the overall benefit-risk profile of BNT162b2 remains favourable. No further changes to the BNT162b2 RSI or additional risk minimisation measures are warranted in addition to those above mentioned.

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.