

Comirnaty : Periodic safety update report assessment

19 December 2023 to 18 December 2024

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period from 19 December 2023 to 18 December 2024, 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.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMADOC-1700519818-1988259
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000257861

PRAC PSUR assessment report

EURD list no.: PSUSA/00010898/202412

Active substance(s): tozinameran (BNT162B2), tozinameran/riltozinameran (BNT162B2 Original/Omicron BA.1), tozinameran/famtozinameran (BNT162B2 Original/Omicron BA.4-5), raxtozinameran (BNT162B2 Omicron XBB.1.5)

Period covered by the PSUR: 1 year to 18 December 2024

Centrally authorised Medicinal product(s):	Marketing Authorisation Holder
For presentations: See Annex A	
BNT162B2	BioNTech Manufacturing GmbH

Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Submission deadline	12 March 2025	12 March 2025
☐	Start date	13 March 2025	13 March 2025
☐	PRAC Rapporteur AR	12 May 2025	11 May 2025
☐	PRAC/MAH comments	11 June 2025	11 June 2025
☐	Updated PRAC Rapporteur AR	26 June 2025	26 June 2025
☒	PRAC outcome	10 July 2025	10 July 2025



Procedure resources	
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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for tozinameran (BNT162B2), tozinameran/riltozinameran (BNT162B2 Original/Omicron BA.1), tozinameran/famtozinameran (BNT162B2 Original/Omicron BA.4-5), raxtozinameran (BNT162B2 Omicron XBB.1.5).

2. Assessment conclusions and actions

The MAH submitted the 7th EU Periodic Safety Update Report (PSUR) for BNT162b2, BNT162b2 is used this report to refer to all variants of the vaccine presentation, covering the interval period 19 December 2023 through 18 December 2024.

The active substance of BNT162b2 is highly purified single-stranded, 5'-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the viral spike protein of SARS-CoV-2. The nucleoside-modified mRNA is formulated in 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.

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.

BNT162b2 was approved in the EU through a centralised procedure on 21 December 2020.

During the interval period, 179,315,700 doses of BNT162b2 vaccines were shipped worldwide. Cumulatively, 5,032,571,025 doses of BNT162b2 vaccines were shipped worldwide.

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

There were 21 new signals that were closed during the interval period, which were all enquiries from regulatory authorities: "migraine", "transverse myelitis", "subacute thyroiditis", "tongue discolouration", "sciatica", "tonsillitis", "erysipelas", "angina bullosa haemorrhagica", "polycystic ovaries", "cerebral amyloid angiopathy", "cough", "aphasia", "disturbance in attention", "myocardial necrosis marker increased", "pelvic pain", "paralysis", "erectile dysfunction", "hypertension", "giant cell arteritis", "exacerbation of diabetes mellitus", and "exacerbation of adrenal insufficiency". In addition, "Pulmonary embolism" and "post-menopausal haemorrhage" were ongoing signals and these were also closed during the reporting period. The evidence supporting a causal relationship between BNT162b2 and safety issues addressed in these signals appears insufficient or inconclusive.

The safety topics monitored or reviewed are the following:

Hemophagocytic lymphohistiocytosis (HLH)

Based on the data provided in this PSUR no new safety information could be identified on HLH after exposure to BNT162b2. There is insufficient evidence to establish a causal relationship between BNT162b2 and HLH. Most presented supportive data were already assessed in previous PSUR assessments, such as the probably related case by Park et al. and the systematic review performed by Zhang et al. Further review of cases from clinical trials or the post marketing setting did not retrieve new strongly supportive cases, while there was also no positive statistical association of BNT162b2 cases in the MAH's safety database and reporting of the event HLH.

Idiopathic Inflammatory Myopathies/Myositis

In the signal assessment report on myositis with tozinameran (EPITT 19883), up to 15 January 2023, the MAH retrieved 1,017 cases. Combined with the current review, cumulatively, up to DLP of the current PSUR, a total of 1,217 cases have been identified reporting IIM/autoimmune myositis/IIM flares. A very small number of 23 well documented cases (16 cases in the Signal AR and 7 cases in current review) out of 1,217 cases with a temporal association between vaccination with BNT162b2 and the onset of the relevant myositis events has been identified.

The retrieved literature from 16 January 2023 up to DLP of the current PSUR, did not provide sufficient evidence for the causal association between the occurrence of idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares following BNT162b2 vaccination.

There is currently insufficient evidence to support a causal relationship between BNT162b2 and idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares. The MAH will monitor this topic through routine pharmacovigilance and present in future PSURs only if any significant new information is identified, which is agreed.

Small fiber neuropathy (SFN)

Cumulative review of the occurrence of small fiber neuropathy following BNT162b2 administration retrieved a total of 497 cases, of which 1 was probably related, 22 possibly related, 90 unlikely related and 384 unassessable cases. The 9 cases with confirmed skin biopsy of SFN presented by a Member State in the last PSUR were included in the cumulative review discussed in the current PSUR. These 9 cases were assessed according to WHO causality standards by the MAH and by the PRAC assessor. Based upon review of the post-marketing cases reporting small fiber neuropathy, there is insufficient evidence to support a causal association. From literature, no clear (biological) mechanism for the occurrence of small fiber neuropathy following BNT162b2 administration has been identified. In conclusion, there is currently insufficient evidence to support a causal relationship between BNT162b2 and small fiber neuropathy. It is recognized that SFN is a fairly new clinical entity, but at this point in time and with the data currently available, routine pharmacovigilance is considered sufficient to monitor the topic of SFN.

Considering no new safety information has been identified both in the current and the previous reporting period, there are no conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II), the PRAC recommends to amend the PSUR frequency from 1 year to 2 years (see section 5).

The benefit-risk balance for the use of BNT162b2 Original (tozinameran), BNT162b2 Original/Omicron BA.1 (tozinameran/riltozinameran), BNT162b2 Original/Omicron BA.4-5 (tozinameran/famtozinameran), and BNT162b2 Omicron XBB.1.5 (raxtozinameran) in its authorised indications 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, tozinameran/riltozinameran, tozinameran/famtozinameran, and raxtozinameran 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 also address the following issues in the next PSUR:

- After DLP the following non-peer-reviewed paper/preprint [posted on 18 Feb 2025] was identified: Immunological and Antigenic Signatures Associated with Chronic Illnesses after COVID-19 Vaccination | medRxiv. Within the context of routine monitoring of relevant scientific literature, the MAH is requested to reflect on the findings reported in this paper, or any relevant emerging insights regarding long-COVID-like illness following COVID vaccination.

5. PSUR frequency

☒ Changes of PSUR frequency are proposed

The current frequency of submission should be changed **from 1 year to 2 years** at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the 7th PSUR for COVID-19 mRNA vaccine (Coronavirus disease 2019 messenger ribonucleic acid) Comirnaty®, also referred to as Comirnaty Original (tozinameran), Comirnaty Bivalent Omicron BA.1 (tozinameran/riltozinameran), Comirnaty Bivalent Omicron BA.4/BA.5 (tozinameran/famtozinameran), Comirnaty Omicron XBB.1.5 (raxtozinameran), Comirnaty Omicron JN.1 (bretovameran) or Comirnaty Omicron KP.2 (mRNA encoding KP.2) covering the reporting period 19 December 2023 through 18 December 2024, which is assessed in this report. 'BNT162b2' is used in this report to refer to all variants of the vaccine presentation. If the data assessed in this report applies specifically to one of the variants in the vaccine presentation, this is indicated.

The active substance of each of the BNT162b2 (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). 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.

BNT162b2 (BNT162b2) 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	Presentation (Vial Cap and Vial Label Color or Pre-Filled Syringe)	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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
6 months through 4 years 3 mcg per dose	Yellow	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	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 • Omicron JN.1 • Omicron KP.2

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Color or Pre-Filled Syringe)	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
	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 • Omicron JN.1 • Omicron KP.2
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 BA.1 • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Pre-filled syringe	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2

No changes to the COVID-19 mRNA vaccine 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 UK26 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.

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. Overall, BNT162b2 (any vaccine presentation) received marketing authorisation approval in 104 countries/regions and is currently approved in 87 countries/regions.

BNT162b2 original received marketing authorisation approval in 104 countries/regions and is currently approved in 30 countries/regions. This vaccine presentation was prequalified by the WHO in 2024.

In 2022, to address the emergence of Omicron variants, bivalent formulations were developed. Bivalent Omicron BA.1 and bivalent BA.4/BA.5 received marketing authorisation approval in 46 and 73 countries/regions, respectively and are currently approved in 2 and 23 countries/regions, respectively. In 2024, the bivalent BA.4/BA.5 vaccine was prequalified by the WHO.

In 2023, to address the emergence of new Omicron variant (XBB.1.5), an adapted monovalent

formulation was developed. The monovalent XBB.1.5 vaccine, first authorized in the EU countries on 31 August 2023, has received marketing authorisation and is currently approved in 60 countries/regions and has been prequalified by the WHO.

In 2024, to address the emergence of SARS-CoV-2 variants with multiple mutations (i.e. JN.1, KP.2), two adapted monovalent variant vaccine constructs were developed. The BNT162b2 Omicron JN.1-adapted monovalent COVID-19 vaccine (BNT162B2 JN.1) was first authorized in the EU countries on 03 July 2024 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. The JN.1- adapted monovalent COVID-19 vaccine received marketing authorization approval and is currently approved in 46 countries/regions. It was prequalified by the WHO.

On 26 September 2024, the European Commission granted marketing authorization for Omicron KP.2-adapted monovalent COVID-19 vaccine (BNT162B2 KP.2) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

On 22 August 2024, the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application for individuals 12 years of age and older (BNT162B2® (COVID-19 Vaccine, mRNA)), and granted emergency use authorization for individuals 6 months through 11 years of age (Pfizer-BioNTech COVID-19 Vaccine) of the companies' Omicron KP.2-adapted 2024-2025 Formula COVID-19 vaccine. The KP.2 adapted monovalent variant vaccine received marketing authorization approval and is currently approved in 34 countries/regions.

The formulations and presentations available for use in different age groups are reported in the table below.

Available Presentations of Monovalent and Bivalent Vaccine Variants

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Colour or Pre-Filled Syringe)	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for BNT162b2 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 (Wild type) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	Yellow	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	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 • Omicron JN.1 • Omicron KP.2
	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 • Omicron JN.1 • Omicron KP.2

Available Presentations of Monovalent and Bivalent Vaccine Variants

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Colour or Pre-Filled Syringe)	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for BNT162b2 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 BA.1 • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Pre-filled syringe	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2

During the reporting period,

- the European Medicines Agency (EMA) approved the deletion of BNT162b2 Original (tozinameran), BNT162b2 Bivalent BA.1 (tozinameran/riltozinameran) and BNT162b2 Bivalent BA.4/BA.5 (tozinameran/famtozinameran) presentations for BNT162b2 at the request of the MAH for commercial reasons only;
- in other countries the licenses (EUA or full MA) expired, or have been cancelled or were replaced or withdrawn (for commercial reasons).

The MAHs and the number of countries/regions where BNT162b2 is currently approved are presented in the table below.

Number of Countries/Regions by MAH where BNT162b2 Monovalent and Bivalent Vaccine Presentations are currently Approved

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held					
	BNT162b2 Original	BNT162b2 Bivalent BA.1	BNT162b2 Bivalent BA.4/BA.5	BNT162b2 Omicron XBB.1.5	BNT162b2 Omicron JN.1	BNT162b2 Omicron KP.2
BioNTech	13	0	8	40	35	34
Pfizer	14	2	13	19	10	0
Fosun Pharma	0	0	1	1	1	0
Local MoH	2 ^a	0	0	0	0	0
Local Government	1 ^b	0	1	0	0	0
All	30	2	23	60	46	34

a. Moldova, Kenya.

b. Ghana.

In addition, World Health Organization (WHO) had approved the transition from the Emergency Use Listing (EUL) to Prequalification (PQ) of BNT162b2.

During the reporting period, the European Medicines Agency (EMA) approved the deletion of BNT162b2 Original (tozinameran), BNT162b2 (Original and Omicron Bivalent BA.1) (tozinameran/riltozinameran) and BNT162b2 (Original and Omicron Bivalent BA.4/BA.5) (tozinameran/famtozinameran) presentations for BNT162b2 at the request of the MAH for commercial reasons only.

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

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 COVID-19 mRNA vaccines for safety reasons, either by a HA or by the MAH.

Rapporteur assessment comment:

Noted.

1.3.2. Changes to reference safety information

The RSI for this PSUR is the BNT162b2 (COVID-19 mRNA vaccine) CDS version 29.0 dated 27 November 2024, in effect at the end of the reporting period and included in Appendix 1 of the PSUR (not reproduced here).

Four previous CDS versions (version 25.0 dated 26 January 2024, version 26.0 dated 03 April 2024, version 27.0 dated 01 July 2024 and version 28.0 dated 09 September 2024) were also in effect during the reporting period.

The following safety-related changes were made during this reporting interval:

- Section 4.4 Special warnings and precautions for use (CDS version 28.0)
- Section 4.5 Interaction with other medicinal products and other forms of interaction (CDS version 29.0)
- Section 4.6 Fertility, pregnancy and lactation (CDS version 28.0)
- Section 4.8 Undesirable effects (CDS versions 25.0, 27.0, 28.0 and 29.0)
- Section 4.9 Overdose (CDS version 26.0)
- Appendix A and Appendix B (CDS versions 25.0, 27.0 and 28.0)

Rapporteur assessment comment:

The RSI valid at the beginning of the reporting interval was CDS version 25.0, dated 26 January 2024. The CDS has been updated multiple times during the reporting interval by the MAH.

The reference information used by the rapporteur is the SmPC. The safety information added to the CDS as outlined by the MAH above is reflected in the SmPC of BNT162b2 (version 21-11-2024).

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 72,486 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

- BNT162b2 original: 65,513 participants of which 35,589 received BNT162b2 original only (of which 167 were exposed in utero); 22,813 had received BNT162b2 original post-unblinding and had received placebo before (22,060) or vice-versa (753); 5393 received BNT162b2/placebo; 564 received BNT162b2/SIIV as first dose and placebo as second dose; 564 received placebo/SIIV as first dose and BNT162b2 as second dose; 78 received BNT162b2 original and also BNT162b1; 590 received BNT162b2 original and also BNT162b2 (B.1.351).
- Variant and variant-adapted vaccines based on BNT162b2: 11,836 participants of which 753 received BNT162b2 (B.1.351); 372 received BNT162b2 (B.1.617.2); 768 received BNT162b2 (B.1.1.7 + B.1.617.2); 20 received BNT162b2 (B.1.1.7); 72 received BNT162b2 (B.1.1.529); 1814 received BNT162b2 Omi; 1814 received BNT162b2 bivalent (original/Omi); 102 received BNT162b2 bivalent [original/Omi BA.1 (B.1.1.529)]; 2797 received BNT162b2 bivalent (original/Omi BA.4/BA.5); 2632 received BNT162b2 Omi XBB.1.5; 216 received BNT162b2 (Omi JN.1); 127 received BNT162b2 (Omi KP.2); 104 received BNT162b5 bivalent (original/Omi BA.2); 62 received BNT162b5 bivalent (original/Omi BA.4/BA.5); 60 received BNT162b6 bivalent (original/Omi BA.4/BA.5); 63 received BNT162b7 monovalent (Omi BA.4/BA.5); 60 had received BNT162b7 bivalent (original/Omi BA.4/BA.5).
- Early development candidates: 522 participants of which 30 received BNT162a1; 300 received BNT162b110; 96 received BNT162b3; 96 received BNT162c2.
- Other treatments: 6524 participants (168 of them were exposed in utero) received placebo.

Of note, BNT162b2 is also being utilised in 4 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B747102611 [BNT162b2/20vPnC (187) and BNT162b2/placebo (185)];
- 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)/bIRV/QIV, bivalent BNT162b2 (original/Omi BA.4/BA.5)/tIRV in the clinical study C5261001,12 as a study vaccine.

In CTs C526100213 and C526102314, 8750 and 1247 participants received blinded therapy, respectively.

- C548: 772 participants received BNT162b2 as a study vaccine in combination with QIV/RSVpreF (312) or RSVpreF/placebo (310) or placebo (150); 301 other participants received placebo/RSVpreF (152) or placebo/QIV (149) in study C5481001.15
- C568: 641 participants received blinded therapy in study C5681001.

Of note, bivalent BNT162b2 (original/Omi BA.4/BA.5) or monovalent Omi XBB.1.5 are 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 BNT162-21.17

Rapporteur assessment comment:

Noted.

1.3.3.2. Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative Exposure

Previously publicly available regional information on vaccine doses administered is no longer consistently available for estimation of cumulative worldwide exposure. The best estimate of the post-marketing exposure is based on the worldwide estimated cumulative number of shipped doses, which is detailed below.

The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group reported in the shipment tracker (Order Book) from 01 December 2020 through 22 December 2024 is showed in the table below. Approximately a total of 5,032,571,025 doses of BNT162b2 monovalent and bivalent presentations were *shipped* worldwide. Out of the cumulative number of shipped doses, 3,946,055,525 were monovalent original vaccine (including PBS and Tris/sucrose), 717,702,100 were bivalent vaccines and 368,813,400 were monovalent Omicron presentations (of which 237,508,600 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); cumulatively, there were 4,546,909,545 doses for adult presentations and 485,661,480 doses for paediatric presentations. Overall, 2,588,253,585 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW (rest of the world).

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

Age Group	Paediatrics				Adults			
Vaccine Presentation → Region/Country ↓	Original	Bivalent	Monovalent	Total	Original	Bivalent	Monovalent	Total
EU/EEA, US, Japan	166,965,500	21,606,900	12,548,840	201,121,240	1,519,322,120	478,411,740	245,462,340	2,243,196,200
ROW	276,122,200	2,424,400	5,993,640	284,540,240	1,983,645,705	215,259,060	104,808,580	2,303,713,345
Total	443,087,700	24,031,300	18,542,480	485,661,480	3,502,967,825	693,670,800	350,270,920	4,546,909,545

Table 5 to 11 in MAH's PSUR (not reproduced here) show the worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group.

Interval exposure

Approximately a total of 179,315,700 doses of BNT162b2 monovalent and bivalent presentations were shipped worldwide during the reporting interval from 18 December 2023 through 22 December 2024, as shown in the table below. Out of the shipped doses during the reporting period, 949,220 were original vaccine (Tris/sucrose), 2,140,020 were bivalent vaccines and 176,226,460 were monovalent presentations (of which 44,921,660 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); there were 169,235,820 doses for adult presentations and 10,079,880 doses for paediatric presentations. Overall, 69,537,760 doses of BNT162b2 monovalent and bivalent presentations were shipped to ROW.

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

Age Group Vaccine Presentation → Region/Country ↓	Paediatrics				Adults			
	Original	Bivalent	Monovalent	Total	Original	Bivalent	Monovalent	Total
EU/EEA, US, Japan	0	0	5,523,360	5,523,360	30,500	0	104,224,080	104,254,580
ROW	0	72,000	4,484,520	4,556,520	918,720	2,068,020	61,994,500	64,981,240
Total	0	72,000	10,007,880	10,079,880	949,220	2,068,020	166,218,580	169,235,820

Table 13 to 16 in MAH's PSUR (not reproduced here) show the worldwide estimated interval number of shipped doses by vaccine presentation (original, bivalent BA.4/BA.5 and XBB.1.5) region and countries and by age group.

Rapporteur assessment comment:

Cumulatively, worldwide a total of 5,032,571,025 (4,853,255,325 in previous PSUSA period) doses of BNT162b2 were shipped.

During the reporting period (covering 1 year), in the EU-EEA countries a total of 8,590,680 doses of BNT162b2 were *shipped* in Europe. In the previous PSUSA period (covering 6 months) 405,462 doses of BNT162b2 were *administered*. The numbers of administered BNT162b2 vaccine were derived by the MAH from the European Centre for Disease Prevention and Control. However, since October 5th 2023 the ECDC no longer provided updates on the doses administered in the EU/EEA countries.

In the PRAC AR of the PSUR #4 (EMA/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 BNT162b2 as presented in future PSURs. The MAH indicated that previously publicly available regional information on vaccine doses administered is no longer consistently available. Currently, the ECDC website contains data on COVID 19 vaccination of consecutive doses in the EU/EEA until 5 October 2023. EU/EEA Member States were requested to report to ECDC basic indicators (number of individuals receiving one vaccine during the reporting period starting from 01 September 2023, vaccine product) and data by target groups, but not dose number. The MAH may therefore stop reporting on *administered* (cumulative) dose numbers for BNT162b2 since this data is no longer available to the MAH.

1.3.4. Data in summary tabulations

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 of MAH's 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, C4591048 and C4591054.

Appendix 2.1.1 of MAH's PSUR (nor 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 BNT162-17.

Rapporteur assessment comment:

Cumulatively in clinical trials, a total of 2270 (2180 in previous PSUSA period) cases with 2925 (2825 in previous PSUSA period) SAEs were reported in MAH's safety database. Of note: current PSUR reporting period is one year, previous reporting period was 6 months.

Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 of MAH's PSUR (not reproduced here), provides the overall (including monovalent [original and Omicron] and bivalent presentations) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources.

Appendix 2.2.1 through Appendix 2.2.8 of MAH's PSUR (not reproduced here) provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [monovalent original, bivalent Omicron BA.1, bivalent Omicron BA.4/BA.5, Omicron, Multivalent NOS, Monovalent Omicron XBB.1.5, monovalent Omicron KP.2 and monovalent Omicron JN.1]. 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 2024 and the interval data are from 19 December 2023 to 18 December 2024. This appendix is organised according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non interventional sources.

Rapporteur assessment comment:

During the interval period, post-marketing there were 34,843 (vs 107,046 previous interval period) cases reporting 113,127 (vs 357,748 previous interval period) AEs.

Cumulatively, a total of 1,980,329 (vs 1,946,152 previous PSUR) cases with 6,553,265 (vs 6,426,327 previous PSUR) AEs were reported in MAH's safety database.

1.3.5. Findings from clinical trials and other sources

Table 17 below summarises the study treatments in the clinical studies by original vaccine or the variant-adapted vaccine.

Table 17. Clinical Trials During the Reporting Period: Study Treatments – Original and Variant-Adapted Vaccines

Original	BNT162b2	C4591007, C4591015, C4591024, C4591031, C4591036 ^a , BNT162-17
Variant-Adapted Vaccines	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 ^b	C4591044
	Original + Omi BA.4/BA.5	C4591036 ^a , C4591044, C4591048
	Omi BA.1	C4591031
	Omi BA.4/BA.5	C4591044
	Omicron XBB.1.5	C4591048, C4591054
	Omicron JN.1	C4591054
	Omicron KP.2	C4591048, C4591054

a. Low-Interventional.

b. BNT162b5.

Completed clinical trials

During the reporting period, there were 2 interventional safety studies (PASS) that were completed with final CSRs (C4591015 and C4591024) and are summarized below.

C4591015 is a Phase 2/3, placebo-controlled randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARSCoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older.

MAH Conclusions: BNT162b2 was safe and well-tolerated in maternal and infant participants. Among maternal participants who received BNT162b2, local reactions and systemic events following vaccination were predominantly mild to moderate in severity and short lived (median duration 1.0 to 3.0 days). Reactogenicity after each dose was generally higher among participants in the BNT162b2 group compared to what was observed in the placebo group.

The frequency of maternal and infant participants with any AE/SAE reported from Dose 1 to 1 month after Dose 2 of BNT162b2 was similar to what was observed in the placebo group.

No maternal participants had any AEs leading to withdrawal and none died. Two infants, 1 in the BNT162b2 group (HIV-positive maternal participant) and 1 in the placebo group, had fatal SAEs that were assessed by the investigator as not related to study intervention. Overall, there were few AESIs reported in infants from birth to 6 months of age. Numerical differences between infant participants with reported congenital anomalies were observed between groups, with anomalies reported in 8/156 participants in the BNT162b2 group and 2/159 in the placebo group. For each anomaly observed, the frequency difference between the BNT162b2 and placebo groups was low with 95% confidence intervals that encompassed zero. Apart from atrial septal defect, all anomalies were single occurrences.

The clinical data were reviewed in the context of the available data on background rates of the observed congenital anomalies. Taking this and the low number of events reported in this study into consideration, the findings were not determined to be indicative of a safety risk for infants.

There were no reports of myocarditis or pericarditis in maternal or infant participants during the study.

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

MAH Conclusions:

Based on the available safety data from 124 participants (37, 65, 15 and 7 participants 2 to <5 years of age, 5 to <12 years age, 12 to <18 years age, and ≥ 18 years of age, respectively) from study vaccination through end of study, BNT162b2 at the age appropriate 3 μg , 10 μg , and 30 μg dose level was generally well tolerated across all age groups, and disease subsets, with mostly mild or moderate reactogenicity and few reported AEs. The majority of AEs were in the infections and infestations SOC and all AESIs were likely related to participant's underlying condition. There were no deaths and no SAEs assessed as related by the investigator.

Rapporteur assessment comment:

The final results of these two completed clinical trials have been assessed within the grouped Variation procedure EMA/VR/0000224683 as follows:

- Sections 4.6, 4.8 and 5.1 of the SmPC were updated regarding pregnancy related information based on final results from interventional study **C4591015**, listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly.

- Sections 4.4, 4.8 and 5.1 of the SmPC were updated regarding information for immunocompromised individuals based on final results from interventional study **C4591024**, listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly.

Other Trials that Reported New Significant Safety/Efficacy Information

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

Remaining Trials

During the reporting interval, there were 4 completed clinical trials (BNT162-17, C4591007, C4591031, and C4591044) 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.

BNT162-17 is a Phase 2 trial to evaluate the safety and immunogenicity of SARS-CoV-2, monovalent and multivalent RNA-based vaccines in healthy participants.

MAH conclusions [only safety results are reproduced here]:

Safety

Based on the totality of the safety data, the BNT162b2-based variant vaccines BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.529), and BNT162b2 were generally well tolerated and had acceptable safety profiles in healthy participants at the doses tested.

There were no SAEs related to IMP or AEs that led to treatment or study withdrawal. Two events of myocarditis (one SAE that was not related to IMP, and one non-serious AESI [PT: myocarditis; investigator term: probable myocarditis] that was related to IMP [BNT162b2 (B.1.617.2)]), and no events of pericarditis were reported. The safety profiles of the four BNT162b2-based variant vaccines were comparable with BNT162b2.

C4591007 is 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.

MAH conclusions: Additional safety data analyzed in this final CSR are consistent with previously reported results.

There were no confirmed cases of myocarditis/pericarditis in Study C4591007. The low percentage of participants ≥ 5 to < 12 years of age and ≥ 12 to < 16 years of age with elevated troponin I levels at baseline and after vaccination with BNT162b2 in Study C4591007 are not suggestive of increased risk of subclinical myocarditis and pericarditis in individuals > 5 to < 12 years of age and > 12 to < 16 years, both male and female, after BNT162b2 vaccination.

C4591031 is a Phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.

MAH conclusions:

Substudy D: The tolerability and safety profile of BNT162b2 Omi when administered as a third, fourth,

and/or fifth dose was safe and well tolerated and consistent with results previously reported in clinical studies for BNT162b2 30 µg in this age group.

Substudy E: The tolerability and safety profile of monovalent BNT162b2 30 µg, monovalent BNT162b2 60 µg, monovalent BNT162b2 Omi 30 µg, monovalent BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 30 µg, and bivalent BNT162b2 + BNT162b2 Omi 60 µg up to 6 months after vaccination was acceptable and consistent with the known safety profile of BNT162b2 and previously reported AE profile for Omicron BA.1-modified BNT162b2 vaccines.

C4591044 is an interventional, randomized, active controlled, Phase 1/2/3 study to investigate the safety, tolerability, and immunogenicity of BNT162b RNA-based vaccine candidates in COVID-19 vaccine – experienced healthy individuals

MAH conclusions:

Results for combined Cohort 2 and analyses (below) are for participants 18 through 55 (n=313) and >55 years of age (n=306) who received a 30 µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (Dose 4).

Cohort 2 and Cohort 3

The safety profile within 6 months after vaccination (Dose 4) with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at the 30 µg and 60 µg dose level was well tolerated across all age groups, with few reported AEs.

The AE profile through 6 months after study vaccination consisted mainly of reactogenicity events, labelled reactions (eg, lymphadenopathy) and other AEs that occur in a general adult population. The incidence of severe and life-threatening events was low. No new or concerning safety findings were noted 6 months after vaccination.

Appendix 6.4 provides final study reports that became available during the reporting interval for all PASS.

Rapporteur assessment comment:

Based on review of the provided study summaries the MAH's conclusion is endorsed that no clinically important new information has emerged from 2 interventional safety studies (PASS) that were completed with final CSRs (C4591015 and C4591024), and clinical trials BNT162-17, C4591007, C4591031, and C4591044.

Note that final study reports have been assessed separately in the following procedures:

C4591015 and C4591024 in procedure EMA/VR/0000224683

C4591007 in procedure EMEA/H/C/005735/P46/070

C4591031 in procedure EMEA/H/C/005735/II/0217

C4591044 in procedure EMA/VR/0000231586

Ongoing clinical trials

During the reporting period, there were 3 ongoing sponsor-initiated clinical trials.

Safety Trials:

- PASS:
 - **Original and Variant-Adapted Vaccines**
 - **C4591036** is a *Low-interventional cohort study of myocarditis/pericarditis associated with BNT162B2 in persons less than 21 years of age*. No clinically important new information

has emerged from this ongoing PASS.

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

Rapporteur assessment comment:

The protocol version **4.0** for study **C4591036**, has been previously assessed within procedure EMEA/H/C/005735/MEA/041.7.

According to the agreed milestones, data collection has started 21 Nov 2022 and will continue until 21 Nov 2030 [estimated]. Annual progress reports are planned from 30 Jun 2025 onwards, through 30 Jun 2030. Final Study Report is due 28 Feb 2031 [estimated].

Other Trials that Reported New Significant Safety/Efficacy Information

During the reporting period, there were no ongoing trials that reported new significant safety/efficacy information.

Remaining Trials

There were 2 ongoing CTs with variant-adapted version(s) of the vaccine (C4591048, and C4591054).

➤ **Variant-Adapted Vaccines**

- **C4591048** is 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** is 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.*

Study C4591048 reported 2 SAEs considered related to the vaccination by the investigator during the reporting period. Substudy A reported an event of pyrexia (1 day post vaccination) and Substudy E reported an event of seizure (12 days post vaccination).

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

Rapporteur assessment comment:

Noted.

Long-term Follow-up

According to the MAH there is no new significant 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 being utilised as study vaccine in other 3 Pfizer-sponsored clinical development programs (C526, C548 and C568) and in another BioNTech-sponsored clinical development program (BNT162b4). See Section New Safety Data Related to Fixed Combination Therapies below for details.

New Safety Data Related to Fixed Combination Therapies

During the reporting period, 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, C5261002, C5261023, with QIV and RSV preF vaccines in Study C5481001, and with the recombinant influenza vaccine in Study C5681001.

BNT162b2 was also being utilised as study vaccine 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:

The MAH declared that no new clinically important safety information was identified from *Long-term Follow-up, Other Therapeutic Use, or Fixed Combination Therapies*.

FINDINGS FROM NON-INTERVENTIONAL STUDIES

Request 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.*

MAH Response

As per communication dated 26 September 2023 from Health Canada "As noted by the MAH and following the April 2023 PRAC meeting, it was recommended to terminate the Study C4591010 due to low enrollment with no further study reports required. The MAH will be requested to remove Study C4591010 from the Canadian addendum to reflect the updated RMP at the next regulatory opportunity", no further study reports for study C4591010 is required.

Study C4591010 is no longer a Category 3 commitment in the EU-RMP version 9.0 by request from PRAC (procedure EMEA/H/C/005735/MEA 0.11.8). Thus, no interim/final reports were submitted to EMA during the reporting period. Please refer to Appendix 5.5 and Appendix 5.6 [not reproduced in this AR] for the interim reports of studies C4591021 and C4591022 submitted in the reporting period, respectively.

Rapporteur assessment comment:

Note that the 5th and 3rd interim study reports of **C4591021** and **C4591022**, respectively, which were included within this PSUR submission have previously been assessed separately in the following procedures:

C4591021 (formerly named ACCESS/VAC4EU) 5th interim study report in procedure EMEA/H/C/005735/MEA/017.9

[Assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 mRNA vaccine Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following BNT162b2 vaccination]

The PRAC previously concluded:

Following assessment of the results in this 5th interim report describing the characteristics and incidence rates for the 37 AESIs in more than 12 million vaccinated individuals and 12 million matched unvaccinated controls, the PRAC Rapporteur concluded that:

No new important safety information could be identified, and, no additional characterisation of the AESIs is warranted.

In summary,

- *The incidence rates of AESIs were generally very low in the risk intervals studied and were comparable with available published background incidence rates from previous studies in unvaccinated cohorts.*
- *The divergence in cumulative incidence observed for several of the cardiovascular [CV] events with long risk windows (e.g. 365 days) resulted in small increases in risk in some of the data sources. According to the MAH these increases could be explained by a number of factors:*
 - a) *Some of these CV events have presented with mild symptoms that did not require immediate medical attention, and vaccinated individuals may have sought medical attention more frequently than those who were unvaccinated (healthy vaccinee effect).*
 - b) *Differences in the composition of the unvaccinated cohort as follow-up progresses. Unvaccinated individuals were censored in the unvaccinated cohort if they were vaccinated and were then followed up in the vaccinated cohort from that time point. Consequently, the individuals who remained in the unvaccinated cohort were those who were never vaccinated and who were possibly less likely seek medical attention at all if it was not urgently needed.*
 - c) *These differences may have been minimal earlier in follow-up, however, may have become more pronounced as follow-up progressed.*
- *Results for CVST, Bell's Palsy and glomerulonephritis all showed no evidence of an increased risk in the vaccinated cohort based on adjusted HRs.*
- *Adjusted HRs for secondary amenorrhea were slightly elevated in EpiChron and CPRD Aurum.*
- *For hypermenorrhea, only the adjusted HR in EpiChron was slightly elevated. [Heavy menstrual bleeding is considered an ADR and is stated with frequency 'not known' in the currently approved BNT162b2 PI].*
- *The MAH's commitment to continue to monitor and further refine these events for inclusion in the final study report is noted.*

C4591022 3rd interim study report in procedure EMEA/H/C/005735/MEA/054.2

[Pfizer-BioNTech COVID-19 vaccine exposure during pregnancy: a non-interventional post-approval safety study of pregnancy and infant outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.] Study C4591022 is a post marketing commitment (PMC) to the FDA and designated as a category 3 Post-Authorization Safety Study (PASS) per EU RMP.

The EU Product Information (PI) of BNT162b2 was amended (EMA/H/C/005735/IB/0110, issued 28/02/2022) to implement the recommendation on vaccination with BNT162b2 in pregnant and

breastfeeding women as requested by the CHMP following a LEG procedure (EMA/H/C/005735/LEG/045) on use of Covid-19 vaccines in pregnant women.

Based on the assessment of the 3rd interim study report, the PRAC previously concluded that:

As of 17 July 2023 (data cut off) the full sample had been recruited: 100% of the vaccine exposure cohort, and 134.2% of the comparator cohort. There is over-enrolment into the comparator cohort as confirmation of eligibility cannot be made until the post-partum interview when the data on exposures has been completed.

No formal comparisons were made by the MAH, as only a subset of the full sample of completed pregnancies were included. Based on the provided data no safety concerns could be identified for the pregnancy and infant outcomes.

Completed non-interventional studies

Safety studies

No safety studies were completed during the reporting period.

Other studies

During the reporting period, the studies C4591042, C4591053, C4591057, and C4591060 were completed. No new safety information emerged from these non-interventional studies; the summary of results from these studies is provided below.

C4591042 is a retrospective cohort study evaluating patient characteristics, healthcare resource utilization and costs among patients with COVID-19 in England.

MAH conclusions: Although the burden of COVID-19 has reduced following the roll-out of COVID-19 vaccines in the UK, substantial economic burden due to COVID-19 was observed on the NHS. Importantly, this study showed much of the burden during the study period was driven by COVID-19-related hospitalisations, and that older adults are associated with higher burden. Findings from this study can be used to inform the long-term strategy for resource allocation in the management of COVID-19.

C4591053 evaluated 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.

MAH concluded that vaccination against COVID-19 may reduce the risk of long COVID in both immunocompetent and immunocompromised patients. However, no association was found between frequency of primary care visits and vaccination among patients diagnosed in 2021. Future studies with larger sample size, higher vaccine uptake, and longer study periods during the pandemic are needed to further quantify the impact of vaccination on long COVID.

C4591057 investigated booster immunization in children aged 6 months to 4 years.

The MAH concluded that booster immunization with BNT162b2 is well-tolerated in children aged 6 months to 4 years. Based on the results of this study, there are no new safety concerns or risks were identified in this study.

C4591060 a retrospective large database study evaluating HRU and costs associated with COVID-19 in Colombia.

The MAH concluded that most COVID patients were treated only in an outpatient setting mirroring low-cost expenses. However, for severe and critical COVID cases the total healthcare costs were substantially higher due to the LoS in general ward and ICU.

Rapporteur assessment comment:

The MAH's conclusion regarding the provided summaries of the results from C4591042, C4591053, C4591057, and C4591060 is noted. These studies are not listed in the RMP pharmacovigilance plan [as PASS, any category].

Ongoing Non-interventional studiesSafety Studies:

- PASS: Non-interventional studies C4591009,¹ C4591010,² C4591021,¹ C4591022,¹ C4591038,¹ C4591049,³ C4591051,⁴ C4591052, C4591055,⁵ and C4591062⁶ are PASS. No clinically important information has emerged from PASS. The MAH provided Summary of the interim report of the NISs C4591021 and C4591022 submitted during the reporting period [not reproduced in this AR].⁷
- 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.

Rapporteur assessment comment:

See comments/summaries above regarding the 5th and 3rd interim study reports of Category 3 PASSs **C4591021** and **C4591022**, respectively, which have previously been assessed separately.

The 2nd interim report of C4591009 has been assessed in procedure EMEA/H/C/005735/MEA/037.6

The 3rd interim report of C4591010 has been assessed in procedure EMEA/H/C/005735/MEA/011.9

The [Sep 2023] interim report of C4591038 has been assessed in procedure EMEA/H/C/005735/MEA/047.4.

US study C4591051 has been terminated because *bivalent COVID-19 vaccine is no longer authorised for use in the US, which diminish the value to conduct study C4591051. Also note that real-world safety data of the MAH's bivalent COVID-19 vaccine in Europe will be available from study C4591052 for the same exposure vaccine of interest with similar study design, population, endpoints, and analyses at an earlier timeline (final study report 30 April 2026), which is considered appropriate to further characterize the safety profile of the MAH's bivalent COVID-19 vaccine.* The MAH's justification to terminate study C4591051 has therefore been accepted within procedure EMEA/H/C/005735/MEA/64.3.

The former C4591052 ACCESS/VAC4EU study is now named C4591021.

The MAH's conclusion regarding voluntary studies C4591049, C4591055 and C4591062 is noted [No further details were provided with this PSUR submission].

¹ Studies C4591009, C4591021, C4591022, and C4591038 are requirements by the US FDA and are Category 3 commitments in the EU-RMP version 13.2. For study C4591009, an interim CSR was submitted to the US FDA and EMA 30 April 2024 (no new safety information reported); final CSR will be submitted by 31 March 2026.

² Study C4591010 is no longer a Category 3 commitment in the EU-RMP version 9.0 by request from PRAC (procedure EMEA/H/C/005735/MEA 0.11.8). Thus, no interim/final reports were submitted to EMA during the reporting period.

³ Study C4591049 is a voluntary study designed to provide real-world safety information on a cohort of people receiving the Pfizer-BioNTech COVID-19 vaccine. Interim report 1 was submitted to FDA (28 February 2024) during the reporting period.

⁴ Study C4591051 is no longer a Category 3 commitment in the EU-RMP 13.1 as agreed upon by PRAC (procedure EMEA/H/C/005735 MEA/064.3).

⁵ Study C4591055 is a voluntary study addressing risk factors for myocarditis.

⁶ The interim CSR was submitted to the US FDA on 28 June 2024.

⁷ Interim CSR was published in March 2024 for study C4591021 and in January 2024 for study C4591022.

Other Studies

There were 8 ongoing non-interventional studies:

- C4591014,⁸ *Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- C4591025,⁹ *A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.*
- C4591034, *Patient-Reported Outcomes Associated With COVID-19 and Influenza: A Prospective Survey Study on Outpatient Symptomatic Adults with Test-Confirmed Illness in the United States.*
- C4591059, *Use and Effectiveness of COVID-19 Vaccines using state vaccine registries and insurance claims data.*
- C4591065, *Effectiveness of BNT162b2 formulations using state vaccine registry and insurance claims data.*
- C4591068, *Estimated Vaccine Effectiveness (VE) and Durability of Pfizer/BioNTech 2024–2025 COVID-19 (Coronavirus Disease 2019) Vaccine.*
- C4591071, *COENZA: Study on COVID-19 and Influenza vaccinations based on a sample of the French National Health Insurance database (ESND).*
- C4591072, *Korean Post Marketing Surveillance for BNT162b2 Injection.*

An interim report from Study C4591062 was completed during the reporting period. This non-interventional study used US commercial claims data from the Optum pre-adjudicated medical and adjudicated pharmacy claims database and included 113,459 individuals who received the BNT162B2 2023-2024 Formula between 11 September 2023 and 15 January 2024. The interim report did not identify any new safety signals associated with vaccination with the BNT162B2 2023-2024 Formula, although the study may be underpowered due to a short accrual period and a small number of events. Among individuals who received a seasonal influenza vaccination on the same day as the BNT162B2 2023-2024 Formula, there was a non-significant increased incidence of non-febrile convulsions/seizures (relative incidence in the risk window compared to the control window: 3.18; 95% CI: 0.93–14.32), although this estimate is based on few events.

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

Rapporteur assessment comment:

The MAH declared that no new safety information emerged from completed and ongoing non-interventional studies.

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-MAH sponsored clinical trials/studies.

⁸ PAM-MEA-013.

⁹ Study C4591025 is a committed study, which was requested by the Ministry of Food and Drug Safety in Korea.

Medication errors

The MAH provided a comprehensive overview of medication errors [summarised here] broken down by source (Clinical trial vs. post-authorisation), category (with/without harm, potential, intercepted), vaccine formulation (monovalent original or bivalent or multivalent NOS or monovalent Omicron XBB.1.5 or Omicron JN.1 or Omicron KP.2), age group (6 months-<5 y, 5-<12 yrs, 12 yrs and older, unknown age).

The MAH concluded that overall, among the 5642 relevant PM medication error cases, 278 cases (0.8% of the total interval cases, 4.9% 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.

Rapporteur assessment comment:

Based on review of medication errors broken down by source (Clinical trial vs. post-authorisation), category (with/without harm, potential, intercepted), vaccine formulation (monovalent original or bivalent or multivalent NOS or monovalent Omicron XBB.1.5 or Omicron JN.1 or Omicron KP.2), age group (6 months to <5 yrs, 5 to <12 yrs, 12 yrs and older, unknown age), no particular trends or patterns were identified.

NON-CLINICAL DATA

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

LITERATURE

PRAC Request: 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 BNT162b2 (also besides the database Medline and Embase) that is published during the reporting period.*

On 12 December 2024, the PRAC requested the MAH to include and provide a reflection/discussion on the recently published paper regarding long-term sequelae of myocarditis after mRNA COVID-19 vaccine administration, in the next PSUR, due for submission by 26 February 2025.

Myocardial injury safety signal for mRNA COVID-19 vaccines (MACiV study findings)

Background:

Reference – Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13.

MAH Response

Please refer to the content of **Appendix 1** [of this AR] for the full assessment; the MAH conclusion is reported below.

MAH Conclusion

Long term outcomes and cardiac magnetic resonance [CMR] findings have been subject to close monitoring for myocarditis. According to the MAH, Jain *et al* does not meet the requirements for a new safety signal, as it does not provide a new aspect of the myocarditis association with BNT162b2. Importantly, the authors stated that patient-centered clinical outcomes are reassuring. Additionally, this study focuses on a primary outcome (*i.e.*, abnormal imaging finding) that has an uncertain applicability on clinical practice, and hence, on the overall benefit-risk profile of the product. Finally, a larger study with longer follow-up reporting on clinical (rather than imaging) outcomes has been recently published (Semenzato *et al*, in the Clinical subsection below). In this study, the authors found that patients with post-vaccine myocarditis, contrary to those with post-COVID-19 myocarditis, present a more favorable prognosis when compared to conventional myocarditis.

Overall, myocarditis is an ADR of the vaccine that is listed in the label of BNT162b2, is an important identified risk in the RMP and is subject to close monitoring using routine and additional PV activities. To further elucidate the long term outcomes, the MAH currently conducts a low-interventional study using primary data from the Pediatric Heart Network (PHN), a NIH-funded consortium of leading research hospitals across the US, Canada, and other countries that conducts research in cardiovascular disease, to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period (C4591036). The MAH will continue to closely monitor this topic.

Rapporteur assessment comment:

The MAH's response including a discussion on long-term outcomes and cardiac magnetic resonance [CMR] findings reported by the publication Jain *et al*. is accepted. (See **Appendix 1** of this AR for the full assessment).

In this longitudinal retrospective observational cohort multicenter study across 38 hospitals in the United States, 333 patients with COVID-19 vaccine-associated myocarditis (C-VAM) were compared with 100 patients with multisystem inflammatory syndrome in children (MIS-C). The initial clinical course in C-VAM was more likely to be mild (80% vs. 23%, $p < 0.001$) and cardiac dysfunction was less common (17% vs. 68%, $p < 0.0001$), when compared to MIS-C. However, Late gadolinium enhancement [LGE] on cardiac MRI was more prevalent in C-VAM (82% vs. 16%, $p < 0.001$), indicating myocardial injury. The authors stated that mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (interquartile range [IQR] 114–285 days) were reassuring. No cardiac deaths or heart transplantations were reported until the time of submission of this report for all groups.

In summary, the MAH noted that the findings in the paper do not identify new safety information based on the following:

- The presence of late gadolinium enhancement in longer term follow-up data of vaccine-induced myocarditis is not a new finding.
- The clinical outcomes are favourable and do not correlate with LGE findings
- Imaging parameters may not be enough to drive decision making

- A study with larger population and longer follow-up points towards a favorable prognosis of post-COVID-19 mRNA vaccination myocarditis

The MAH's commitment is endorsed to continue to closely monitor this topic, e.g. within the context of the ongoing low-interventional study **C4591036** using primary data from the Pediatric Heart Network (PHN), to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period.

The study protocol of study C4591036 has been agreed within procedure EMEA/H/C/005735/MEA/041.7.

According to the agreed milestones, data collection has started 21 Nov 2022 and will continue until 21 Nov 2030 [estimated]. Annual progress reports are planned from 30 Jun 2025 onwards, through 30 Jun 2030. Final Study Report is due 28 Feb 2031 [estimated].

Nonclinical (Published)

The MAH's 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 4 clinical studies that presented relevant safety findings on myocarditis cases after vaccination with any BNT162b2 vaccine presentation. The first one of these publications is the one for which the PRAC asked the MAH to discuss it, while the other 3 provide important information characterising the known myocarditis risk and are presented below.

1. Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACIV) multicenter study. *Lancet*. 2024;76:1-13.
<https://doi.org/10.1016/j.eclinm.2024.102809>

Please refer to **Appendix 1** for the full assessment.

2. Semenzato L, Le Vu S, Botton J, et al. Long-Term Prognosis of Patients With Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies. *JAMA*. 2024;332:1367-77.

Importance: Although patients with myocarditis after COVID-19 mRNA vaccination appear to have a good prognosis near hospital discharge, their longer-term prognosis and management remain unknown.

Objective: To study the cardiovascular complications of post-COVID-19 mRNA vaccination myocarditis and other types of myocarditis during an 18-month follow-up, as well as disease management based on a study of the frequency of medical procedures and drug prescriptions.

Design, setting, and participants: In this cohort study based on the French National Health Data System, all individuals aged 12 to 49 years hospitalised for myocarditis in France between December 27, 2020, and June 30, 2022, were identified.

Exposure: Individuals were categorized as having postvaccine myocarditis (within 7 days after COVID-19 mRNA vaccine), post-COVID-19 myocarditis (within 30 days of SARS-CoV-2 infection), or conventional myocarditis.

Main outcomes and measures: The occurrence of clinical outcomes (hospital readmission for myopericarditis, other cardiovascular events, all-cause death, and a composite outcome of these events) over the 18 months following hospital admission were analyzed using weighted Cox models to standardize

the comparisons with the conventional myocarditis group. Also, medical management after hospital discharge was longitudinally assessed using generalized estimated equation models.

Results: In total, 4635 individuals were hospitalised for myocarditis: 558 with postvaccine myocarditis, 298 with post-COVID-19 myocarditis, and 3779 with conventional myocarditis. Patients with postvaccine myocarditis were younger than those with post-COVID-19 and conventional myocarditis (mean [SD] age of 25.9 [8.6], 31.0 [10.9], and 28.3 [9.4] years, respectively) and were more frequently men (84%, 67%, and 79%). Patients with postvaccine myocarditis had a lower standardized incidence of the composite clinical outcome than those with conventional myocarditis (32/558 vs 497/3779 events; weighted hazard ratio, 0.55 [95% CI, 0.36-0.86]), whereas individuals with post-COVID-19 myocarditis had similar results (36/298 events; weighted hazard ratio, 1.04 [95% CI, 0.70-1.52]). The standardized frequency of medical procedures and drugs prescribed in patients with postvaccine myocarditis or post-COVID-19 myocarditis followed a similar trend in the 18 months following hospital discharge to that of patients with conventional myocarditis.

MAH Conclusions and relevance: Patients with post-COVID-19 mRNA vaccination myocarditis, contrary to those with post-COVID-19 myocarditis, show a lower frequency of cardiovascular complications than those with conventional myocarditis at 18 months. However, affected patients, mainly healthy young men, may require medical management up to several months after hospital discharge.

3. Choi Y, Lee JS, Choe YJ, et al. Myocarditis and Pericarditis are Temporally Associated with BNT162b2 COVID-19 Vaccine in Adolescents: A Systematic Review and Meta-analysis. *Pediatr Cardiol.* 2024 Oct 15. doi: 10.1007/s00246-024-03618-2.

The incidence of myocarditis and pericarditis has been documented in adolescents after COVID-19 vaccinations. This study aims to assess the risk of myopericarditis in adolescents following COVID-19 vaccination, using a meta-analysis of the published cases. A comprehensive literature search of the following databases on July 5, 2023: MEDLINE, EMBASE, PubMed, and the Cochrane Library was performed. The authors performed a meta-analysis using a random-effects model to estimate the incidence of myopericarditis per million of administered COVID-19 vaccine doses or COVID-19 infections. A total of 33 studies were included in the meta-analysis. The incidence of myopericarditis per million COVID-19 infections (1583.9 cases, 95% CI 751.8-2713.8) was approximately 42 times higher than that for COVID-19 vaccine administrations (37.6 cases, 95% CI 24.2-53.8). The risk of myopericarditis after COVID-19 vaccination was particularly high among the 16-19 age group (39.5 cases per million, 95% CI 25.8-56.0), males (43.1 cases per million, 95% CI 21.6-71.9), and those who received the second dose (47.7 cases per million, 95% CI 22.2-82.2). There were no significant differences in the incidence of myopericarditis per million COVID-19 vaccine administrations between Europe, the Western Pacific, and the Americas ($p = 0.51$). Adolescents faced a potential risk of myopericarditis after COVID-19 vaccination, but this risk is less harmful than that of myopericarditis following COVID-19 infection.

4. Albertson TE, Hansen C, Bihari S, et al. Serum Troponin I Assessments in 5- to 30-Year-Olds After BNT162b2 Vaccination. *Infect Dis Ther.* 2024;13(4):699-714.

Introduction: Rare myocarditis and pericarditis cases have occurred in coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine recipients. Troponin levels, a potential marker of myocardial injury, were assessed in healthy participants before and after BNT162b2 vaccination.

Methods: Vaccine-experienced 12- to 30-year-olds in phase 3 crossover C4591031 Substudy B (NCT04955626) who had two or three prior BNT162b2 30- μ g doses were randomized to receive BNT162b2 30 μ g followed by placebo, or placebo followed by BNT162b2 30 μ g, 1 month apart. A participant subset, previously unvaccinated against COVID-19, in the phase 3 C4591007 study (NCT04816643) received up to three vaccinations (BNT162b2 10 μ g or placebo [5- to 11-year-olds]) or open-label BNT162b2 30 μ g (12- to 15-year-olds). Blood samples collected pre-vaccination, 4 days post-

vaccination, and 1-month post-vaccination (C4591031 Substudy B only) were analyzed. Frequencies of elevated troponin I levels (male, > 35 ng/l; female, > 17 ng/l) were assessed.

Results: Percentages of 12- to 30-year-olds (n = 1485) in C4591031 Substudy B with elevated troponin levels following BNT162b2 or placebo receipt were 0.5% and 0.8% before vaccination, 0.7% and 1.0% at day 4, and 0.7% and 0.5% at 1 month, respectively. In Study C4591007 (n = 1265), elevated troponin I levels were observed in 0.2, 0.4, and 0.2% of 5- to 11-year-old BNT162b2 recipients at baseline and 4 days post-dose 2 and 3, respectively; corresponding values in 12- to 15-year-olds were 0.4, 0.4, and 0.7%. No 5- to 11-year-old placebo recipients had elevated troponin levels. No myocarditis or pericarditis cases or deaths were reported.

Conclusions: Among 5- to < 30-year-olds in both studies, troponin levels were rarely elevated ($\leq 1.0\%$) and similar before and post-vaccination; troponin levels were also similar between BNT162b2 and placebo in 12- to 30-year-old and 5- to 11-year-old recipients in the respective studies. No myocarditis or pericarditis cases were reported. These findings did not provide evidence that BNT162b2 causes troponin elevations. No utility of routine measurement of troponin levels in asymptomatic BNT162b2 recipients was identified.

Myocarditis is an important identified risk; please refer to Section **Error! Reference source not found.** for the cases retrieved in the reporting period and for the evaluation of this important identified risk.

Rapporteur assessment comment:

In this publication, the troponin levels, a potential marker of myocardial injury, were assessed in healthy phase 3 clinical trial [studies C4591031 and C4591007] participants before and after BNT162b2 vaccination. Note that studies C4591031 and C4591007 are described in Section 1.3.5. *Completed clinical trials*, above.

The study showed that among 5 to < 30-year-olds in both studies, troponin levels were rarely elevated ($\leq 1.0\%$) and were similar before and post-vaccination; troponin levels were also similar between BNT162b2 and placebo in 12- to 30-year-old and 5- to 11-year-old recipients in the respective studies. No myocarditis or pericarditis cases were reported.

No new safety information was identified.

OTHER PERIODIC REPORTS

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

1.3.6. Lack of efficacy in controlled clinical trials

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

Rapporteur assessment comment:

Noted.

1.3.7. Late-breaking information

The MAH submitted EU RMP Version 14.0 after PSUR DLP for up-versioning of RMP version 13.2 following the positive CHMP Opinion for variation EMA/VR/0000231586. In this updated RMP, the MAH proposed to remove the following studies/milestones from Part III.2, Part V, Part VI, and annexes as applicable:

C4591007, C4591015, C4591024, C4591031 (SSE), C4591044, C4591014, WI255886 and C4591051. New milestone, key objectives, design and study population of study C4591048 were aligned according to protocol amendment #5. The MAH also proposed a new milestone for clinical study report submission of study C4591021.

Rapporteur assessment comment:

The MAH submitted an updated (up-versioned) RMP (version 14.0) after PSUR DLP following approval of variation procedure EMA/VR/0000231586. In this variation procedure, the MAH submitted the final study report from study C4591044 (category 3 RMP study) and proposed a protocol amendment for study C4591048 (category 3 RMP study). This updated RMP was not based on important safety, efficacy, and/or effectiveness findings. There were no proposed changes to the BNT162b2 product information in this variation procedure, which was endorsed by the CHMP Rapporteur.

Request for next PSUR:

After DLP the following non-peer-reviewed paper/preprint [posted on 18 Feb 2025] was identified:

[Immunological and Antigenic Signatures Associated with Chronic Illnesses after COVID-19 Vaccination | medRxiv](#), which was also [amongst others] commented on in:

[Immune markers of post-vaccination syndrome indicate future research directions | Yale News](#)

[Rare link between coronavirus vaccines and Long Covid-like illness starts to gain acceptance | Science | AAAS](#)

Also critical remarks were made by:

[The truth about that viral 'post-vaccination syndrome' study | STAT](#)

[The rare flip-side of the immunological coin: Post-vaccine syndrome \(PVS\).](#)

Within the context of routine monitoring of relevant scientific literature, the MAH is requested to reflect on the findings reported in this paper, or any relevant emerging insights regarding long-COVID-like illness following COVID vaccination.

2. Signal and risk evaluation

2.1. Summary of safety concerns

The MAH stated the EU-RMP in effect at the beginning of the reporting period was version 11.0 (EMA/H/C/005735/II/0188). The safety concerns of BNT162b2 at the beginning of the reporting period were:

Table 1 safety concerns at the beginning of the reporting period

Important identified risk	Myocarditis and Pericarditis
Important potential risk	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
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The MAH stated having removed the missing information "Interaction with other vaccines" from the list of safety concerns in RMP version 12.0 based on the results of study C4591030 (procedure EMEA/H/C/005735/II/0201). The MAH proposes to remove this missing information topic from the list of safety concerns in future PSURs. The MAH also stated that no new safety concerns for inclusion in the EU-RMP were identified during the reporting period.

During the reporting period, the MAH submitted updated versions of the RMP in the following variations:

- EMEA/H/C/005735/II/0201
- EMEA/H/C/005735/II/0206/G
- EMEA/H/C/005735/IB/0210
- EMA/VR/0000231586

Rapporteur assessment comment:

As indicated by the MAH, "Interaction with other vaccines" was removed as RMP safety concern in procedure EMEA/H/C/005735/II/0201 during this reporting interval. The other mentioned procedures affecting the RMP concern submissions of final clinical study reports and/or protocol amendments including updated milestones.

Currently, assessment of the RMP updated to version 14.1 is currently ongoing in procedure EMA/VR/0000262269 in which the MAH proposes to remove the safety concern 'Use in pregnancy and breastfeeding' (missing information).

Removing "Interaction with other vaccines" from the PSUR summary of safety concerns will be assessed in section 2.4. "Characterisation of risks" of this assessment report.

2.2. Signal evaluation

The MAH presented an overview with new signals detected, signals with ongoing evaluations, and signals that were closed during the reporting interval in Table 25 of the PSUR [not replicated in this assessment report]. The MAH stated that review of safety topics and evaluation of signals take into consideration safety data available for monovalent (original, Omicron XBB.1.5, Omicron JN.1, Omicron KP.2), and bivalent (Omicron BA.1 and Omicron BA.4/BA.5) vaccine presentations.

The MAH categorised all 23 signals as "not a risk" and stated that routine signal detection continues, all signals were closed. Note: all 23 signals result from enquiries from regulatory authorities:

- The signal "migraine" originates from an enquiry from the regulatory authority Australia TGA.

- The signals “transverse myelitis”, “subacute thyroiditis”, “tongue discolouration”, “sciatica”, “tonsillitis”, “erysipelas”, “angina bullosa haemorrhagica”, “polycystic ovaries”, “cerebral amyloid angiopathy”, “cough”, “aphasia”, “disturbance in attention”, “myocardial necrosis marker increased”, “pelvic pain”, “paralysis”, and “pulmonary embolism” originate from enquiries from the SFDA (Saudi Food and Drug Authority).
- The signals “erectile dysfunction”, “hypertension”, “giant cell arteritis”, “exacerbation of diabetes mellitus”, and “exacerbation of adrenal insufficiency” originate from enquiries from the Rwanda FDA.
- The signal “post-menopausal haemorrhage” originates from an enquiry from EMA/PRAC.

“Pulmonary embolism” and “post-menopausal haemorrhage” were ongoing signals [not newly detected during reporting period]. The other signals were new.

The MAH stated that there were no ongoing signals during this reporting period.

The MAH presented a tabular overview of signals in Appendix 3 of the PSUR. To improve readability of the assessment report, the tabular overview of all signals is not replicated in this assessment report due to the number of signals.

Migraine

The MAH provided the following evaluation:

On 25 January 2024, the MAH received a request from Australia TGA to make safety-related changes to the Australia product information for BNT162b2. The TGA’s pharmacovigilance branch has recently assessed the risk of migraine with COVID-19 vaccines. The TGA assessment concluded that there are sufficient safety grounds to update the Australian product information for BNT162b2 to adequately communicate the risk to healthcare practitioners. This is based on evidence from published literature and reported cases of migraine with significant rates of emergency department assessment or hospital admission required as well as the distinct presentation of migraine compared to tension-type headaches. In response to the TGA’s request, an evaluation of BNT162b2 and migraine was conducted, including various data sources such as clinical trial data, the MAH’s safety database data, disproportionality analyses, literature review and observed to expected analyses. Despite uncertainty regarding the mechanism of post-vaccination headache, it is nonetheless a well-recognised post-vaccination systemic reactogenicity event that is collected in the MAH’s COVID-19 vaccine clinical trials. Commensurate with this observation, headache is one of the most frequent spontaneously reported AEs following BNT162b2 vaccination; and is noted as an adverse reaction in the core data sheet and product labelling documents. Migraine as a specific medical condition had not previously been identified by the MAH as a safety signal for BNT162b2.

AE reports of migraine from the placebo-controlled portions of the largest pivotal BNT162b2 clinical trial (C4591001) was more frequent in vaccinated participants compared to placebo participants, however, overall reports of migraine were very low (<1% regardless of group) with overlapping incidence confidence intervals. At the time of evaluation, the global safety database contained 2,040,800 AE reports for BNT162b2 vaccines, of which 17,634 reports contained the event migraine (reporting rate: 0.86%). The spontaneous reports were of variable quality and most did not contain clinical detail that would clearly support migraine diagnoses based on ICDH-3 criteria. Approximately half of the cases in each of the analysed groups were found to be confounded either by medical conditions or medications known to be associated with migraines or headaches. Overall, the majority of the cases co-reported several events along with migraine, precluding a meaningful causality assessment for BNT162b2 and the isolated migraine component. The medical literature is supportive of headache as an expected vaccine reaction and the logical expectation that individuals prone to headache (i.e., individuals with known headache disorders such as tension-type headache or migraine) are more likely to experience post-COVID-19

vaccine headaches than individuals without headache disorders. There is not a substantial body of post-vaccination literature differentiating migraine as a headache subtype or consistently describing post-vaccination headaches as having typical migraine characteristics or features. O/E analyses were <1 except for females in the younger age group (<5 years) which is likely due to the very low number of reported cases in that age group.

Overall, the analyses are not supportive of higher-than-expected reporting of cases of new migraine. While this review supports the known causal association between vaccination with BNT162b2 and headache, there is insufficient mechanistic and clinical information to support that there is a causal relationship between BNT162b2 and migraine. Therefore, the MAH considers that no update to the core data sheet or product labelling is warranted at this time. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored by routine pharmacovigilance. The TGA declined the MAH's position and requested the MAH to update BNT162b2 Australian product information by adding "Headache (including migraine)" in section 4.8 as part of the Nervous system disorders adverse reactions.

Transverse myelitis

The MAH provided the following evaluation:

The MAH received a query from Saudi Food and Drug Authority (SDFA) on 5 January 2024 regarding BNT162b2 and a potential signal of "transverse myelitis" based on the pharmacovigilance monitoring program adopted by SFDA. Transverse myelitis is a neurological disorder causing segmental bilateral acute spinal cord injury and motor, sensory and/or autonomic symptoms as a result of acute inflammation involving both grey and white matter (including neurons, axons, oligodendrocytes and myelin). While transverse myelitis has been reported with vaccinations, causation has not been established. This evaluation of transverse myelitis coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, literature review, and observed to expected analyses.

The placebo-controlled clinical trial data did not provide supportive evidence of a causal association between BNT162b2 and transverse myelitis, although it is acknowledged that rare AEs may not occur in a clinical trial, even when participants may number in the thousands. A cumulative search of the MAH's global safety database was conducted through 31 December 2023 as of 7 January 2024 to identify all BNT162b2 AE reports coded with the MedDRA (version 26.1) PT Myelitis transverse. The search yielded 378 cases out of a total of 2,003,153 cases reported for the BNT162b2 vaccines. The reporting rate for the event is 0.019%. All cases were categorised as serious, 319 (84.4%) were spontaneous in origin, 57 (15.1%) were from literature sources and 2 (0.5%) were reported from clinical studies. Countries reporting ≥ 10 cases were: US (78), UK (57), Germany (43), Saudi Arabia (22), Japan (20), Netherlands (18), Australia (15), France (11), New Zealand and Spain (10 each). There were 227 (60.1%) cases reported in females, 124 (32.8%) in males and 27 (7.1%) with no sex specified. Most post-authorisation cases reported to the safety database did not include diagnostic or clinical detail supporting the diagnosis of transverse myelitis. In the cases that did include enough detail to be categorized as BC Levels 2 and 3, many also contained confounding factors and potential alternative causes of transverse myelitis other than vaccination with BNT162b2. The large population published studies from various geographic regions are overall unsupportive of an association between vaccination for COVID-19 and the occurrence of transverse myelitis. The O/E analysis is also unsupportive.

In summary, there is not sufficient evidence to conclude that BNT162b2 administration causes transverse myelitis and therefore, the product labelling does not warrant changes. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored with routine pharmacovigilance.

Subacute thyroiditis

The MAH provided the following evaluation:

The MAH received a query from Saudi Food and Drug Authority (SDFA) on 5 January 2024 regarding BNT162b2 and a potential signal of “subacute thyroiditis” based on the pharmacovigilance monitoring program adopted by SFDA. Subacute thyroiditis, also known as De Quervain’s thyroiditis or granulomatous thyroiditis, is the most common cause of painful thyroiditis. Subacute thyroiditis, presumed to be caused by viral infections or post-viral inflammatory responses, generally develops 2 to 8 weeks following viral upper respiratory tract infections and cases tend to increase during virus outbreaks. It has been hypothesised that viral antigens in vaccines may trigger inflammation in the thyroid, similar to an infectious agent. This evaluation of subacute thyroiditis coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH’s safety database data, disproportionality analyses, literature review, and observed to expected analyses.

The placebo-controlled clinical trial data did not provide supportive evidence of a causal association between BNT162b2 and subacute thyroiditis, although it is acknowledged that uncommon AEs may not occur in clinical trials, even when participants number in the thousands. A cumulative safety database search of the MAH’s global safety database through 31 December 2023 as of 7 January 2024 was conducted using MedDRA (Version 26.1) to identify cases with PT: Thyroiditis subacute. A total of 349 cases (0.017% of total 2,003,153 cases for BNT162b2 vaccines) were retrieved. Out of these 349, (286, 81.9%) were spontaneous, (61, 17.5%) were literature, and 1 each were solicited and clinical study cases. Cases included females (260, 74.5%) and males (84, 24.1%) and sex unknown/no data (5, 1.4 %). The patients ranged in age from 23-95 years (mean = 47.9 years). Of these 349, there were 212 serious cases (60.7%) and 137 (39.3%) cases were non-serious. The number of reported post-authorisation subacute thyroiditis cases that did not include alternative explanations or confounding factors was relatively low (72 cases) when taking into consideration the unprecedented number of doses of BNT162b2 that have been administered worldwide and the number of AEs reported to the safety database. While the large population study of AESIs in >1.3 million individuals was not designed to compare the incidence of subacute thyroiditis between non-vaccinated individuals and those vaccinated with BNT162b2, the low number of subacute thyroiditis reports following BNT162b2 administration (1 per 100,000 doses after dose 1, 0 per 100,000 after Dose 2) is reassuring even though it does not prove a lack of association. Likewise, the smaller cohort studies did not provide comparative incidences of subacute thyroiditis in vaccinated vs unvaccinated cohorts, rather they provided clinical descriptions of subacute thyroiditis presentation and course. The disproportionality analysis in the published literature was inconsistent with that in the MAH’s safety database, although limitations of this signal detection exercise, such as potential masking of signals, is acknowledged. The O/E analyses and interim results of the non-interventional PASS (C4591021) are also not supportive of a relationship between BNT162b2 and subacute thyroiditis.

In summary, there is not sufficient evidence to conclude that BNT162b2 administration causes subacute thyroiditis and, therefore, no product labelling changes are warranted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored with routine pharmacovigilance.

Erectile dysfunction

The MAH provided the following evaluation:

On 9 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of “erectile dysfunction”. Erectile dysfunction can be classified as organic (i.e., vasculogenic, neurogenic, cavernous factors, hormonal, drug induced), psychogenic or mixed. This evaluation of erectile dysfunction

coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

In the blinded placebo-controlled follow-up period of the pivotal C4591001 study, erectile dysfunction was observed in 6 participants; 1 participant in the BNT162b2 group (considered unrelated by the investigator) and 5 participants in the placebo group. The literature on erectile dysfunction and BNT162b2 is limited; 2 small studies suggest that COVID-19 vaccination has either no effect, or a beneficial effect on erectile function. Erectile dysfunction has not met threshold for statistical disproportionate reporting within the MAH's global safety database. Erectile dysfunction has multiple potential aetiologies including psychosocial factors which are not only poorly reported in spontaneous post-marketing data but were potentially exacerbated by a global pandemic. It is noted that 40.5% of the reports in this dataset were received in 2021. A search of the safety database cumulatively through 31 January 2024 was conducted for all BNT162b2 vaccines for cases coded with the MedDRA version 26.1 PTs: Erectile dysfunction, Psychogenic erectile dysfunction, Organic erectile dysfunction. A total of 625 relevant cases (0.03% of the 2,030,113 cases with BNT162b2 as the suspect drug). These 625 cases reported a total of 3361 events. The majority of cases (605, 96.8%) are spontaneous reports. A total of 116 cases were confounded and the majority of the remaining cases lacked information on the patient's medical history or concomitant medications. Given that 8 of the 12 most commonly prescribed drugs list erectile dysfunction as a side effect and it is estimated 25% of cases of erectile dysfunction are due to medications, the lack of concomitant medication information is an important potential confounder. Almost half of the cases reported an onset either the same day as vaccination or within 3 days of vaccination; from a perspective of biological plausibility, it seems unlikely that a pathological process (vascular, neurological, local) could be initiated and have end-organ effect in such a short time frame. Erectile dysfunction is common and the occurrence coincidental to vaccination is possible.

To conclude, the totality of the data does not provide sufficient evidence to conclude that vaccination with BNT162b2 causes erectile dysfunction, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will be monitored using routine pharmacovigilance.

Hypertension

The MAH provided the following evaluation:

On 9 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of "hypertension". Hypertension has been reported as an adverse reaction after administration of the oral cholera vaccine, while the product labels of other vaccines routinely administered to people of advanced age, such as the quadrivalent influenza vaccine or the Herpes zoster vaccine, do not note hypertension as an adverse reaction. This evaluation of hypertension coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Large clinical studies did not show a difference in the incidence of hypertension compared to placebo. The scientific literature did not reveal convincing evidence that vaccination with BNT162b2 causes hypertension, most studies had several limitations or were small and without comparator groups. Post-marketing reports revealed a large amount of hypertension events in individuals (38178 cases out of a total of 2,047,788 cases in the safety database, i.e., 1.86% of total cases) who received BNT162b2, however, the lack of a control group and incomplete information are major limitations of spontaneous reporting and the multitude of potential confounding factors affecting blood pressure make conclusions based on spontaneous reports difficult. Hypertension is one of the most common medical conditions worldwide and there is a high prevalence of undiagnosed and uncontrolled hypertension. In addition,

Hypertension (SMQ narrow) has not met a threshold for statistically significant disproportionate reporting within the MAH's global safety database.

Given the totality of the available information, a causal association of hypertension after vaccination with BNT162b2 is not supported and no changes to the product information are warranted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Giant cell arteritis

The MAH provided the following evaluation:

On 9 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of "giant cell arteritis". Regarding background data, there has been recognition of clinical overlap in the presenting symptoms and signs of COVID-19 and giant cell arteritis and there have been suggestions of a potential association between influenza vaccine and the development of giant cell arteritis in some publications presenting case reports. This evaluation of giant cell arteritis coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, MAH's safety database data, disproportionality analyses, and literature review.

Large scale clinical trials did not report any cases of giant cell arteritis in either the BNT162b2 or placebo groups. There was relatively little in the published medical literature on COVID-19 vaccines and giant cell arteritis. One group performed a disproportionality analysis for giant cell arteritis on Vigibase data and found that COVID-19 vaccines were associated with an increased reporting in giant cell arteritis. All other literature data were case series or case reports. Overall, the available literature did not provide evidence of a causal association between BNT162b2 and giant cell arteritis. The O/E analyses revealed ratios <1, suggesting that the number of reports of giant cell arteritis are lower than would be expected based on the background rate of giant cell arteritis in an unvaccinated population. Finally, there was a relatively low number of giant cell arteritis spontaneous reports (394 cases out of a total of 2,040,800 cases in MAH's safety database, i.e., 0.02% of total cases). They were of varying quality, with most lacking information that would allow the confident attribution of giant cell arteritis to the vaccine.

Given the totality of the available information, a causal association of giant cell arteritis after vaccination with BNT162b2 is not supported and no changes to the product information are necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will be monitored using routine pharmacovigilance.

Exacerbation of diabetes mellitus

The MAH provided the following evaluation:

On 9 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of "exacerbation of diabetes mellitus". Diabetes mellitus is estimated to affect approximately 530 million adults worldwide, with a global prevalence of 10.5% among adults aged 20 years to 79 years. A mechanism by which BNT162b2 vaccination could cause diabetes mellitus exacerbation has not been elucidated. There has been speculation of how SARS-CoV-2 infection may lead to glucose alteration. This evaluation of exacerbation of diabetes mellitus coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

The non-clinical and clinical trial data are unsupportive of a causal association between BNT162b2 and exacerbation of diabetes mellitus. In the MAH's global safety database, exacerbation of diabetes mellitus was not identified as a statistical signal. A total of 223 cases were retrieved from the MAH's safety database (out of a total of 2,047,746 cases, i.e., 0.01% of total cases). Seventy-nine cases reported

glycaemic alteration in the context of significant medical conditions such as acute infection, and ischemic events, thereby confounding a thorough assessment of the role of vaccination. Glycaemic control in patients with diabetes mellitus is often difficult to consistently achieve. Eight cases of glycaemic alteration following >1 dose of vaccine did not consistently provide sufficient information for complete assessment, as in some cases glucose values, latency from vaccination to event or complete information on concomitant medication and pre vaccination glucose values were not provided. The medical literature revealed a small number of differently designed studies and had inconsistent findings. The medical literature consisting of large population data was not supportive of changes in blood glucose following vaccination.

To conclude, in the context of the unprecedented use of BNT162b2 (hundreds of millions of doses) and the large number of AE reports received from around the world, the totality of the data does not allow a conclusion that vaccination with BNT162b2 causes exacerbation of diabetes mellitus, therefore no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Exacerbation of adrenal insufficiency

The MAH provided the following evaluation:

On 9 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of "exacerbation of adrenal insufficiency". Adrenal insufficiency is a relatively rare but potentially serious condition characterised by reduced production of glucocorticoids and/or mineralocorticoids and adrenal androgens due to the destruction of the adrenal gland or lack of its stimulation. HCPs who have published cases describing adrenal crises in patients with adrenal insufficiency following COVID-19 vaccination, have theorised that they may have been caused by a strong immune response, including the release of proinflammatory cytokines, following vaccination. This evaluation of exacerbation of adrenal insufficiency coincident with BNT162b2 vaccination provided information from several data sources, such as nonclinical data, clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

There were no signs of adrenal insufficiency in the non-clinical repeat-dose studies or DART study. No AEs of acute adrenal insufficiency were reported in clinical trial data. The literature review revealed a limited number of articles that were mostly case reports. Two small studies (<90 and <170 participants, respectively) looked at the use of additional glucocorticoid following COVID-19 vaccination in patients with adrenal insufficiency and concluded that prophylactic administration of glucocorticoids in such patients was not needed. Sixty-eight cases were retrieved from the global safety database for the MAH's COVID-19 vaccine (out of a total of 2,047,746 cases in the database, reporting rate 0.003%). Although there are a small number of cases (24 cases) with no clear explanation of the cause of adrenal insufficiency exacerbation, given the context of the extensive vaccine exposure that has occurred with the MAH COVID-19 vaccine, this is not unexpected. There was no emerging statistical signal of disproportionality for acute adrenal insufficiency based on EB05 scores.

Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and the exacerbation of adrenal insufficiency. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Tongue discolouration

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and Tongue discoloration. The tongue can often provide clinical clues to systemic conditions

and demonstrate a number of conditions unrelated to other systemic diseases. This evaluation of tongue discolouration coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

During the placebo-controlled period of study C4591001, 21,926 participants ≥ 16 years of age received BNT162b2 and 21,921 participants ≥ 16 years of age received placebo. One participant in the placebo group reported tongue discolouration, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0-0.1 versus 0 participants in the BNT162b2 group (IR/100 PY 0.0, 95% CI: 0.0-0.0). No relevant literature was retrieved. Tongue discolouration has multiple potential triggers which are poorly reported in spontaneous post-marketing data. A total of 116 cases were retrieved from the MAH's global safety database for the MAH's COVID-19 vaccine (out of 2,051,801 cases in the database, reporting rate 0.005%). Most cases of tongue discolouration in the MAH's global safety database had either insufficient information for a proper evaluation or an alternative potential trigger for tongue discolouration. Given the context of the extensive vaccine exposure that has occurred with the MAH COVID-19 vaccine, few cases of tongue discolouration are not unexpected. On cumulative review of the relevant PT in MAH's global safety database, the EB05 scores were less than the EB05>2 threshold, thus indicating no emerging statistical signal for the selected PT.

Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and tongue discolouration. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Sciatica

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "sciatica". This evaluation of sciatica coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review. Sciatica is a very common condition with a lifetime incidence between 10% to 40% and an annual incidence of 1% to 5%.

In large scale clinical trials, there were similar numbers of participants reporting sciatica in the vaccine group (n = 14) and the placebo group (n = 11). There were no relevant articles in the published medical literature on BNT162b2 and sciatica. Safety database search yielded 1069 cases reporting sciatica (out of a total of 2,051,801 cases present in the database, reporting rate 0.05%); 1020 were spontaneous reports, 39 were solicited reports and 10 were from a clinical study. Only 22 out of the 1069 cases were considered as relevant. Also, there was no emerging statistical signal of disproportionality for sciatica based on EB05 scores.

Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and sciatica. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Tonsillitis

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "tonsillitis". Tonsillitis is the inflammation of tonsils. It is a common condition, making up approximately 1.3% of outpatient visits. It is generally caused by infections, which may be viral or

bacterial, with viral aetiologies being the most common. This evaluation of tonsillitis coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

In large scale clinical trials, there was a greater number of reports of tonsillitis in the placebo group (n = 8) compared to the vaccine group (n = 2). There were no relevant articles in the published medical literature on BNT162b2 and tonsillitis. The safety database search yielded 792 cases reporting tonsillitis (out of a total of 2,051,801 cases present in the database, i.e., 0.4% of total cases); 738 were spontaneous reports, 44 were solicited reports, 9 were from a clinical study and 1 was from the literature. Of the 792 cases, only 323 had any information on medical history. Of them, 179 had a reported time to onset between 0 to 14 days for the PT tonsillitis. Of the 179 cases, only 46 were medically confirmed and were further analysed. Most cases (n = 40) had confounding factors or an alternative explanation. Also, there was no emerging statistical signal of disproportionality for tonsillitis based on EB05 scores.

Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and tonsillitis. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Erysipelas

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "erysipelas". Erysipelas is an acute bacterial infection of the dermis, hypodermis and its reticular lymphatic vessels and is considered to be a specific type of cellulitis. This evaluation of erysipelas coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Within the Phase 2/3 part of study C4591001, 21,926 participants ≥16 years of age received BNT162b2 and 21,921 participants ≥16 years of age received placebo: 2 participants in the BNT162b2 group reported erysipelas, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0 0.1 versus 0 patients in the placebo group (IR/100 PY 0.0, 95% CI: 0.0-0.0). There was no relevant literature. In the MAH's global safety database, erysipelas was not identified as a statistical signal. The safety database retrieved a total of 475 cases out of 2,051,801 AE reports (0.02%). There is a relatively small number of post-authorisation reports of erysipelas shortly following COVID-19 vaccine administration, in which erysipelas was reported to have developed at the vaccination site. It is conceivable that erysipelas may occur at the vaccination site as a result of aseptic vaccine administration technique, however, the spontaneous reports did not clearly describe this scenario. Some cases had insufficient information about the medical history and concomitant medications, preventing confidence in the diagnosis and assessment of the clinical context and none of the reported cases performed diagnostic examination to confirm an infectious origin. Moreover, some, as per description, were more suggestive of a local reaction or swelling of the injected limb.

To conclude, in the context of the unprecedented use of BNT162b2 (hundreds of millions of doses) and the large number of AE reports received from around the world, the totality of the data does not allow a conclusion that vaccination with BNT162b2 causes erysipelas, therefore no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Angina bullosa haemorrhagica

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "Angina bullosa haemorrhagica". Angina bullosa haemorrhagica is a benign, self-limited condition characterised by the sudden onset of blood-filled blisters in the oral cavity. The aetiology of this oral pathology is unknown, and it is considered to occur in susceptible patients following trauma in the oral cavity. This evaluation of angina bullosa haemorrhagica coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Angina bullosa haemorrhagica is a rare event, no adverse events were reported in the clinical trials and there was no relevant literature. Post-marketing reports revealed a small number of angina bullosa haemorrhagica events (10 cases) in individuals who received BNT162b2, with most cases being confounded. Routine statistical reports did not reveal disproportional reporting.

In the context of hundreds of millions of doses of BNT162b2 administered worldwide, the totality of the available information does not support a causal association between angina bullosa haemorrhagica and vaccination with BNT162b2. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Polycystic ovaries

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "polycystic ovaries". Polycystic ovary syndrome is one of the most common conditions in reproductive aged women affecting 8-13% of all women of reproductive age. The aetiology of polycystic ovary syndrome is a complex trait arising from the interaction of genetic and environmental factors. This evaluation of polycystic ovaries coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Within the blinded placebo-controlled period of Study C4591001 21,926 participants ≥ 16 years of age received BNT162b2 and 21,921 participants ≥ 16 years of age received placebo; 1 participant in the vaccine group reported polycystic ovaries, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0-0.1 versus 0 participants in the placebo group (IR/100 PY 0.0, 95% CI: 0.0-0.0). There was no relevant literature. A cumulative search of the MAH's global safety database was conducted through 31 March 2024 to identify all cases that reported Original BNT162b2, Bivalent (BNT162b2/BNT162b2 Omicron BA.1) and Bivalent (BNT162b2/BNT162b2 Omicron BA.4/BA.5) vaccine, Multivalent NOS and Monovalent Omi XBB.1.5 presentations. as the suspect drug reporting the event coded with the MedDRA Version 26.1 PTs Polycystic ovarian syndrome and Polycystic ovaries. A total of 156 cases were retrieved from the MAH's global safety database out of 2,051,801 total cases (reporting rate 0.007%). The cases have been reported after BNT162b2, BNT162b2 Omicron BA.1, BNT162b2 Omicron BA.4/BA.5, BNT162b2 XBB 1.5 or BNT162b2 multivalent NOS administration. Although there are a small number of medically confirmed, serious cases, most of them had either insufficient information to confirm the diagnosis or had polycystic ovary syndrome as medical history or had underlying comorbidities considered a trigger of polycystic ovary syndrome. Additionally, the number of reports is relatively low given the extensive MAH's COVID-19 vaccine exposure worldwide. Routine statistical reports did not reveal disproportional reporting.

Overall, the totality of available information does not allow a conclusion that vaccination with BNT162b2 causes polycystic ovaries. Therefore, no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Cerebral amyloid angiopathy

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "Cerebral amyloid angiopathy". Cerebral amyloid angiopathy is usually an age-related degenerative condition caused by deposition of beta amyloid in the walls of cerebral small vessels. Different genetic risk factors have been identified. Additionally, non-genetic factors are thought to contribute to the risk of cerebral amyloid angiopathy. For example, uncontrolled hypertension has been reported to be more prevalent among cerebral amyloid angiopathy patients. This evaluation of cerebral amyloid angiopathy coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Cerebral amyloid angiopathy was not reported by participants in either the vaccine (N = 21,926) or placebo (N = 21,921) groups during the placebo-controlled period of the MAH-run pivotal clinical trial C4591001 in participants 12 years and older, nor in participants 16 years and older in the placebo-controlled period of booster study C4591031 SSA, nor in the placebo controlled period of the MAH-run pivotal clinical trial in participants 6 months to <12 years of age, C4591007. There was no relevant literature. A total of 28 cases were retrieved from the MAH's global safety database, out of a total of 2,051,801 (0.001%) cases in the MAH database for the MAH's COVID-19 vaccine. Many cases describing an uncertain cerebral amyloid angiopathy diagnosis, and most patients having multiple underlying comorbidities that may contribute to the presence of cerebral amyloid angiopathy. In addition, cerebral amyloid angiopathy has not met the threshold for statistical disproportionate reporting within the MAH's global safety database.

To conclude, the totality of the data does not provide sufficient evidence to conclude that vaccination with BNT162b2 causes cerebral amyloid angiopathy, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Cough

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "cough". Other than the rare context of anaphylaxis, in which an allergic reaction to the vaccine could affect the lower respiratory tract, there is no known biological mechanism by which vaccination with BNT162b2 may cause cough. This evaluation of cough coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

In the placebo-controlled stages of the pivotal studies, cough was not commonly reported. When reported, the incidences did not differ significantly between the vaccine and placebo recipients. At the time of evaluation, the MAH's global safety database contained 2,051,801 AE reports for BNT162b2 vaccines, of which 34,402 reports contained the event cough (reporting rate: 1.68%). The spontaneous reports were of variable quality, and majority did not contain adequate clinical information for a meaningful assessment of the event cough. Cough was very often reported in the context of infections or potential hypersensitivity reactions involving multiple organ systems. Overall, in all the cases with adequate clinical information, cough could be attributed to an alternative aetiology. While medical literature capturing acute post-vaccination AEs may report cough, its incidence is relatively low across the reviewed studies, and it does not emerge as a notable vaccine-associated event by the authors. The data

across these studies, involving tens of thousands of reports and multiple pharmacovigilance databases, do not depict a strong association between BNT162b2 and reports of cough.

Overall, there is insufficient mechanistic information and a lack of clear and consistent data to support a conclusion of a causal relationship between BNT162b2 and cough. Therefore, the MAH considers that no update to the core data sheet or product labelling is warranted at this time. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Aphasia

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "aphasia". Aphasia is delineated as "the loss of ability to communicate orally, through signs, or in writing, or the inability to comprehend such communications; the loss of language usage ability." This condition can be precipitated by a myriad of cerebral pathologies, with cerebrovascular accident being the predominant aetiology. This evaluation of aphasia coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Clinical trial data in large randomized-placebo-controlled studies did not show a difference in the occurrence of aphasia between BNT162b2 and placebo. There was no published literature describing an association between vaccination with BNT162b2 and aphasia. A cumulative search of the MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA Version 27.0 PT Aphasia. The search yielded 3121 cases reporting aphasia (out of a total of 2,060,299 cases, i.e., 0.15% of total cases); 3023 were spontaneous reports, 71 were solicited reports, 5 were from literature and 22 were from clinical studies. There are a number of medically confirmed serious cases that did not provide clear alternative explanations for aphasia; however, this is not sufficient to conclude a causal association between aphasia and the MAH's COVID-19 vaccine. There was no emerging statistical signal of disproportionality for aphasia based on EB05 scores in the global safety database.

Overall, the totality of available information is not supportive of a causal relationship between the vaccine and aphasia. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Disturbance in attention

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "disturbance in attention". Broadly, attention is defined as the set of processes that allow us to process certain information to the (relative) exclusion of other information. Given the great complexity of information available to our senses at any given time, attention is crucial for sorting out relevant information and limiting the amount of information that gains access to further processing. A disturbance in attention is a sign or symptom that may occur in association with a variety of medical conditions. This evaluation provided information from several data sources, such as clinical trial data, MAH's safety database data, disproportionality analyses, and literature review.

In the blinded placebo-controlled follow-up period of the pivotal C4591001 study, disturbance in attention was reported in 4 participants in the BNT162b2 group and no participant in the placebo group. None of the participants of the C4591031 SSA reported disturbance in attention. During the placebo-controlled

Study C4591007, 1 participant in the BNT162b2 group reported disturbance in attention. The medical literature on disturbance in attention and BNT162b2 was limited. One relevant article was identified that assessed short term AEs reported via an electronic questionnaire and noted a small percentage ($\leq 1.8\%$) of reports of lack of concentration after second and third doses of the MAH COVID-19 vaccine and without a significant difference between the doses. Disturbance in attention has multiple potential aetiologies which are poorly reported in the spontaneous post-marketing data. A cumulative search of MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT "Disturbance in attention". A total of 11,260 AE reports (containing 113,925 events) were retrieved using the above search criteria in the context of 2,060,299 total AE reports in the MAH safety database for the MAH's COVID-19 vaccine (reporting rate 0.5%). Most cases described medical histories or co-reported events that provided more likely explanations for attention disturbances than the vaccine itself. There was no emerging statistical signal of disproportionality for disturbance in attention based on EB05 scores.

Overall, the available information on disturbance of attention and BNT162b2 is not sufficient to conclude a causal association. The MAH considers this signal refuted and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Myocardial necrosis marker increased

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "myocardial necrosis marker increased". An increase in myocardial necrosis marker in serum is a sign of an underlying cardiac condition. Cardiac AESIs that may be associated with increases in myocardial necrosis markers (including myocardial infarction, myocarditis/pericarditis) have been monitored closely and included in aggregate safety reports for regulatory authorities by the MAH since the initial authorisation of BNT162b2. Myocarditis and pericarditis are identified risks for BNT162b2 vaccines and as such are discussed in product labelling. This evaluation provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

The PT "Myocardial necrosis marker increased" was not reported as an AE in the placebo-controlled portions of the large BNT162b2 clinical trials. There is no relevant literature, describing an association between vaccination with BNT162b2 and myocardial necrosis marker increased, except for articles reporting increased myocardial necrosis markers in the context of myocarditis. There was no signal of disproportionality for the AE in the global safety database. A cumulative search of the MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT "Myocardial necrosis marker increased". A total of 175 AE reports (containing 1488 events) were retrieved using the search criteria mentioned above in the context of 2,060,299 total AE reports in the MAH global safety database received for the MAH's COVID-19 vaccine (reporting rate 0.008%). There are a small number of serious cases with no clear explanation, however given the context of the unprecedented vaccine exposure and the known rare risk of myocarditis, this is not unexpected.

The MAH considers this signal refuted, and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Pelvic pain

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "pelvic pain". Acute pelvic pain is a non-specific symptom that may occur in association with many medical conditions. It is generally defined as pain in the anatomic region of the pelvis that has lasted <3 months. The pain can be sharp or dull, focal or diffuse, sporadic or constant. Pain that is exclusive to the mid or upper abdomen, and low back is not considered pelvic pain. Importantly, a patient with chronic pelvic pain can present with an acute process arising de novo or a pain exacerbation that is related to the chronic condition. Over one-third of reproductive-aged women will experience non-menstrual pelvic pain at some point. While most acute pelvic pain is caused by reproductive, urinary, or gastrointestinal tract disorders, abnormalities of musculoskeletal, vascular, and neurologic processes can contribute as well. Because multiple organ systems are contained within the pelvis, a broad differential diagnosis exists for patients with acute pelvic pain. This evaluation provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

In clinical studies of 21,926 participants ≥ 16 years of age in the BNT162b2 group of Study C4591001, 3 reported PT "Pelvic pain" (for an incidence rate of 0.0 per 100 PY). Of 21,921 participants in the placebo group, 3 reported PT "Pelvic pain" (for an incidence rate of 0.0 per 100 PY). There was no relevant medical literature. A cumulative search of the MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT "Pelvic pain". A total of 1660 cases, reporting 10,619 AEs, were retrieved from the MAH's global safety database; 1639 were spontaneous reports, 17 were solicited reports, and 4 were from clinical studies. Contextually, the total number of AE reports for BNT162b2 vaccines in the safety database is 2,060,299 (reporting ratio of 0.08%). The majority of the spontaneous reports of pelvic pain also co-reported potential causes of the pain, given that pelvic pain may originate from any of several anatomic systems. There was no clear and consistent trend pointing toward a disorder that is known to be caused by the vaccine. There was no emerging statistical signal of disproportionality for pelvic pain based on EB05 scores.

Overall, the available information is not supportive of a causal association between pelvic pain and BNT162b2. The MAH considers this signal refuted, and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Paralysis

The MAH provided the following evaluation:

On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for BNT162b2 and "paralysis". Paralysis is a loss of motor function in 1 or more muscles. It may be temporary or permanent, proximal, distal or combined, asymmetric or symmetric, acute, subacute or chronic. It may be progressive or episodic. The potential causes of paralysis vary but include demyelinating conditions such as Guillain-Barré syndrome, neurologic conditions such as transverse myelitis or stroke, infectious diseases such as poliomyelitis, poisoning such as consumption of tetrodotoxin, autoimmune conditions such as myasthenia gravis, metabolic myopathies and genetic conditions such as hyperkalemic periodic paralysis or trauma and nerve injury. The variety of potential causes is reflected in the plethora of diagnostic investigations that can be applied. Apart from patient history and clinical examination, they may include laboratory parameters, imaging studies such as MRI, electrodiagnostic testing, invasive procedures such as lumbar puncture or muscle biopsy, or genetic testing. This

evaluation provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Large scale clinical trials did not report any cases with the PT "Paralysis" in either the BNT162b2 or placebo groups. Overall, the available literature did not provide evidence of a causal association between BNT162b2 and paralysis in general. The safety database was searched for all cases reporting PT "Paralysis" for the BNT162b2 vaccine through 30 April 2024 (MedDRA version 27.0). The search yielded 1847 cases reporting paralysis; 1831 were spontaneous reports, 6 were solicited reports, 4 were from the literature, and 6 were from a clinical study. Contextually, the total number of AE reports for BNT162b2 vaccines in the safety database is 2,060,299. They were of varying quality, with most lacking information that would allow the confident attribution of paralysis to the vaccine and many with confounders or more plausible alternative explanation. There was no signal of disproportionality for the AE in the global safety database.

Overall, the available information on paralysis and BNT162b2 is not sufficient to conclude a causal association. The MAH considers this signal refuted and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Pulmonary embolism

The MAH provided the following evaluation:

A request was received from SFDA on 22 October 2023 pertaining to the occurrence of pulmonary embolism following vaccination with the MAH's COVID-19 Vaccine (BNT162b2). Pulmonary embolism refers to obstruction of the pulmonary artery or 1 of its branches by material (e.g., thrombus, tumour, air, or fat) that originated elsewhere in the body. The source of most emboli is the lower extremity proximal veins and >50 percent of patients with proximal deep vein thrombosis have concurrent pulmonary embolism at presentation. Most pulmonary embolisms move beyond the bifurcation of the main pulmonary artery to lodge distally in the main lobar, segmental, or subsegmental branches of a pulmonary artery. Pulmonary embolism can be bilateral or unilateral, depending on whether they obstruct arteries in the right, left, or both lungs. Smaller thrombi that are located in the peripheral segmental or subsegmental branches are more likely to cause pulmonary infarction and pleuritis. The occurrence of pulmonary embolism is not uncommon, and the incidence rises with increasing age, such that pulmonary embolism has an incidence of >500 per 100,000 after the age of 75 years. Case-fatality rate increases with increasing age. Men have a higher risk for pulmonary embolism compared to women. Other risk factors include genetic conditions (e.g., factor V Leiden mutation) and acquired factors, including recent surgery/trauma, immobilisation, malignancy, pregnancy, obesity, and smoking. This evaluation provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

Within the blinded placebo-controlled follow-up period of both adult studies (defined as from first vaccine received to unblinding date), out of a total of 28,095 participants exposed to BNT162b2 (23,041 from study C4591001 and 5054 from study C4591031 sub-study A) and 28,056 exposed to placebo (23,040 from study C4591001 and 5016 from study C4591031), 21 AEs were reported under the aforementioned PTs (18 from study C4591001 and 3 from study C4591031). Of these 21 AEs, 8 were reported in the BNT162b2 group (all from study C4591001) and the remaining 13 were reported in the placebo group (10 from study C4591001 and 3 from study C4591031). There were no events reported in study C4591007. The extensive literature review of the Original and Bivalent BNT162b2 vaccines did not demonstrate strong support for a causal relationship between pulmonary embolism and vaccination with BNT162b2. A cumulative search of MAH's global safety database was conducted through 15 October 2023 to identify all

the cases that reported BNT162b2 including BNT162b2 Bivalent Omicron BA.1 and BA.4/BA.5 as well as BNT162b2 XBB1.5 as the suspect drug with events coding to the PTs "Pulmonary embolism", "Pulmonary infarction", "Pulmonary microemboli", "Pulmonary thrombosis", "Pulmonary artery occlusion", "Pulmonary artery thrombosis". Safety database search retrieved a total of 8753 cases, corresponding to 0.46% of all the cases (1,914,175) with BNT162b2 as the suspect drug. Of the 8753 cases, 4153 were male patients, 4452 female patients, and the gender was unknown in 148 cases. The age of the patients ranged from 12 years to 102 years (n = 8371), with a mean age of 59.7 years. In 42.9% cases (n = 3754), the age was equal to or over 65 years. The countries reporting the highest number of cases (top 5) were Germany (1913), France (1573), UK (768), US (477), Italy (412). All 8753 cases were assessed as serious. Case outcome was reported as fatal (731), resolved/resolving (4315), or not resolved (2592). In 1115 cases, the outcome was unknown. Of the 8753 cases, 9165 relevant PTs were reported (1 case may report >1 relevant PT): "Pulmonary embolism" (8368), "Pulmonary thrombosis" (390), "Pulmonary infarction" (334), "Pulmonary artery thrombosis" (49), "Pulmonary microemboli" (16), "Pulmonary artery occlusion" (8). All these relevant PTs were assessed as serious. Of the 8753 cases, the clinical outcome of the relevant events was reported as fatal (672), resolved/resolving (4516), not resolved (2153), or unknown (1845). In 16 cases, the relevant PTs occurred before the patients received BNT162b2. In 3930 out of the remaining 8737 cases, there were significant confounding factors, e.g., presence of co-suspect drugs or concomitant drugs known to cause pulmonary embolism such as oral contraceptives, JAK inhibitors, anti-VEGF therapy; pre-existing common risk factors for pulmonary embolism such as pulmonary embolism history, deep vein thrombosis, bedridden, hypercoagulation, obesity; present co-reported events associated with thromboembolism, such as COVID-19, pneumonia/pneumonitis, atrial fibrillation, sepsis, disseminated intravascular coagulation. In 4113 out of the remaining 4807 cases, information important for a medically meaningful assessment of pulmonary embolism (e.g., medical history, concomitant drugs, and/or latency from vaccination) was not reported. Of the remaining 694 cases, 231 cases were not medically confirmed. In 250 out of the remaining 463 cases, the diagnosis of pulmonary embolism was confirmed by imaging studies (e.g., angiogram, computerised tomogram, MRI) or autopsy. Of these 250 cases with confirmatory diagnostic studies, the age of the patients ranged from 17 years to 98 years. In 55.6% cases (n = 138), the age of the patients was ≥65 years. Of the 250 cases, 264 relevant PTs were reported: "Pulmonary embolism" (249), "Pulmonary infarction" (10), "Pulmonary thrombosis" (5). Of the 250 cases, the latency between the dose of BNT162b2 to the occurrence of pulmonary embolism ranged from <1 day to 297 days, with a mean of 19.6 days and a median of 11 days. In 83.6% cases (n = 209), the latency was ≤30 days. However, a temporal association of the AEs following BNT162b2 administration in these reports does not necessarily mean a causal relationship with administration of BNT162b2 and may represent temporally coincidental events. The clinical outcome of the 264 relevant PTs was reported as fatal (10), resolved/resolving (179), not resolved (42) and unknown (33). The most frequently reported medical history (>15 times) included hypertension (96), Tobacco user (22), Depression (20), Dyslipidaemia (20), Asthma (18). The most frequently reported concomitant drugs (>15 times) included acetylsalicylic acid (26), hydrochlorothiazide (23), levothyroxine (23), atorvastatin (20), bisoprolol (20), paracetamol (18), omeprazole (17). Of the 10 cases with fatal outcome, 3 cases were reported from France, and the remaining 7 cases were reported from UK, Japan, Spain, Ireland, Norway, Denmark, Argentina (1 each). The age of the patients ranged from 40 to 98 years. In 5 cases, the age was ≥65 years. In 9 out of the 10 cases, the patients had major risk factors for atherothrombotic disease including hypertension, diabetes mellitus, or hypercholesterolaemia. In the remaining case, the patient had been breathless for 2 weeks before administration of BNT162b2, and the patient also had medical history of chest pain which was treated as pericarditis and pneumonia. The reporting physician noted that it is possible that the patient had a previous undiagnosed pulmonary embolism. No significant findings were identified for these cases with fatal outcome. In summary, upon review of these confirmed cases of pulmonary embolism, the available information is inconclusive to ascertain whether pulmonary embolism was causally related to vaccination or just temporally coincidental in these cases, considering the

limitations of individual case reports. Routine statistical reports did not reveal an emerging statistical signal. In the Observed to expected ratio, based on the selected background rates and the estimated number of exposure person-years calculated using the number of the MAH vaccine doses through 05 October 2023 in the EEA and the length of risk windows, O/E ratios were below 1 overall for risk windows of 21 days and 42-days. The O/E ratios were below 1 for the 14-day risk window with the exception of the 12 to 17-year age group. However, the result was not statistically significant. This suggests that the number of observed cases of pulmonary embolism is not higher than expected in the absence of the MAH COVID-19 vaccines overall and within the queried strata.

In summary, based on clinical data, literature data, routine statistical reports, safety database review, an O/E analysis as well as review of post-authorisation safety studies, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and the development of pulmonary embolism. The MAH considers this safety signal refuted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance. On 14 May 2024, SFDA notification was received noting that they agreed on the recommendation to keep the signal under the routine pharmacovigilance monitoring and follow-up when further evidence is available.

Post-menopausal haemorrhage

The MAH provided the following evaluation:

The EMA PRAC signal assessment report on postmenopausal haemorrhage with BNT162b2 was received on 26 October 2023 [(EPITT ref. No. 19989) EMA/PRC/470614/2023]. Postmenopausal (bleeding) haemorrhage is not uncommon and occurs in approximately 4-11% of postmenopausal women with the incidence inversely related to the time since menopause. There are many possible mechanisms of postmenopausal haemorrhage that can be theorised following COVID-19 vaccination, but there seems to be an absence of strong evidence for any mechanistic pathway. This evaluation provided information from several data sources, such as preclinical data, clinical trial data, the MAH's safety database data, disproportionality analyses, and literature review.

In animal model studies of BNT162b2, no clinical signs of bleeding or haemorrhage were observed. In clinical trials, out of a total of 13857 female participants exposed to BNT162b2 and 13,958 exposed to placebo, 3 AEs of postmenopausal haemorrhage were reported, 1 in the BNT162b2 group and 2 in the placebo group. Ongoing clinical trials have incorporated more detailed questionnaires for participants reporting menstrual abnormalities. Literature data on postmenopausal haemorrhage were limited and did not provide evidence of a causal association with vaccination. In routine statistical reports, no statistical signal of disproportionality was identified for postmenopausal haemorrhage with the BNT162b2 vaccines. The majority of ICSRs in the global safety database were reported in women in the early postmenopausal period, when the incidence of postmenopausal haemorrhage is expectedly higher. Due to the nature of spontaneous case reports the needed clinical information for a meaningful assessment was often missing or incomplete with the main reason for classification as "possibly related based on WHO-UMC criteria" being only limited to a reasonable temporal relationship to vaccination. The conclusions that can be drawn are limited. In the O/E analysis, the number of observed cases of postmenopausal haemorrhage was not higher than expected based on background rates in the absence of the MAH's COVID-19 vaccines for either of the risk windows.

To conclude, the totality of the data does not provide enough evidence to conclude that vaccination with BNT162b2 causes postmenopausal haemorrhage, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance. On 11 March 2024, PRAC Final Assessment Report was received. PRAC agreed there

is insufficient evidence to establish a causal association between BNT162b2 and postmenopausal haemorrhage and to continue to monitor through routine pharmacovigilance.

Rapporteur assessment comment:

The MAH included an overview of the 23 signals at PSUR DLP. All presented signals originate from a request of a competent authority: the origin of 16 signals is a request from the Saudi FDA, the origin of 5 signals is a request from the Rwanda FDA, and finally 1 signal from the Australia TGA and 1 signal from EMA/PRAC. The MAH categorised all these signals as “not a risk” and all signals are closed by the MAH.

The MAH described that the regulatory authorities agreed that pulmonary embolism (Saudi FDA) and post-menopausal haemorrhage (EMA) do not constitute a new risk of BNT162b2. For migraine, a signal identified by the Australia TGA, the MAH stated that the TGA considered that a product information update for BNT162b2 was warranted. For the other 20 signals (all identified by the Saudi FDA or Rwanda FDA) the MAH did not report whether the authority agreed with the outcome of the MAH’s signal assessment (“not a risk”). Based on publicly available information on the websites of the Saudi FDA and Rwanda FDA, it appears that these authorities considered that no updates to the BNT162b2 product information were warranted following assessment of these evaluations.

The evidence supporting a causal relationship between BNT162b2 and these signals appears insufficient or inconclusive. None of the signals shows a consistent pattern suggesting a new risk (such as a positive statistical association combined with strong cases from studies/spontaneous reports and biological plausibility) and therefore the MAH concludes not to update the BNT162b2 product information and to close these signals. It appears all regulatory authorities, except the Australia TGA for the signal “migraine”, did not consider that regulatory action was warranted following signal evaluation.

None of the above signals are currently listed as adverse reactions in the BNT162b2 product information. However, some events included as signals may occur in the context of known adverse reactions. For example “paralysis” is not a known adverse reaction to BNT162b2 but acute peripheral facial paralysis may occur with rare frequency. “Myocardial necrosis marker increased” may occur in the context of the known adverse reaction myocarditis. None of these signals underwent EU signal assessment procedure during this reporting interval, except for post-menopausal haemorrhage as indicated by the MAH.

Some events of these signals are included as adverse event of special interest (AESI) in post authorisation safety studies. For example study C4591021 aims to further characterise AESIs including transverse myelitis and subacute thyroiditis. The fifth interim report of this study (dated 12 March 2024) was appended to the PSUR and assessed in procedure EMEA/H/C/005735/MEA/017.9. The PRAC concluded that no new important safety information could be identified from this interim report.

No further action is considered warranted at this stage.

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Evaluation of important identified risks

2.3.1.1. Myocarditis and pericarditis

Rapporteur assessment comment:

The currently approved BNT162b2 product information (sections 4.4 and 4.8) warns about the very rare risk of myocarditis and pericarditis following vaccination with BNT162b2. These conditions can develop

within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

During the reporting period, the MAH stated that there were 589 potentially relevant cases of myocarditis and pericarditis: 393 cases reported myocarditis, and 233 cases reported pericarditis (in 37 of these 589 cases, both myocarditis and pericarditis were reported).

The MAH referred to PSUR section 11. Literature for relevant safety information on myocarditis [assessed previously in this assessment report] but stated that there was no significant new safety data on pericarditis from literature sources.

The MAH concluded that based on the interval data, no significant new safety information was identified pertaining to the risk of myocarditis and pericarditis with BNT162b2 and stated that the risk and appropriate actions to take are communicated in the BNT162b2 core data sheet.

The MAH used the SMQ "Noninfectious myocarditis/pericarditis (Narrow search)" to retrieve relevant case reports from the safety database.

Myocarditis

The MAH did not retrieve any relevant case reports from clinical trial data.

The MAH retrieved 393 post marketing cases received during this reporting interval. These mostly concerned the monovalent original vaccine (325 cases) and monovalent omicron XBB.1.5 vaccine (43 cases). Of these 325 monovalent original vaccine cases, these events mostly occurred in the year 2021 (89 cases) and in the year 2022 (67 cases), if known. Further characteristics of these cases, as presented by the MAH, are included in the following bullet points:

- Country of incidence: Germany (107), UK (50), Japan (38), France (33), Sweden (26), US (25), Austria (16), and Australia (12).
- Medical confirmation: Medically confirmed cases (213), not-medically confirmed cases (180).
- Subjects' gender: female (157), male (219) and unknown (17).
- Subjects' age in years: n = 343, range: 7 – 95, mean: 43.8, median: 42.0.
- Medical history (n = 166); the most frequently (≥ 10) reported medical conditions included Hypertension (34), Drug hypersensitivity, Tobacco user (13 each), Hypercholesterolaemia, Hypothyroidism (10 each).
- COVID-19 medical history (n = 27): COVID-19 (19), Suspected COVID-19 (6), Coronavirus infection, COVID-19 immunisation (1 each).
- Co-suspect medications (≥ 2): Elasomeran, Influenza vaccine inact sag 4V, pembrolizumab (4 each), Influenza vaccine inact split 4V (3), COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19) (2).
- Number of relevant events: 399.
- Relevant event seriousness: serious (399).
- Reported relevant PTs: "Myocarditis" (334), "Myopericarditis" (49), "Carditis" (8), "Eosinophilic myocarditis", "Giant cell myocarditis" (3 each), "Chronic myocarditis" and "Hypersensitivity myocarditis" (1 each).

- Relevant event outcome: fatal (21), resolved/resolving (131), resolved with sequelae (40), not resolved (84), unknown (123).
- Risk factors:
Of the 393 cases reporting events indicative of myocarditis, 213 cases (54.2%) were medically confirmed. Of the 393 cases, in 93 cases (23.7% 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 131 cases (33.3%) 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 316 cases (80.4%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

The MAH further provided age-stratified data on myocarditis in the PSUR (section 16.3.1.1.1. Important Identified Risks – Myocarditis). The MAH also provided information on the case reports with a fatal outcome in this section. These data are not replicated in this assessment report.

Pericarditis

The MAH did not retrieve any relevant case reports from clinical trial data.

The MAH retrieved 233 post marketing cases received during this reporting interval. These mostly concerned the monovalent original vaccine (181 cases) and monovalent omicron XBB.1.5 vaccine (32 cases). Further characteristics of these cases, as presented by the MAH, are included in the following bullet points:

- Country/region of incidence (≥ 10): France (36), UK (25), Australia, Germany (22 each), Italy (16), Sweden (15), US (12), Greece, Japan (11 each), Canada, Netherlands, and Norway (10 each). The remaining 33 cases were distributed among 17 countries.
- 106 cases were medically confirmed, 127 cases were not medically confirmed cases.
- Subjects' gender: female (132), male (99) and unknown (2).
- Subjects' age in years: $n = 211$, range: 7 – 96, mean: 45.7, median: 45.0.
- Medical history ($n = 103$); the most frequently (≥ 5) reported medical history included Hypertension (16), Asthma, Obesity (9 each), Non-tobacco user (8), Pericarditis (7), Drug hypersensitivity, Ex-tobacco user, Hypothyroidism (6 each), and Seasonal allergy (5).
- COVID-19 medical history ($n = 23$): COVID-19 (18), Suspected COVID-19 (3), Coronavirus infection, and Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (≥ 2 occurrences), ($n = 23$); relevant co-suspect medications included Elasomeran, Influenza vaccine inact split 4V (7 each), Influenza vaccine (3), and COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19) (2).
- Number of relevant events: 233.
- Relevant event seriousness: serious (233).
- Reported relevant PTs: "Pericarditis" (224), "Pericarditis constrictive", "Pleuropericarditis" (4 each), and "Autoimmune pericarditis" (1).
- Relevant event outcome: fatal (6), resolved/resolving (81), resolved with sequelae (8), not resolved (78), unknown (60).

- **Risk factors:**

Of the 233 cases reporting events indicative of pericarditis, 106 cases (45.5%) were medically confirmed. Of the 233 cases, in 66 cases (28.3% 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 233 cases, in 81 cases (34.8%) 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) did not match a suspected vaccine induced event. Of the 233 cases, in 167 cases (71.7%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

The MAH further provided age-stratified data on pericarditis in the PSUR (section 16.3.1.1.2. Important Identified Risks – Pericarditis). In addition, the MAH provided information on the case reports with a fatal outcome in this section. These data are not replicated in this assessment report.

Rapporteur assessment comment:

The MAH presented aggregate data on the events of myocarditis and pericarditis. All presented data originate from post marketing cases. As the MAH indicates, the cases received for myocarditis and pericarditis overlap as some cases report both events.

These 393 relevant cases for myocarditis and 233 relevant cases for pericarditis received during this reporting interval should be interpreted in the context of 15,265 cumulative cases relevant for myocarditis and 11,820 cumulative cases relevant for pericarditis at PSUR DLP from the post marketing setting. Most cases were reported following exposure to the monovalent original vaccine. The MAH declared that most cases were confounded (by medical history and/or co-reported events) and/or contained only limited information.

No information was identified in this overview that warrants updates to the BNT162b2 product information: the presented information on myocarditis/pericarditis suggests a pattern in line with the currently approved BNT162b2 product information.

"Myocarditis and Pericarditis" is an important identified risk in the BNT162b2 RMP. "Myocarditis and Pericarditis" is further addressed through the following additional pharmacovigilance studies: C4591036, C4591009, C4591021, C4591038, and C4591052.

2.3.2. Evaluation of important potential risks

The MAH stated that there were no important potential risks for BNT162b2 during this reporting period.

2.3.3. Evaluation of other risks (not considered as important)

The MAH stated that no new safety issues/signals or reporting pattern changes were detected following review of the incremental data in:

- Cases potentially reflective of AESIs, including AESIs in subjects with malnutrition or HIV infection
- Reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions
- Local adverse reactions, and/or severe reactogenicity

- Evaluation of special situations: overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect
- Cases reporting fatal outcome
- Lack of therapeutic efficacy
- The use in frail patients with co-morbidities, and/or interactions with other vaccines
- The use in elderly

Rapporteur assessment comment:

The MAH removed information from the above topics from the applicable section(s) of the submitted PSUR. This is acceptable: in previous PSURs the MAH was requested to only discuss these topics in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.

2.3.3.1. Hemophagocytic lymphohistiocytosis (HLH)

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUR/00010898/202312), the following request was made:

The MAH was requested to 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 provided the following summary:

To date, no plausible biological mechanism has been identified to support the development of HLH in patients vaccinated with BNT162b2, nor is there evidence to suggest that vaccination with BNT162b2 directly causes HLH. Data from pivotal clinical trials and placebo-controlled follow-up assessments did not reveal any cases of HLH. Safety follow up beyond 6 months after dose 2, identified a single report in a 51-year-old male. Similarly, in Study C4591006, a required non-interventional post-authorization clinical study, adverse events of PTs Liver disorder and HLH were reported in a 50-year-old female and were assessed by the MAH as unrelated to the vaccination. A comprehensive literature review did not provide evidence of a causal relationship. The review of the 130 post-marketing cases from the safety database indicated that the majority (56.9%) were females, with a mean age of 49.3 years. When applying the WHO causality assessment framework, one case was classified as "probably related", 31 cases as "possibly related", 58 as "unlikely related", 39 as "unassessable" cases and one as a duplicate case. Routine statistical reports did not reveal an emerging statistical signal for BNT162b2. Overall, the totality of evidence does not substantiate a causal relationship between BNT162b2 and HLH. Consequently, there is no need to update the Product Information or RMP at this time. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

The MAH provided a comprehensive response in Appendix 5.2 of the submitted PSUR, which is partially replicated below:

Haemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare 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.

Immune dysregulation with unchecked inflammation leads to the typical clinical presentation of fever, cytopenia, splenomegaly, and/or haemophagocytosis; ferritin >500 mcg/L, bicytopenia and soluble CD25 (IL-2 receptor) elevation. HLH is treated with immunosuppressive agents and/or chemotherapy. Treatment of paediatric HLH using HLH-2004 (diagnostic criteria, not reproduced here) or multi-agent chemotherapy can be applied in adult patients, although the dose may need to be adjusted. Allogenic hematopoietic stem cell transplantation is recommended in patients who become reactivated or are refractory to the initial treatment to improve survival.

Clinical trial data

In pivotal clinical trial C4591001, none of the participants ≥ 16 years of age had a medical history of HLH. During the placebo-controlled follow up period from Dose 1 to 1 month after Dose 2 of BNT162b2, there were no reports of HLH in 21,926 participants in the vaccine group and 21,921 participants in the placebo group. Similarly, of 6,666 participants ≥ 16 to 55 years of age and 5,240 participants >55 years of age who originally received vaccine and had 6 months of follow-up after dose 2, there were no reports of HLH.

In safety follow-up beyond 6 months after dose 2, there was a report of HLH in a C4591001 participant in the US (AER [REDACTED]). In addition, in study C4591006, a required non-interventional post-authorization clinical study of BNT162b2 in Japan, adverse events of PTs Liver disorder and HLH (AER [REDACTED]) were reported. The MAH provided case narratives in the evaluation report, these are not replicated in this assessment report.

There have been no reports of HLH in 12-15 year olds participating in C4591001, nor in C4591007, the paediatric pivotal clinical trial for participants <12 years of age.

The MAH concluded that data from clinical trials do not support a causal association between vaccination with BNT162b2 and the development of HLH.

In Study C4591006, a required non-interventional post-authorization clinical study of BNT162b2 in Japan, adverse events of PTs Liver disorder and Haemophagocytic lymphohistiocytosis (AER [REDACTED]) were reported in a 50 year old woman with a medical history of neuromyelitis optica, a demyelinating autoimmune disorder of the central nervous system since 2003 treated with prednisolone 2.5 mg daily and osteoporosis, received dose 1 of Comirnaty on 22 February 2021 and dose 2 on 15 March 2021, both in the left deltoid. At 28 days after dose 2, the subject had fever (38 °C) and swollen cervical, axillary and sub-clavicular lymph nodes. Approximately 19 days later, she was hospitalized for a work-up with severe malaise; at the time her physical exam was not remarkable except for neck lymphadenopathy; she was afebrile. She was discharged 73 days later. Over the course of her hospitalization, the reported Tmax was 38.5 °C. Liver function abnormalities waxed and waned (AST max 329 uL, ALT max 479 uL, AP 246 uL, GGT 161 uL). Other labs of note included CRP 2.0 mg/dL increased; WBC $6.96 \times 10^3/uL$ (Lym 14.0% decreased), Hb 11.8 g/dL decreased, Hematocrit 35.9% decreased, Fib 408 mg/dL increased, D-dimer 2.2 ug/mL, SARS-CoV-2 RNA (negative several times), ANA was "80 times," T. SPOT was negative, EBV infection was observed, CMV antigen was negative, soluble IL-2 receptor 729 (no range provided), ferritin 7532.5 (no range provided), lumbar puncture WNL, unspecified culture results were negative. CT scan with contrast showed multiple lymph nodes enlarged from the left axilla to under the clavicle

accompanied by mild adipose tissue turbidity around them; LNs of non-significant size scattered in the neck and right axilla and from the abdomen to the pelvis and in the groin. No abnormalities observed in the liver. A liver ultrasound showed moderate hardness of the liver, fibrosis and moderate fatty liver. A liver biopsy was performed but no results provided. The investigator reported the adverse event as "liver disorder due to broad macrophage activation syndrome after vaccination." Over the course of her hospitalization, the patient received solumedrol 125 mg for 3 days and prednisolone was increased to 60 mg daily and ultimately decreased after the start of cyclosporin 200 mg on 30 June 2021 which was noted to cause an improvement in LFTs that was not observed with prednisolone. On 22 July 2021 the patient's liver disorder and HLH were considered recovered. The investigator assessed the event as related to vaccination.

Rapporteur assessment comment:

There were no reported HLH cases in the placebo-controlled follow up period of study C4591001 among 21,926 participants in the vaccine group (follow up 1 month after dose 2 of BNT162b2). Of these participants, there were also no HLH cases among the almost 12,000 participants with 6 month follow-up after dose 2.

The MAH identified one case of HLH reported from this study (C4591001) in the safety follow-up beyond 6 months after dose 2. The time to onset of the event was 275 days, which is not considered a reasonable time relationship and the investigator assessed HLH as not related to BNT162b2 vaccination: this case is assessed as unlikely related.

The MAH also retrieved a case of HLH from study C4591006 in Japan. This case was assessed as related to vaccination by the investigator. Despite the investigator's causality assessment as related and reasonable time to onset (symptoms 28 days after dose 2 followed by the patient's hospitalisation 19 days later), there are difficulties interpreting this case report due to discrepancies and confounding. For example, the case reports that there were no abnormalities in the liver, but also that there was liver fibrosis. Confounding factors include EBV infection and underlying autoimmune disorder. Both autoimmune conditions and infections are associated with HLH. Although the causality is considered possible according to the WHO-UMC classification, its challenging to evaluate the role of the vaccination in this case.

Study C4591006 is not included in the EU RMP of BNT162b2.

Literature

The MAH conducted a literature search up to 18 December 2024 to identify newly available articles describing BNT162b2 and the MedDRA PT Haemophagocytic lymphohistiocytosis in the Medline and Embase database.

The search revealed 2 relevant articles described below, case reports are analysed as part of the MAH's safety database review.

- 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.

- 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 (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:

Both articles were already referenced by the MAH in the previous PSUR and assessed in the corresponding assessment report: *As noted by the authors of this qualitative analysis [Zhang et al.], 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.*

Following the assessment of the publication by Zhang et al., the MAH was requested in previous PSUR to perform a cumulative review including all published HLH reports. In the following section (MAH’s global safety database), approximately a quarter of case reports in the MAH’s safety database originate from publications in the scientific literature – these other publications are therefore assessed as part of the assessment of the cases in the MAH’s safety database.

MAH’s global safety database

The safety database was searched cumulatively for BNT162b2 vaccines adverse event reports to 18 December 2024 using the MedDRA PT: “haemophagocytic lymphohistiocytosis”. The search of the safety database retrieved 130 cases reporting 1,015 adverse events. The total number of cases in the safety database were 1,983,208, with 130 cases representing 0.0065% of all cases.

Of the 130 cases, 74 (56.9%) were female while 56 (43.1%) were male. The mean age was 49.3 years, with the breakdown as follows:

- Less than or equal to 17 years: 12.3% of cases
- 18 - 30 years: 16.2% of cases
- 31 - 50 years: 17.7% of cases
- 51 - 64 years: 20.8% of cases
- 65 - 74 years: 10% of cases
- Greater than or equal to 75 years 19.2% of cases
- Age reported as unknown 3.8% of cases

The top 10 reporting countries were Japan (28.5%), US (13.8%), Germany (12.3%), France (11.5%), Italy (5.4%), Australia (3.8%), UK (3.8%), Spain (3.1%), Taiwan (3.1%) and Portugal (2.3%).

71.5% of cases were spontaneous, 26.2% were literature cases while 2.3% of cases were from clinical trials.

All cases were deemed serious. There were 31 cases (23.8%) reported as fatal, 25 cases (19.2%) reported as unresolved, 29 cases (22.3%) reported as resolved, 1 case reported as resolved with

sequalae, 28 cases (21.5%) reported as resolving and in 16 cases (12.3%) with the outcome unknown at the time of the report.

As requested by PRAC, the MAH conducted a WHO-UMC causality assessment per case (irrespective of the source, e.g. spontaneous report, case from literature, case from study, etc). A detailed report can be found in Appendix A, and a narrative line-listing of the 130 cases is available in Appendix B of Appendix 5.2 of the submitted PSUR.

Out of the 130 cases, the MAH assessed 1 case as probably related, 31 as possibly related, 58 as unlikely related, 39 as unassessable, and 1 duplicate case.

Probably related case [REDACTED]

A 21-year-old male subject received BNT162b2, as dose 2 for COVID-19 immunisation. The subject had no relevant medical history. The subject's concomitant medications were not reported. He was in good physical condition before receiving the 2nd dose of the BNT162b2 vaccine two weeks ago. He experienced general weakness, a fever, myalgia, and a skin rash without an itching sensation. He was transferred from another hospital with an uncontrolled high fever (above 39 °C), profound pancytopenia, and an elevated total bilirubin concentration (10.27 mg/dL). He was started on empirical intravenous antibiotics (tazoperan, piperacillin and tazobactam, 4.5 g, q8h) for fever of unknown origin and steroid pulse therapy (intravenous methylprednisolone, 1.5 mg/kg/day) four days before the transfer. Physical examination revealed an erythematous rash on the patient's arms and upper chest, icteric conjunctivae, and splenomegaly. No clinical features of thrombosis were observed. CT of the subject's neck, chest, and abdomen/pelvis demonstrated hepatosplenomegaly (spleen size, 13 cm) with periportal edema and gallbladder wall thickening, minimal pelvic ascites and bilateral pleural effusion, and no focus of infection. Blood and urine cultures were negative. Upon 18F-fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET)-CT, liver uptake was relatively even (standardized uptake value max/mean, 3.2/2.3), and FDG activity was not increased in the spleen. A bone marrow biopsy revealed normocellular marrow with substantial histiocytosis and active hemophagocytosis, without any malignant cell infiltration. A real-time polymerase chain reaction of oro- and nasopharyngeal swabs was negative for SARS-CoV-2 and other respiratory viruses. Furthermore, there was no evidence of acute or active infection with cytomegalovirus; Epstein-Barr virus; parvovirus B19; hepatitis A, B, and C; HIV; or Korean endemic viruses related to hemorrhagic fever with renal syndrome. Autoimmune antibody tests, conducted to rule out the possibility of an underlying autoimmune disease, were also negative. Overall, the subject's test results met the HLH-2004 diagnostic criteria, with an HScore of 319 (>99% probability of hemophagocytic syndrome). The subject subsequently received high-dose dexamethasone (20 mg/day for seven days) and a 25% dose reduction on a weekly basis without etoposide or other treatment modalities. Nineteen days after steroid pulse therapy, the subject was discharged in good physical condition without any constitutional symptoms, with normal laboratory values and the disappearance of the skin rash. After discharge, the subject received oral steroids alone, which were tapered weekly, and finally stopped after the third month of follow-up without any evidence of HLH relapse.

Rapporteur assessment comment:

This published case¹⁰ by Park et al. was also discussed and (assessed as probably related) during the assessment of PSUR 5. This case concerned a 21-year-old man with secondary HLH 2 weeks following a 2nd dose of BNT162b2. The patient did not have primary HLH or other contributors to secondary HLH and met the HLH-2004 diagnostic criteria with an HScore of 319 (>99% probability of hemophagocytic syndrome). Patient had no known medical history or comedications, no active or recent bacterial or viral infection or autoimmune disease. The MAH assessed this case as probable which could be agreed

¹⁰ Park et al. *A Case of Hemophagocytic Lymphohistiocytosis following Second Dose of COVID-19 Vaccination*. *Acta Haematol.* 2023;146(1):65-71

considering the reasonable TTO and confirmed HLH-2004 diagnostic criteria. However, the event of HLH could also have occurred coincidentally following vaccination.

Possibly related cases

The MAH stated that there were 31 cases assessed and conservatively adjudicated as possibly related to vaccination due to a reasonable temporal relationship. Majority of the cases could also be explained by alternative factors such as ongoing hepatic disease; concomitant infections like Epstein-Barr virus, cytomegalovirus, C difficile, parvovirus; coexisting malignancies like acute myeloblastic leukemia, prostate cancer, breast cancer, malignant lymphoma; other coexisting conditions like Systemic Lupus Erythematosus, Sjogren's disease and other autoimmune diseases that may confound or otherwise contribute to the development of HLH in these subjects.

Unlikely related cases

The MAH stated that there were 58 cases assessed as unlikely related to vaccination due to a latency period that was not probable as well as coexisting diseases or concomitant drugs that could provide alternative explanations for the development of HLH in these subjects.

Unassessable cases

The MAH stated that of the 130 reported cases, 39 cases were deemed unassessable due to insufficient information or contradictory data that cannot be supplemented or further verified.

The MAH concluded that a review of the 130 cases retrieved from the safety database did not show enough evidence of a causal relationship between BNT162b2 vaccine and the development of HLH.

Rapporteur assessment comment:

The MAH performed a thorough assessment of all received HLH cases, which is appreciated. The assessor agrees with the number of cases assessed as 'probably related' (1) or 'unassessable' but considers that about half of the cases that were assessed as unlikely related by the MAH should be considered as possibly related to BNT162b2 exposure.

In interpreting these case reports it is useful to consider that HLH may occur idiopathically or be triggered by undiagnosed infection or malignancy. Although HLH primarily occurs in paediatric patients, about half of these case reports occurred in patients ≥ 50 years of age, although no particular pattern in age groups is identified.

Routine statistical reports

To support routine signal detection activities in addition to the non-statistical reports, the MAH generates statistical reports including EB05. The MAH concluded that the EB05 is less than the EB05>2 threshold, thus indicating no emerging statistical signal for all vaccine formulations.

Summary and conclusion

The MAH concluded: overall, the totality of evidence does not substantiate a causal relationship between BNT162b2 and HLH. Consequently, there is no need to update the product information or risk management plan at this time. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Rapporteur assessment comment:

The MAH's conclusion that there is insufficient evidence to establish a causal relationship between BNT162b2 and HLH is endorsed. Most presented supportive data were already assessed in previous PSUR assessments, such as the probably related case by Park et al. and the systemic review performed by

Zhang et al. Further review of cases from clinical trials or the post marketing setting did not retrieve new strongly supportive cases, while there was also no positive statistical association of BNT162b2 cases in the MAH's safety database and reporting of the event HLH.

The MAH's proposal to monitor this topic through routine pharmacovigilance, and to only present it in future PSURs if any significant new information is identified, is endorsed.

2.3.3.2. Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUSA/00010898/202312), the following request was made:

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.

MAH Response (Appendix 5.3 of the PSUR)

Idiopathic inflammatory myopathies (IIMs) is an umbrella term that includes multiple diseases such as dermatomyositis, polymyositis, myositis as part of a rheumatic disease overlap syndrome. These diseases share the clinical manifestation of progressive muscle weakness and the histopathologic finding of inflammatory infiltrates of varying degrees in muscle tissue.

Medical history and concomitant medications are important for the differential diagnosis of IIMs, as IIMs share some clinical and pathologic manifestations with, and need to be distinguished from, known causes of myopathy including, drug (such as statins, corticosteroids, colchicine and hydroxychloroquine), and metabolic causes. Of note viral myositis can also be a cause of myopathy. Influenza A and B viruses and enteroviruses are commonly reported causes of viral myositis. SARS-CoV-2 has also been associated with viral myositis, either due to direct myocyte invasion or induction of autoimmunity.

In general, adult-onset idiopathic inflammatory myopathy (IIM) is associated with an increased cancer risk within the 3 years preceding and following IIM onset. Particularly for dermatomyositis, this condition can manifest as a paraneoplastic syndrome, thus a screening for malignancy is often recommended in patients with dermatomyositis.

Non-Clinical Data

Non-clinically, the BNT162b2 platform has been evaluated in 2 good laboratory practice (GLP) repeat dose toxicity studies and 1 development and reproductive toxicity study. There were no clinical signs that could be attributed to myositis or autoimmune reactions (eg, chronic limping, lethargy, lameness) in those studies. Administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week for a total of 3 weekly cycles of dosing was tolerated without evidence of systemic toxicity in the GLP compliant repeat dose toxicity studies.

Expected inflammatory responses to the vaccine were evident such as oedema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants, and lower albumin:globulin ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunisations.

Microscopically, there was no evidence of an inflammatory response in muscle sites examined beyond the injection site on necroscopy (eg, gastrocnemius, tongue, and heart). All inflammation in the muscle was at the injection site and associated with the injection.

Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the 3-week recovery phase, approximately 23 days after the last dose, indicating no long-term inflammation.

Clinical Trial Data

MAH-run clinical trials were searched for the following MedDRA 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. No new adverse events of idiopathic inflammatory myopathies/ autoimmune myositis were observed in the clinical trial database since the last evaluation.

Literature Data

The literature was searched from 16 January 2023 to 18 December 2024 for BNT162B2 or BNT162b2 and 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.

A total of 119 literature articles were retrieved, of which 22 articles were considered relevant by the MAH and are summarized individually in MAH's PSUR (not reproduced here).

See below tabulated summary of literature discussed by MAH plus PRAC assessor remarks:

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
Jung SW, Jeon JJ, Kim YH, et al. Long-term risk of autoimmune diseases after mRNA-based SARS-CoV-2 vaccination in a Korean, nationwide, population-based cohort study. Nat Commun. 2024;15(1):6181. doi: 10.1038/s41467-024-50656-8	Observational study in Korea (data from the Korea Disease Control and Prevention Agency-COVID-19-National Health Insurance Service (NHIS) cohort)	Individuals (n=9,258,803) who had the BNT162b2 vaccine did not incur a higher risk of developing dermato/polymyositis when compared to historical controls (adjusted hazard ratio 0.99; 99% confidence interval 0.72-1.35).	No increased risk observed for autoimmune connective tissue diseases (in vaccinated individuals compared to historically unvaccinated).
Copland E, Patone M, Saatci D, et al. Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England. Nat Commun. 2024;15(1):3822. doi: 10.1038/s41467-024-47745-z	Observational English National Immunization Management Service (NIMS) database of COVID-19 vaccination	Post hoc matched cohort study including all vaccinated children aged 5–17 years and matched unvaccinated children, irrespective of SARS-CoV-2 test status during the study period. No	No increased risk observed for developing myositis in vaccinated children aged 5-17 years of age compared to matched unvaccinated children.

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
		differences were observed regarding myositis in all groups of the matched population.	
Ou TS, Sun YS, Lai CC, et al. Immune-mediated diseases after vaccinations with AZD1222, BNT- 162b2, &/or mRNA-1273: An observational investigation of 78 patients. Int Immunopharmacol. 2024; 127:111455. doi: 10.1016/j.intimp.2023.111455	Retrospective observational study from Taiwan (n=78 patients)	There were 28 events of immune mediated disease in the BNT162b2 vaccinated, with 2 relating to idiopathic inflammatory myopathy. No further information on these two specific events is presented	One of the two reported cases of myositis had a history of SLE. No other information could be retrieved on the reported cases from this literature report. Not enough information for causality assessment.
Panchawagh S, Bohdana D, Kuwana M, et al. Delayed adverse events following COVID-19 vaccination in patients with systemic sclerosis and other autoimmune diseases: a substudy of the COVAD-2 cohort. Rheumatol Int. 2023;43(12):2211-2220. doi: 10.1007/s00296-023-05441-z	Global, cross-sectional, patient self-reported e-survey conducted from February to June 2022.	The authors concluded that certain co-existing autoimmune conditions in systemic sclerosis, including myositis, can potentially increase the risk of minor adverse events (such as myalgia).	No increased risk observed for developing idiopathic inflammatory myopathies (IIM) flares in patients with pre-existing sclerosis (n=179) or systemic autoimmune disease (SAID)(n=4171) compared to healthy controls. Myalgia is listed in SmPC section 4.8.
Shaharir SS, Daskaliuk B, Ravichandran N, et al AB1312 myositis patients without autoimmune multimorbidity at lower risk of delayed onset covid-19 vaccine adverse events than other autoimmune diseases: results from the covad study. Annals of the Rheumatic Diseases 2023;82:1885.	Conference abstract reporting on an international patient self-reporting e-survey (=COVAD-2) from February to June 2022	The authors concluded that patients with idiopathic inflammatory myopathies were at a lower risk of delayed onset COVID-19 vaccine adverse events compared to other systemic autoimmune and inflammatory disorders.	No increased risk observed for developing idiopathic inflammatory myopathies (IIM) flares in patients with pre-existing IMM.
Béldi TG, Nagy-Vincze M, Szabó K, et al. POS1219 incidence, features and outcome of disease relapse after covid-19 vaccination in patients with idiopathic Inflammatory myopathies. Annals of the Rheumatic Diseases 2023;82:944.	Conference poster abstract presenting prospective cohort study of 176 patients with idiopathic inflammatory myopathy.	The authors reported that the active state of myositis at time of injection ($p<0.0001$; odds ratio: 31.2, confidence interval: 9.0 – 108) and the application of BNT162b2 vaccination ($p=0.026$; odds ratio: 4.06, confidence interval: 1.1 – 14.7) were	Poster abstract contains too little information on study background, statistical methods used and which other vaccines were analysed. SmPC contains information in 4.4 not to vaccinate during active infectious disease. Immunization of individuals with auto-immune disease during flares is not preferable in clinical practice (except during a pandemic state when the benefit of vaccination

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
		significantly associated with the occurrence of relapse. Active disease state at the time of vaccination probably contributes to the increased risk of post vaccination myositis flare.	should be weighed against possible flare ups).
Doskaliuk B, Sen P, Joshi M, et al. POS1259 systemic sclerosis and covid-19 vaccine-associated delayed adverse events: insights from the covid-2 study. <i>Annals of the Rheumatic Diseases</i> 2023;82:972-973	Conference abstract reporting on an international patient self-reporting e-survey (=COVAD-2) from February to June 2022	No new information compared to Panchawagh S <i>et al.</i>	Same conclusion as Panchawagh <i>et al</i> (see literature ref above).
Ju HJ, Lee JY, Han JH, et al. Risk of autoimmune skin and connective tissue disorders after mRNA- based COVID-19 vaccination. <i>J Am Acad Dermatol.</i> 2023;89(4):685-693. doi: 10.1016/j.jaad.2023.05.017	Observational study in South Korea (data from the Korea Disease Control and Prevention Agency-COVID-19-National Health Insurance Service (NHIS) cohort)	The risk of dermato/polymyositis was not higher in vaccinated individuals with BNT162b2 than in controls (adjusted hazard ratio 1.36, 95% confidence intervals 0.73-2.54).	Using real-world data, the authors found that mRNA-based COVID-19 vaccination was not associated with a significantly increased risk of alopecia areata, vitiligo, psoriasis, sarcoidosis, Behcet disease, Crohn disease, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis, and dermato/ polymyositis; these risks were not increased by age, sex, type of mRNA vaccine, or cross-vaccination status.
Nelli F, Giannarelli D, Fabbri A, et al. Immune-related adverse events and disease outcomes after the third dose of SARS-CoV-2 mRNA-BNT162b2 vaccine in cancer patients receiving immune checkpoint inhibitors. <i>Cancer Immunol Immunother.</i> 2023;72(10):3217-3228. doi: 10.1007/s00262-023-03489-1	Prospective, observational, cohort study including 56 patients that received the third BNT162b2 dose and with advanced solid malignancies receiving immune checkpoint inhibitors.	Immune-related adverse events (including, but not limited to myositis) did not differ before and after the third dose.	No increased risk observed for developing IIM in cancer patients receiving immune checkpoint inhibitors after receiving the 3 rd dose of BNT162b2.
Martora F, Battista T, Ruggiero A, et al. The impact of COVID-19 vaccination on inflammatory skin disorders and other cutaneous diseases: A Review of the published literature.	Review of published literature up to 20 April 2023 aiming to investigate the current literature	The authors stated that these are reports of a few cases suggesting this association with the COVID-19 vaccination. They also	The percentage of cutaneous AEs is extremely low if compared with the number of vaccines administered. The causal temporal correlation between cutaneous reaction and vaccination cannot be ruled out in most of the cases (= the conclusion

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
Viruses. 2023;15(7):1423. doi: 10.3390/v15071423	regarding cutaneous reactions following COVID-19 vaccination, including dermatomyositis.	stated that “unlike the other reactions we have reported, where both the numbers and the mechanisms proposed at the base are valid, in these cases certainly further studies will be necessary to establish the true correlation.	of the authors of the article). Erythema multiforme and rash are already labeled in section 4.8 of the SmPC.
Šinkovec Savšek T, Zajc Avramovič M, Avčin T, et al. Disease relapse rate in children with autoimmune rheumatic diseases after COVID-19 infection and vaccination. <i>Pediatr Rheumatol Online J</i> . 2023;21(1):46. doi: 10.1186/s12969-023-00829-4.	Observational study from Slovenia.	For juvenile dermatomyositis, 2 out of 92 subjects (2%) had a relapse following COVID-19 infection whereas 0 out of 47 (0%) had a relapse following vaccination	No increased risk observed for autoimmune rheumatic disease relapse after COVID-19 vaccination in this pediatric cohort.
Connolly CM et al. Humoral response to 3rd dose Sars-Cov-2 vaccine in patients with idiopathic inflammatory myopathies. <i>Clinical and Experimental Rheumatology</i> . Conference: 4th Global Conference on Myositis, GCOM 2022. Prague Czechia. 41(2) (pp 422), 2023. Date of Publication: 2023	Conference abstract reporting on an international patient self-reporting e-survey (=COVAD-2) from February to June 2022.	Adults with a patient-reported diagnosis of idiopathic inflammatory myopathy who completed three-dose SARS-CoV-2 vaccination. It was reported that dose 3 was well tolerated with only 2 (3.4%) participants reporting disease flare.	Two observed cases with disease flare, 3.4% of total patients analyzed. No causality assessment provided of the two cases.
Gazit T, Eviatar T, Shear J, et al. Development of autoantibodies following BNT162b2 mRNA COVID-19 vaccination and their association with disease flares in adult patients with Autoimmune Inflammatory Rheumatic Diseases (AIIRD) and the general population: Results of 1-year prospective follow-up study. <i>Vaccines (Basel)</i> . 2023 Feb 17;11(2):476. doi: 10.3390/vaccines11020476 *	Observational study in the sera of 463 adult patients with AIIRD compared to 55 controls from the general population prior to, and following the second and third vaccine doses with BNT162b2, and at 1-year of follow-up.	In the AIIRD group, 17 out of 463 (3.7%) patients had inflammatory myositis. Disease flares among AIIRD patients occurred in a minority of patients from the available data (5.8%, n = 27 of 423 patients following two vaccine doses and 7.2%, n = 29 of 212 patients following three vaccine doses).	17 (out of 463) patients with AIIRD reported inflammatory myositis. 27 patients reported disease flare of existing AIIRD after second vaccination. No observed versus expected analysis was provided.
Hoff LS, Ravichandran N, Shinjo SK, et al. COVAD Study Group. COVID-19 severity and vaccine breakthrough infections in	Large observational study with secondary data	The authors concluded that patients with IIMs reported fewer	Article focus is on efficacy in patients with autoimmune disease. No discussion is provided in the

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
idiopathic inflammatory myopathies, other systemic autoimmune and inflammatory diseases, and healthy controls: a multicenter cross-sectional study from the COVID-19 Vaccination in Autoimmune Diseases (COVAD) survey. Rheumatol Int. 2023;43(1):47-58. doi: 10.1007/s00296-022-05229-7	from the COVAD study. The study aimed to compare the frequency, profile, and severity of COVID-19 infection both prior to and post-vaccination in patients with idiopathic inflammatory myopathies.	COVID-19 cases than Healthy Controls (HC) and other SAIDs, but had higher odds of all-cause hospitalization from COVID-19 than HCs. Breakthrough Infections were associated with the use of immunosuppressants and were uncommon in IIMs.	article on flare up of IIM after vaccination with BNT162b2.
Traboco L, et al. COVID19 vaccination-related short-term adverse events in patients with idiopathic inflammatory myositis and autoimmune multimorbidity: Results from the COVAD survey. International Journal of Rheumatic Diseases. Conference: 24th Asia-Pacific League of Associations for Rheumatology Congress, APLAR 2022. Hong Kong Hong Kong. 26(Supplement 1) (pp 63-64), 2023. Date of Publication: January 2023	Conference abstract reporting on the observational COVAD study.	Author conclusion: COVID-19 vaccination is safe with minimal to no risks of short-term AEs in patients with IIM without other concomitant autoimmune diseases. The presence of autoimmune multimorbidity conferred higher self-reported short-term risks of overall, major, and minor COVID-19 vaccination-related AEs seven days post-vaccination in IIM patients, particularly in those with active IIM.	No published paper (yet), only conference abstract. No information available on methods used. Patients with active disease AID and/or IIM (and other comorbidities) reported higher major adverse events. It is not specified in the abstract what the 'major AEs' are. No further information available on this conference abstract.
Doskaliuk B, Ravichandran N, Sen P, et al. COVAD study group. Long-term safety of COVID vaccination in individuals with idiopathic inflammatory myopathies: results from the COVAD study. Rheumatol Int. 2023;43(9):1651-1664. doi: 10.1007/s00296-023-05345-y.	Observational study using data from the second COVAD study. It studied delayed-onset adverse events (>7 days) in patients with idiopathic inflammatory myopathies.	IIM patients with active disease, overlap myositis, autoimmune comorbidities, and ChadOx1 nCoV-19 (Oxford/AstraZeneca) recipients reported AEs more often, while those with inclusion body myositis, and BNT162b2 (Pfizer) recipients reported fewer AEs. Vaccination is reassuringly safe in individuals with IIMs,	Post-vaccination fares of underlying autoimmune disease were less frequent among IIMs than SAIDs [OR 0.8 (0.6–1.0), p = 0.032] in patients with IIMs who received the BNT162b2 (Pfizer) vaccine. However, the authors noted that among BNT162b2 (Pfizer) vaccine recipients, patients with IIMs were at a threefold higher risk of rash compared to HCs [OR 3.0 (1.4–6.3), p=0.004]. Rash is already labeled in section 4.8 of the SmPC.

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
		with AEs, hospitalizations comparable to SAIDs, and largely limited to those with autoimmune multimorbidity and active disease.	
Heshin-Bekenstein M, Ziv A, Toplak N, et al. Safety and immunogenicity of BNT162b2 mRNA COVID-19 vaccine in adolescents with rheumatic diseases treated with immunomodulatory medications. Rheumatology (Oxford). 2022 Nov 2;61(11):4263-4272. doi: 10.1093/rheumatology/keac103	International observational study.	The authors concluded that vaccination of patients with juvenile-onset autoimmune inflammatory rheumatic diseases demonstrated good short-term safety and efficacy.	A total of 91 patients and 40 healthy controls were included. No observed versus expected analysis was provided. 1 disease flare was observed and one case of renal failure and pulmonary hemorrhage respectively.
Gil-Vila A, Ravichandran N, Selva-O'Callaghan A, et al; COVAD Study Group. COVID-19 Vaccination in Autoimmune Diseases (COVAD) study: Vaccine safety in idiopathic inflammatory myopathies. Muscle Nerve. 2022 Oct;66(4):426-437. doi: 10.1002/mus.27681	COVAD international survey study	Patients with active idiopathic inflammatory myopathies reported more frequent major (odds ratio, 2.7; interquartile range, 1.04-7.3) and minor (odds ratio, 1.5; interquartile range, 1.1-2.2) adverse events than patients with Inactive idiopathic inflammatory myopathies. . In adjusted analysis, dermatomyositis was associated with higher risk of headache compared with other idiopathic inflammatory myopathies.	Headache is already labeled in section 4.8 of the SmPC.
Dey M, et al. COVID-19 vaccination-related short-term adverse events in patients with idiopathic inflammatory myositis and autoimmune multimorbidity: Results from the COVID-19 vaccination in autoimmune diseases survey. Arthritis and Rheumatology. Conference: American College of Rheumatology Convergence,	Conference abstract on COVAD international survey study.	The authors again concluded that COVID-19 vaccination is safe with minimal to no risks of short-term AEs in patients with idiopathic inflammatory myopathies without other concomitant	No increased risk observed for autoimmune disease relapse after COVID-19 vaccination.

Literature reference	Type of study	Conclusions authors and /or MAH	PRAC assessor remarks
ACR 2022. Philadelphia, PA United States. 74(Supplement 9) (pp 332-336), 2022. Date of Publication: September 2022		autoimmune diseases.	
Naveen R, Sen P, Griger Z, et al. COVAD Study Group. Flares in IIMs and the timeline following COVID-19 vaccination: a combined analysis of the COVAD-1 and -2 surveys. Rheumatology (Oxford). 2024 Jan 4;63(1):127-139. doi: 10.1093/rheumatology/kead180	Study reporting a combined analysis of COVAD studies.	The authors found that patients with IIMs were at an equal risk of disease flares in the post-COVID-19 vaccination period similar to other autoimmune rheumatic diseases.	No comparison made with flares in auto-immune disease patients without vaccination or compared to historical data of disease flare up. Not clear if flares occur more often in vaccinated patients with autoimmune disease compared to non vaccinated/pre pandemic auto immune disease.
van Dam KPJ, Wieske L, Stalman EW, et al. Immunity against SARS-CoV-2 Study Group. Patient-reported daily functioning after SARS-CoV-2 vaccinations in autoimmune neuromuscular diseases. Eur J Neurol. 2024 Dec;31(12):e16409. doi: 10.1111/ene.16409. Epub 2024 Sep 5	Substudy of a prospective observational multicenter cohort study.	Among the 66 patients with IIM, 44 (66.7%) received the BNT162b2 as primary immunization. Overall, patient-reported outcome measures scores related to vaccination did not differ from scores unrelated to vaccination.	No increased risk observed for autoimmune disease relapse after COVID-19 vaccination.

* Gazitt T, et al. Sept 2022 (=Reference 19 in MAH literature overview) left out in table above since it is of the same research group and same data as Gazitt T, et al. 2023 Feb 17;11(2):476. doi: 10.3390/vaccines11020476 (= reference 13 in MAH literature overview).

Rapporteur assessment comment:

The literature discussed by the MAH concerns conference/poster abstracts (n=6, all on COVAD study results, see below), cohort studies (n=9) and a literature review (n=1). No literature case reports were presented by the MAH. There were new publications (n=5) discussed which used the COVAD-1 and COVAD-2 survey studies/databases. Patients with systemic autoimmune rheumatic disease (AIRD) were excluded from COVID-19 vaccine trials. The COVAD study (<https://link.springer.com/article/10.1007/s00296-021-05046-4>) (later renamed COVAD-1) is a long-term ongoing global patient self-reported survey study, with the goal of evaluating the long-term efficacy, as well as the short and long-term adverse effects and disease flares in AIRD patients vaccinated against COVID-19. The COVAD-2 survey (<https://link.springer.com/article/10.1007/s00296-022-05157-6>) serves as a follow-up survey for past respondents and a standalone survey for new participants. No new safety information was identified from the published results (either published papers or in conference/poster abstracts) on the COVAD-1 or COVAD-2 studies. The AIRD study population included patients with inflammatory myopathies. Most published results on the COVAD studies focused on disease relapse after vaccination (Panchawagh et al, Dey et al, Naveen R et al). No evidence was found in these studies that indicates increased disease flares after COVID-19 vaccination in patients with auto-immune diseases. Post-vaccination flares of underlying autoimmune disease were less frequent among IIMs than SAIDs [OR 0.8 (0.6–1.0), p = 0.032] in patients with IIMs who received the BNT162b2 (Pfizer) vaccine (Daskaliuk et al). However, Daskaliuk et al also noted that among BNT162b2 (Pfizer) vaccine recipients, patients with IIMs were at a threefold higher risk of rash compared to healthy controls [OR 3.0 (1.4–6.3),

p=0.004]. And Gil-Vila et al observed in an adjusted analysis that dermatomyositis was associated with higher risk of headache compared with other idiopathic inflammatory myopathies. Rash as part of a hypersensitivity reaction and headache are both already labeled in section 4.8 of the BNT162b2 SmPC. No new safety information was identified in patients with auto-immune diseases from studies using the COVAD-1 and COVAD-2 databases.

Five observational cohort studies (Jung et al, Copland E et al, Ou TS et al, Nelli F et al, Ju HJ et al) were presented by the MAH that studied if there was increased risk to develop autoimmune disease after COVID-19 vaccination. The study of Ou TS et al contained title information of BNT162b2 on the development recent or aggravation of immune modulatory diseases. No differences were observed in the other 4 studies (3 in adults and 1 pediatric study) for development of autoimmune diseases in vaccinated (BNT162b2) individuals compared to (historically) unvaccinated.

Four observational cohort studies (Gazitt et al, Šinkovec Savšek et al, Heshin-Bekenstein et al, van Dam et al) focused on disease flare up in patient groups with existing (autoimmune) diseases. No incidence of increased flare up after BNT162b2 vaccination could be observed from these studies.

The MAH discussed one review article by Martora et al. Among the retrieved literature articles describing cutaneous diseases following COVID-19 vaccination, dermatomyositis was included. The percentage of cutaneous AEs is extremely low when compared with the number of vaccines administered. The causal temporal correlation between cutaneous reactions and vaccination cannot be ruled out in most of the cases. The authors stated that these are reports of a few cases (dermatomyositis) and that "unlike the other reactions we have reported, where both the numbers and the mechanisms proposed at the base are valid, in these cases certainly further studies will be necessary to establish the true correlation".

No potential biological mechanism was described in the retrieved literature.

From the retrieved literature (from 16 January 2023 up to DLP of the current PSUR), the causal association of the occurrence of idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares following BNT162b2 vaccination could not be established.

Results MAH global safety database

The search of the MAH global safety database retrieved 220 cases with 1499 AEs. The events were reported in females for 130 (59.1%) cases and in males for 81 (36.8%) cases. The other (9) cases did not report the gender of the patient.

Four (4) patients (1.8%) were ≤17 years old. Ages ranged from 18-30 years old in 18 (8.2%) patients, 31-50 years old in 69 (31.4%) patients, 51-64 years old in 55 (25.0%) patients, 65-74 years old in 38 (17.3%) patients, ≥75 years old in 28 (12.7%) patients, and unknown in 8 (3.6%) patients. The mean age was 53.6 years.

The top 10 countries where the relevant events occurred were Germany (64 cases, 29.1%), Japan (24 cases, 10.9%), UK (22 cases, 10.0%), Sweden (16 cases, 7.3%), US (11 cases, 5.0%), Australia (10 cases, 4.5%), France (10 cases, 4.5%), Denmark (6 cases 2.7%), New Zealand (6 cases, 2.7%) and Finland, Norway, Spain, Turkey with 5 cases each (2.3%).

The majority of the cases were reported from spontaneous sources (176 cases, 80.0%). Forty-two (42) cases (1.9%) were reported from literature. One case (0.5%) was from solicited sources and one (0.5%) from clinical studies.

Regarding seriousness, 186 cases (84.5%) met serious case criteria and 34 (15.5%) were nonserious. There were 9 cases with a fatal case outcome. Medical confirmation of the events was attained in 121 out of 220 cases (55%).

Case-By-Case Analysis

As requested by PRAC, a case-by-case analysis is presented in Appendix A of appendix 5.3 in MAHs PSUR. Each case is presented in a summarized version along with an overall assessment/justification in the last two columns. Additionally, a narrative line listing containing all details for each analyzed case is provided in Appendix B of appendix 5.3 in MAHs PSUR.

The overall categorization of the cases by the MAH is as follows:

- 27 cases with alternative explanation (such as concomitant statin use, dermatomyositis presenting as a paraneoplastic condition, prior autoimmune disorders that increase the risk of other autoimmune disorders).
- 22 cases not relevant to IIMs/autoimmune myositis (such as cases describing localized symptoms on the injection site, cellulitis, overlap syndrome not affecting the muscles).
- 164 cases with minimal medical information for causality assessment (many non- medically confirmed cases) and mostly without medical history or concomitant medications reported. In some cases, only the event of "myositis" was reported, without evidence of chronicity or a specific IIM/autoimmune myositis and it was unclear if clinical investigation was performed. In other cases, it was unclear whether myositis was interchanged as a term with myalgia, which is a known ADR.
- 7 cases were well documented and were thus considered remaining cases

The 7 remaining cases include 6 different subjects (2 cases on the same individual, with the first describing initial event presentation and the second a reoccurrence following the second dose). None of them was fatal.

Detailed information on the 7 well documented, remaining cases can be found in the two appendices and a brief summary of the cases is presented as follows:

Case [REDACTED] describes a 55-year-old male from [REDACTED] who developed antisynthetase syndrome (positive anti-jo1 antibodies) one month after the 3rd dose. Subject described as with no relevant medical history. Remission was achieved with methotrexate.

Case [REDACTED] describes a 79-year-old female from [REDACTED] who developed dermatomyositis 43 days after the 4th dose. It is mentioned that dermatomyositis has manifested as dermatitis in the eyebrow area, without evidence of muscle involvement (positive anti-TIF1 gamma antibodies, amyopathic dermatomyositis). The subject had no relevant medical history. However, considering the advanced age, it is unclear if a screening for malignancy was performed (dermatomyositis may manifest as a paraneoplastic syndrome).

Case [REDACTED] describes a 74-year-old female from [REDACTED] who developed dermatomyositis approximately 2 months following the 4th dose. There were no relevant medical conditions in subject's medical history. The subject was hospitalized for muscle weakness and breathing problems. The dermatomyositis outcome is reported as recovering. Considering the advanced age of the subject, it is unclear if a screening for malignancy was performed (dermatomyositis may manifest as a paraneoplastic syndrome).

Cases [REDACTED] and [REDACTED] are the same literature report describing a 22-year-old female from [REDACTED] that developed anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMG-CoA) immune-mediated necrotizing myopathy. Case [REDACTED] describes the clinical course of the

events following the first dose, whereas case [REDACTED] following the second dose. The patient received the first dose on 15 August 2021 and one week later she developed muscular weakness and loss of walking ability. Upon hospitalization and blood tests mainly showing elevated creatine kinase (21921 U/ml), a hypothesis of immune-mediated myositis was made, and the subject was treated with intravenous methylprednisolone and unspecified symptomatic treatment. After 10 days the subject was discharged and was advised to investigate on an outpatient basis. After hospital discharge, the subject was vaccinated again on 07 January 2022 (approximately 5 months later) and presented again with marked deterioration in motor strength and losing ability to walk one week after vaccination. Following hospitalization, elevated creatine kinase (13159 U/ml) was detected again and a second cycle of methylprednisolone was started. The patient was discharged five days later. During outpatient investigation, a muscle biopsy and a myositis panel analysis revealed positive titers for anti-3-hydroxy-3-methylglutaryl- coenzyme A reductase (anti-HMG-CoA). Treatment with methotrexate (15 mg/week) and corticosteroids (80 mg/day) was initiated; however, the patient persisted with severe muscle weakness, high levels of creatine kinase, and dependency on a wheelchair for locomotion. A gradual reduction of corticosteroids was attempted, and the patient presented with a recurrence of symptoms and renewed increase in creatine kinase levels. The authors decided to continue with intravenous immunoglobulin; however, the patient has not yet undergone treatment due to unavailability. The authors concluded to the diagnosis of probable post- vaccination immune-mediated necrotizing myositis due to the absence of other factors that may have led to the development of autoantibodies (medicines; e.g., statins, drugs) and the temporal relationship between exposure and event.

Case [REDACTED] is a literature case report that describes a 40-year-old female subject from the [REDACTED] with symptoms of shortness of breath, muscle pain and weakness, and skin rash that started one day following the second dose of BNT162b2. Following an unspecified extensive work-up, the patient was diagnosed with dermatomyositis. The subject had no relevant medical conditions, however she had recently been admitted to the hospital six months prior for similar complaints, in addition to hemoptysis. Therefore, the authors consider it a dermatomyositis flare-up. However, it is unclear if the dermatomyositis was diagnosed 6 months prior or if the subject was under any immunosuppressive medication for dermatomyositis. Condition remitted following high-dose corticosteroid and IVIG therapy.

Case [REDACTED] is a literature case report describing a 64-year-old female from [REDACTED] who developed dermatomyositis 28 days following the 3rd dose of BNT162b2. The main symptom was a persistent and expanding rash. The subject had no relevant medical history. A myositis-associated panel came back with strongly positive anti-MDA5 and Ro-52, and weakly positive anti-Mi-2a antibodies. No muscle involvement is mentioned. Lung involvement was revealed on CT scan, but without symptoms. The condition remitted with rituximab, methylprednisolone and azathioprine.

Routine Statistical Reports

To support routine signal detection activities in addition to the non-statistical reports, the MAH generates statistical reports including EB05>2. The objective of this analysis was to identify emerging new events as statistical signals for more in-depth review. On cumulative review of relevant PTs in MAH's safety database, the EB05 scores were as follows:

PT	BNT162b2 original	BA.1	BA.4/5	XBB.1.5	Multivalent NOS	JN.1	KP.2
Anti-melanoma differentiation-associated protein 5 antibody positive	0.6	-	0.3	-	-	-	-
Anti-SRP antibody positive	0.2	-	-	-	-	-	-
Antisynthetase syndrome	0.9	-	0.2	-	-	-	-
Autoimmune myositis	0.9	-	0.2	-	-	-	-
Dermatomyositis	1.0	0.4	0.7	0.3	-	-	-
Focal myositis	0.5	-	-	-	-	-	-

Idiopathic inflammatory myopathy	0.6	-	-	-	-	-	-
Immune-mediated myositis	0.3	-	0.1	-	0.3	0.3	-
Inclusion body myositis	0.6	-	0.3	-	-	-	-
Juvenile polymyositis	0.4	-	-	-	-	-	-
Lupus myositis	0.1	-	-	-	-	-	-
Myositis	1.1	1.5	0.7	0.9	0.2	0.2	-
Necrotising myositis	0.4	0.3	-	-	-	-	-
Orbital myositis	0.7	-	-	-	-	-	-
Overlap syndrome	0.8	-	-	-	-	-	-
Polymyositis	0.9	-	0.2	0.6	0.3	-	-

The EB05 is less than the EB05>2 threshold for all PT's, thus indicating no emerging statistical signal for all vaccine formulations.

Rapporteur assessment comment:

Noted.

MAH Summary and conclusion on idiopathic inflammatory myopathies (IIM)/autoimmune myositis

The totality of the evidence from 16 January 2023 up to 18 December 2024 regarding vaccination with COVID-19 mRNA vaccine and IIMs/IIM flares is summarized below:

- Non-clinical studies in rats have not shown any evidence of autoimmune myositis, and no long-term inflammation as would be expected in such an autoimmune response.
- No new cases were retrieved in MAH-run clinical trials.
- The majority of literature studies, including but not limited to large ones, actively support the safety of BNT162b2 on individuals with IIMs and have not associated BNT162b2 with any new-onset IIMs.
- Post-marketing data showed a very small number of 6 subjects (7 cases) out of a total of 220 in the reporting period that were well documented, had a reasonable temporal relationship and no apparent alternative explanation. Four subjects corresponded to dermatomyositis, one to antisynthetase syndrome and one to anti-HMG-CoA immune-mediated necrotizing myopathy. In two cases of dermatomyositis, a screening for malignancy was not mentioned, despite dermatomyositis being associated with malignancies (paraneoplastic syndrome).
- Routine statistical reports showed that the EB05 (product specific Bayesian Multi-Item Gamma Poisson Shrinker) is less than the EB05 >2 threshold, thus indicating no emerging statistical signal for the selected PTs and each vaccine variant (including but not limited to the new JN.1 and KP.2 vaccine variants).

Overall, there is no new evidence to support a causal relationship between vaccination and the development of IIM and IIM flares. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Rapporteur assessment comment:

The MAH has taken a conservative approach for their causality classification of the 220 post-marketing cases. The classification of the causality for the 220 cases by the MAH is as follows: 27 cases with alternative explanation, 22 cases considered not relevant, 164 cases with minimal information. Of the 220 cases, 7 remained which were discussed in detail by the MAH (see below). To sample the causality

assessment of the MAH of the presented cases, the first 48 cases in the table "case details and WHO-UMC causality assessment" of appendix 5.3 of MAHs PSUR were reassessed in detail by the PRAC assessor by checking the line listings. Of these 48 cases 5 cases were assessed as unlikely related to BNT162b2 vaccination, 22 cases as unclassifiable and 18 cases as possible related to BNT162b2 vaccination.

The MAH discussed 7 cases in detail. Of these 7 cases the causality is assessed by the PRAC assessor as possible for 5 cases and the case [REDACTED] (initial vaccination) together with [REDACTED] (second vaccination of the same individual) is assessed as probable related, see below.

Case [REDACTED] a 55-year-old male developed antisynthetase syndrome (positive anti-jo1 antibodies) one month after the 3rd dose BNT162b2. According to the literature antisynthetase syndrome commonly manifests in the fifth decade of life. The exact cause of antisynthetase syndrome is not fully understood. Affected individuals have autoantibodies. These autoantibodies are believed to be produced after a 'triggering' event such as a viral infection or exposure to certain drugs. Individuals may have a genetic predisposition to developing antisynthetase syndrome (<https://rarediseases.org/rare-diseases/antisynthetase-syndrome/>). Due to TTO and appearance after 3rd vaccination the causality of antisynthetase syndrome with myositis is assessed as possible. The previous 2 vaccinations could have sensitized the patient to develop antisynthetase syndrome, however the exact cause of antisynthetase syndrome is not exactly clear and the syndrome manifests in this patient at 55 years of age which the common decade of disease manifestation with this syndrome.

It was noted that in some cases, including case [REDACTED] the diagnosis antisynthetase syndrome was made. Upon searching the 220 cases line listings by the assessor an additional 9 cases were identified of antisynthetase syndrome. Of these 9 cases, 7 were assessed with a causality "possible" myositis and antisynthetase syndrome. The other 2 cases of antisynthetase syndrome had limited information and therefore causality was unclassifiable. Antisynthetase syndrome is a rare, chronic disorder that can affect multiple systems of the body. Affected individuals have autoantibodies that target aminoacyl-tRNA synthetases. The disorder is immune-mediated and the autoantibodies are believed to be produced after a 'triggering' event such as a viral infection or exposure to certain drugs. Antisynthetase syndrome was evaluated in the past in EPITT signal 19883 as part of myositis with tozinameran. Considering the vaccine exposure and the rarity of this event routine pharmacovigilance is considered sufficient to monitor antisynthetase syndrome.

Case [REDACTED] 79-year-old female who developed dermatomyositis 43 days after the 4th dose (booster). It is mentioned that dermatomyositis has manifested as dermatitis in the eyebrow area, without evidence of muscle involvement (positive anti-TIF1 gamma antibodies, amyopathic dermatomyositis). In May 2023 the woman was diagnosed with Interface dermatitis via skin biopsy. Interface dermatitis can be a result of dermatomyositis, erythema multiforme or drug interactions (amongst others). The case medical history included hyperparathyroidism, cerebrovascular accident, hypertension, dyslipidemia, and thyroid nodule. It was not specified if these conditions were ongoing or resolved and concomitant medication information was not provided. Due to TTO this case of dermatomyositis is assessed as possible.

Case [REDACTED] on 17Jul2023 after dose 4 (booster) a 74-year-old female developed dermatomyositis, dyspnea and muscular weakness with reported onset Aug2023. The patient was hospitalized for aggravating reported symptoms in Oct2023. The patient had medical history of hypertension and hypoparathyroidism and was tested (two times) for COVID-19 infection which was negative. No other information available in this case. Assessed as possible due to compatible TTO.

Case [REDACTED] (initial vaccination, published case report DOI: 10.1155/2023/7061783) and [REDACTED] (second vaccination) concern a 22-year-old female who received dose 1 on 15Aug2021. The initial symptoms were paresthesia in the shoulder girdle and tightness and pain in the

upper limbs and attributed to her profession. However, the symptoms progressed to weakness of the lower limbs, severe girdle weakness, and loss of walking ability. The patient was admitted to the hospital in December 2021. Magnetic resonance imaging of the shoulder and pelvic girdles was performed, which showed diffuse edema of the musculature. Electromyography showed increased activity of insertion, fibrillation potentials, and discharge of acute positive waves at rest in the deltoid, triceps, biceps brachii, pronator teres, first dorsal interosseous, abductor pollicis brevis muscles, trapezius, iliopsoas, quadriceps, tibialis anterior, gastrocnemius medial, and adductor magnus. The diagnosis of probable post-vaccination immune-mediated necrotizing myositis (IMNM) was made by the reporters due to the absence of other factors that may have led to the development of autoantibodies (medicines; e.g., statins, drugs) and the temporal relationship between exposure and event. The patient inadvertently received the second dose of the Pizer-BioNTech (BNT162b2) COVID-19 vaccination on January 7, 2022. One week later, she experienced further marked deterioration in motor strength, losing the ability to walk, and requiring a second cycle of intravenous methylprednisolone (1 g per day for five days). In addition, her creatine kinase level was elevated (13,519 U/mL). The patient was then readmitted to the hospital for treatment and was discharged five days later. A muscle biopsy was taken and immunohistochemistry and transmission electron microscopy was performed. The results were suggestive for IMNM. Anti-3-hydroxy-3-methylglutarylcoenzyme A reductase (anti-HMG-CoA) was positive at titers almost 10 times above the reference value. A genetic panel was done, and one heterozygous variant of the uncertain significance of the dysferlin gene was described (NM003494.4(DYSF): c.2093C lesser than T (p.Ala698Val)). Type 2 girdle muscular dystrophy is a condition of autosomal recessive inheritance, requiring two causative variants in distinct alleles for the complete expression of the clinical picture. Due to the genetic variant in the dysferlin gene of this patient she might be susceptible to developing IMNM after vaccination. However medical information on childhood vaccinations is not available. The patient deteriorated after the inadvertent second BNT162b2 vaccination. Taken together, the causality in this case of IMNM is assessed as probably related to the BNT162b2 vaccination by the assessor.

Case [REDACTED] (literature report "Dermatomyositis Flare-Up Following the SARS-CoV-2 Vaccine: A Case Report and Literature Review", Cureus, 2023; Vol:15(8), DOI:10.7759/cureus.44324) concerns a 40-year-old female who presented to the emergency department with shortness of breath, muscle pain and weakness, and skin rash for two days. She had been recently diagnosed with dermatomyositis six months prior based on clinical presentation, laboratory investigations, and characteristic muscle biopsy findings. She had been on treatment with mycophenolate mofetil, prednisone, and hydroxychloroquine since. She reported receiving the second dose of the BNT162b2 COVID-19 vaccine one day prior to the onset of symptoms. Physical examination revealed erythematous plaques over her cheeks, upper chest, and arms, in addition to Gottron papules on her hands. She had reduced proximal muscle strength and scattered dry crackles bilaterally on lung auscultation. The SARS-CoV-2 PCR test was negative. CT scan of the chest showed evidence of pneumonitis. A diagnosis of the dermatomyositis flare-up potentially secondary to the SARS-CoV-2 BNT162b2 vaccine was established. It is agreed with the reporters that the causality of myositis flare up is possibly related to BNT162b2 vaccination due to TTO.

Case [REDACTED] (literature report <https://doi.org/10.31138/mjr.280124.nom>) concerns a 64-year-old female describing a rare case of new-onset anti-MDA-5 dermatomyositis following the third dose of the mRNA COVID-19 vaccine. The patient presented with rash typical of dermatomyositis (heliotrope rash, Gottron's papules, "V" sign), interstitial lung disease (ILD), strongly positive anti-MDA-5 antibodies and absence of prominent muscle involvement. Clinical images in different stages of the disease were presented in the literature case report which shows the dermatomyositis progressed over a period of approximately twenty months. This case is assessed by the reporters as possibly related to NBT162b2 vaccination which is agreed.

Overall, causality cannot be ruled out based on suggestive TTO for at least 23 cases and 1 probable case reporting myositis. However, based solely on the few cases with close TTO out of 220 cases total, a causal association of the occurrence of IIM following BNT162b2 administration cannot be established. Apart from a suggestive TTO, in most cases assessed as possible related, the additional medical information provided was scarce. Furthermore, with 23 cases assessed as possible and 1 probable, compared to the exposure of BNT162b2, a coincidence in reporting myositis cannot be ruled out.

Overall conclusion on idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares;

In the Signal assessment report on myositis with tozinameran (EPITT 19883), up to 15 January 2023, the MAH retrieved 1,017 cases. Combined with the current review, cumulatively, up to DLP of the current PSUR, a total of 1,217 cases have been identified reporting IIM/autoimmune myositis/IIM flares. A very small number of 23 well documented cases (16 cases in the Signal AR and 7 cases in current review) out of 1,217 cases with a temporal association between vaccination with BNT162b2 and the onset of the relevant myositis events were identified.

From the retrieved literature (EPITT signal + review) from 16 January 2023 up to DLP of the current PSUR), the causal association of the occurrence of idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares following BNT162b2 vaccination could not be established.

Furthermore the MAH's score for disproportionality EB05 is less than the EB05 >2 threshold, thus indicating no emerging statistical signal for the selected PTs.

There is currently insufficient evidence to support a causal relationship between BNT162b2 and idiopathic inflammatory myopathies, autoimmune myositis, and IIM flares. The MAH will monitor this topic through routine pharmacovigilance and present in future PSURs only if any significant new information is identified, which is agreed. Additionally the MAH is requested to monitor antisynthetase syndrome with routine pharmacovigilance as separate topic of interest.

2.3.3.3. Small Fiber Neuropathy

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUSA/00010898/202312), the following request was made: The MAH should provide a cumulative review of all evidence concerning small fiber neuropathy following vaccination with BNT162b2. 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.

In response, the MAH provided cumulative data concerning small fiber neuropathy following administration with BNT162b2 up to 18 December 2024.

Clinical trial data

Participant [REDACTED] A 60-year-old, white female participant with a past medical history of hypercholesterolemia. This participant had an AE of small fiber neuropathy (verbatim term - Type C small fiber neuropathy) with an onset date 220 days after receiving Dose 2 of the 2-dose primary series, BNT162b2 30 µg. The event was considered resolved with sequelae 279 days after onset.

Rapporteur assessment comment:

One non-serious AE of small fiber neuropathy reported with an onset date of 220 days after second dose of BNT162b2. The event was considered resolved with sequelae 279 days after onset. It is unclear if a

diagnostic test has been performed to confirm the small fiber neuropathy in this case.

Causality considered as unlikely due to the improbable latency of 220 days and unclear if a diagnostic test has been performed.

Literature data

A cumulative search of literature was conducted through 18 December 2024, to identify articles describing BNT162b2 and the MedDRA PT Small fiber neuropathy in the Medline and Embase database.

There was one relevant study (conference abstract) from Italy analyzing adverse events following immunization potentially linked to SFN [Giannandrea A, Blonda M, Antonacci S, et al. Symptoms Potentially Related to Small Fiber Neuropathy (SFN) and Anticovid Vaccines. Drug Safety. Conference: 21st Annual Meeting of the International Society of Pharmacovigilance, ISoP 2022. Verona Italy. 45(10) (pp 1234-1235), 2022. Date of Publication: October 2022. DOI: <https://dx.doi.org/10.1007/s40264-022-01219-7>.]. Due to the concise conference abstract format, there was limited information on methodology and results. The authors used data from the NPN (National Pharmacovigilance Network) referring to an unspecified area of Italy (resident population 1,221,857) during a time period of 27 December 2020 to 26 April 2022. There were 624 cases in the NPN, of which 346 cases (1,164 adverse events) corresponded to BNT162b2, whereas the remaining ones were from other vaccines such as Spikevax and Vaxzevria. The authors stated that 17.3% out of 1,164 events (number of cases not specified) corresponded to symptoms related to SFN (such as other pains, burning, itching, paraesthesia, tingling, numbness, allodynia).

The authors state that 3 cases of BNT162b2 have a causality assessment outcome of "correlatable", although the meaning of "correlatable" is not clarified and it is also not specified if causality assessment was performed for SFN or for other events reported in the case. The authors acknowledge that a diagnostic procedure for SFN was not performed.

Summary by the MAH: The limited literature does not provide evidence for a causal relationship with vaccination with BNT162b2.

Rapporteur assessment comment:

In the study by Giannandrea A et al, data from the National Pharmacovigilance Network (NPN) referring to an unspecified area of Italy (resident population 1,221,857) were used to analyze adverse events following immunization (AEFI) potentially linked to small fiber neuropathy. A total of 624 reports relating to vaccines anti-COVID (AEFI) were received in the period from 27 December 2020 until 26 April 2022. Of the 624 reports, 346 reports concerned BNT162b2 with 201 AEFI potentially linked to small fiber neuropathy (described symptoms were: other pains, burning, itching, paraesthesia, tingling, numbness, allodynia). The causality assessment was described by the authors as potentially linked/"correlatable" to small fiber neuropathy in 3 (out of 201) cases. It is agreed with the MAH that it is not clear what is the meaning of "correlatable" and whether the causality assessment was performed for small fiber neuropathy. Lastly, the authors acknowledge that a diagnostic procedure for small fiber neuropathy was lacking. Therefore, a causal association cannot be confirmed based on the data from this study.

There are published patient cases of COVID-19 infection and Pfizer and Moderna vaccine administration causing neurological conditions including Guillain-Barre syndrome, transverse myelitis, and small fiber

neuropathy^{11,12,13,14,15,16,17,18}. The mechanism underlying the development of small fiber neuropathy after COVID-19 infection and/or after COVID-19 vaccination is not known. Up to 50% of cases of small fiber neuropathy remain idiopathic even in the absence of vaccination, as observed by a large cohort involving over 900 patients (de Greef B.T.A. et al, 2018¹⁹).

Post-vaccine neuropathy is likely immune-mediated from either hypersensitivity to the vaccine solvent or to the active components of the vaccine itself. Waheed W et al. mentioned as a proposed pathophysiologic mechanism for vaccine-associated polyneuropathy an immune-mediated hypersensitivity to the solvent/adjuvant (polyethylene glycol). In Schelke MW et al ²⁰, the presence of the ACE2 antibody in the published case suggests an immune reaction to the vaccine itself as the vaccine mRNA encodes the spike protein that binds to ACE2 receptors. ACE2 antibodies have been described after infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

No clear (biological) mechanism for the occurrence of small fiber neuropathy following BNT162b2 administration has been identified from literature.

Global Safety Database Review

Up to 18 December 2024, the MAH revealed 497 cases reporting 7,350 adverse events. 74.2% of cases were female, 24.5% male and in 1.2% no gender was provided.

The mean age was 44 years, 2% of cases were less than 17 years old, 11.7% 18-30 years, 52.7% 31-50 years, 24.1% 51-64 years, 4.2% 65-74 years, 1.2% greater than 75 years of age and in 4% of cases the age was unknown.

The top 10 reporting countries were Germany (37.8%), US (11.9%), France (10.9%), Italy (8%), Finland 6.2%, Australia (4.6%), UK (3.8%), Netherlands (2%), Austria and Israel (1.8% each).

98.2% of cases were spontaneous and 1.8% literature cases. 84.9% of cases were serious and 15.1% were non-serious.

There was one fatal case ([REDACTED]) of assisted suicide. This case was classified as unassessable by the MAH and a causal relationship between BNT162b2 and Assisted suicide, Fibromyalgia, Small fiber neuropathy was assessed by Swissmedic according to WHO as being Unassessable/Unclassifiable.

Out of the 497 cases there was 1 probable related, 22 possible related, 90 unlikely related and 384 unassessable cases.

¹¹ Waheed W, Carey ME, Tandan SR, Tandan R. Post COVID-19 vaccine small fiber neuropathy. Muscle and Nerve. 2021;64(1):E1-2

¹² Khokhar F, Khan A, Hussain Z, Yu J. Small fiber neuropathy associated with the Moderna SARS-CoV-2 vaccine. Cureus. 2022;14(6):e25969-2. 10.7759/cureus.

¹³ Oaklander AL, Mills AJ, Kelley M, Toran LS, Smith B, Dalakas MC, et al. Peripheral neuropathy evaluations of patients with prolonged long COVID. Neurol Neuroimmunol Neuroinflamm. 2022 May 1;9(3):e1146. 10.1212/NXI.0000000000001146.

¹⁴ Safavi F, Gustafson L, Walitt B, Lehky T, Dehbashi S, Wiebold A, et al. Neuropathic symptoms with SARS-CoV-2 vaccination. medRxiv. 2022;202205.16.22274439. 10.1101/2022.05.16.22274439.

¹⁵ Lahoz Fernandez PE, Miranda Pereira J, Fonseca Risso I, Baleeiro Rodrigues Silva P, Freitas Barboza IC, Vieira Silveira CG, et al. Guillain-Barre syndrome following COVID-19 vaccines: a scoping review. Acta Neurol Scand. 2022 Apr 1;145(4):393-8. 10.1111/ane.13575.

¹⁶ Keh RYS, Scanlon S, Datta-Nemdharry P, Donegan K, Cavanagh S, Foster M, et al. COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National Immunoglobulin Database. Brain. 2022 Feb 18;awac067. 10.1093/brain/awac067.

¹⁷ Novak P, Giannetti MP, Weller E, Hamilton MJ, Mukerji SS, Alabsi HS, et al. Network autonomic analysis of post-acute sequelae of COVID-19 and postural tachycardia syndrome. Neurol Sci. 2022;43(12):6627-38. 10.1007/s10072-022-06423-y.

¹⁸ Abrams RMC, Simpson DM, Navis A, Jette N, Zhou L, Shin SC. Small fiber neuropathy associated with SARS-CoV-2 infection. Muscle Nerve. 2022;65(4):440-3. 10.1002/mus.27458.

¹⁹ de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, et al. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. Eur J Neurol. 2018;25(2):348-355.

²⁰ 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.

Probable case [REDACTED]:

A 39-year-old male without previous history of vaccine reaction presented 134 days after receiving the first dose of the Pfizer COVID-19 vaccination in his left deltoid with subacute onset of left arm pain and numbness. The pain initially presented as achy pain in the left shoulder and progressed to the entirety of the left arm after day 10 post-vaccination. The patient also began noticing numbness and tingling in the left arm, median forearm, ulnar hand, and medial scapular region. These symptoms generalized rapidly over 3 weeks postvaccination and persisted after presentation at our clinic. Symptoms generalized to the patient's right side in a non-length dependent symmetrical distribution, involving the proximal arms and legs. He also developed fasciculations in his extremities that progressed to burning dysesthesias and numbness in all his extremities over the same 3-week timeframe.

On review of systems, the patient denied fevers, chills, weight loss, neck pain, back pain, urinary/fecal incontinence, bulbar involvement, rash, and tick bites. On neurological exam, the patient was alert and oriented to person, place, time, and situation. Cranial nerves were intact. Motor exam revealed normal bulk and tone with 5/5 strength in upper and lower extremities. Notably, sensation to temperature was decreased over the area of complaint.

Coordination was appropriate as determined by finger-nose-finger and heel-to-shin testing. Gait, including tandem gait, was normal, and Romberg was negative. Normal electrodiagnostic study was performed 163 days after onset of symptoms (including right median, ulnar, peroneal, and tibial motor nerves; right median, sural, ulnar, and superficial radial sensory nerves; and needle examination of the right rectus femoris, vastus medialis, vastus lateralis, tibialis anterior, gastrocnemius, deltoid, biceps, triceps, extensor digitorum communis, and first dorsal interosseous muscles) with symptoms at this point equally generalized on the right and left upper and lower extremities. Skin biopsy collected 148 days after symptom onset to test epidermal nerve fiber density of the left calf, and left foot was abnormal. Left calf epidermal nerve fiber density was 2.95 (normal >4), and left foot epidermal nerve fiber density was 1.83 (normal >3). Additionally, sweat gland nerve fiber density of the distal left arm was 7.4 (normal >39) and sweat gland nerve fiber density of the left calf was 3.0 (normal >36.5). The following laboratory tests were normal or negative: complete blood count, comprehensive metabolic profile, hemoglobin A1c, vitamin B12, thyroid-stimulating hormone, Lyme disease antibodies, Babesia duncani antibody, Ehrlichia chaffeensis antibody, Anaplasma phagocytophilum antibody, Bartonella species antibody, antinuclear antibody screen, serum immunofixation, and protein electrophoresis.

Neuromuscular antibody report from [REDACTED] was notably positive for IgG versus Fibroblast Growth Factor Receptor 3 (FGFR3) of 17,000 (nrl <3,000) and negative for all other autoantibodies in the sensory neuropathy/neuronopathy panel.

Based on these results, the patient was diagnosed with COVID vaccination-induced FGFR3 small fiber neuropathy and was treated with IVIG. The patient began receiving 45 g Gamunex IVIG daily x 2 days q 4 weeks delivered over 3.5 h each day 290 days following onset of symptoms. Follow-up physical exam was within normal limits, and temperature sensation was restored in the affected areas. Repeat skin biopsy 405 days post-vaccination and status post-three IVIG sessions revealed a normal epidermal nerve fiber density of the left calf and left foot (8 and 5.62, respectively). Sweat gland nerve fiber density test of the left foot was also still abnormal at a value of 20.5. At patient follow-up 430 days after symptom onset, he reported marked improvement of symptoms including numbness and pain.

MAH comment: The MAH classified this case conservatively as probably related to vaccination with BNT162b2. However no medical history was provided so the assumption was made that the patient was healthy. There was no information regarding previous/concomitant infection with COVID-19. Despite the

clinical associations reported so far, the relevance of FGFR3 antibodies remains unclear. No *in vivo* or *in vitro* studies clearly demonstrated the pathogenicity of TS-HDS and FGFR3 Abs.²¹

Rapporteur assessment comment:

Of note, this concerns a published case report: *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.*

Based on the data provided, it is agreed that the causality can be considered probably related. Small fiber neuropathy was confirmed by skin biopsy, there is a plausible latency of 134 days after the first dose of BNT162b2, and no disease or other drugs that could provide plausible explanations for the occurrence of small fiber neuropathy.

Possible related cases:

22 cases

were

conservatively judged as possibly related to vaccination due to the temporal relationship to vaccination, however the overwhelming majority of those cases had confounding factors that likely contributed to the development of small fiber neuropathy such as Hypothyroidism, Vitamin B12 deficiency, Autoimmune thyroiditis, Hypertension, Hyperlipidaemia, Gout, Metabolic syndrome, Psoriatic arthritis, Naloxone treatment indication alcohol or opioid use disorder, Lewy body dementia, Neurodermatitis, confounded by Covid vaccination with Sinopharm, concurrent Epstein-Barr infection, very long latency of 500 days or confounded by Covid infection.

Unlikely related cases:

90 cases were judged as unlikely related to vaccination describing an event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) and disease or other drugs provide plausible explanations.

Unassessable cases:

384 cases were judged as unassessable containing a report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory or the data cannot be supplemented or verified.

Summary: A review of the 497 post-marketing cases does not provide enough evidence that vaccination with BNT162b2 is causally related to the development of small fiber neuropathy.

Rapporteur assessment comment:

The MAH has taken a conservative approach for their causality classification of the 497 post-marketing cases. The classification of the causality for the 497 cases is agreed with: 1 probably related, 22 possibly related, 90 unlikely related and 384 unassessable cases.

Conditions other than nerve fiber damage may mimic small fiber neuropathy, including venous insufficiency, spinal stenosis, myelopathy and psychosomatic disturbances. Out of the total 497 post-marketing cases, the assessor counted 71 cases with a diagnostic test (i.e. skin biopsy) result which confirmed small fiber neuropathy. A conservative approach was taken with regards to the results reported

²¹ Morelli L, Serra L, Ricciardiello F, et al. The role of antibodies in small fiber neuropathy: a review of currently available evidence. *Rev Neurosci.* 2024;35(8):877-893. <https://doi.org/10.1515/revneuro-2024-0027>.

in the cases, meaning cases with 'suggestive' or 'suspected' results were included, while cases with the results 'normal findings' or 'negative results' were excluded. The causality classification by the MAH for these 71 cases was: 1 probably related, 19 possibly related, 28 unlikely related (improbable latency in 18/28 cases), and 23 unassessable cases.

Based upon review of the post-marketing cases reporting small fiber neuropathy, there is insufficient evidence to support a causal association.

Routine Statistical Reports

To support routine signal detection activities in addition to the non-statistical reports, the MAH generates statistical reports including EB05. 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 PT Small fiber neuropathy were as follows:

Formulation	BNT162b2 original	Omicron BA.1	Omicron BA.4/BA.5	Multivalent NOS	XBB.1.5	JN.1	KP.2
EB05	1.4	0.4	0.3	0.7	0.5	-	0.3

Summary: The EB05 is less than the EB05>2 threshold, thus indicating no emerging statistical signal for all vaccine formulations.

Rapporteur assessment comment:

Noted.

Summary and Conclusion by the MAH

There is no biologic plausibility that vaccination with BNT162b2 can lead to the development of small fiber neuropathy. No potential mechanism has been established and up to 50% of cases of small fiber neuropathy remain idiopathic even in the absence of vaccination, as observed by a large cohort involving over 900 patients^{20,22}. Clinical data does not indicate any causal relationship with vaccination. The very limited literature did not provide any evidence for a causal relationship. A review of the 497 post-marketing reports revealed a younger population with a mean age of 44 years, the majority (74%) were female. When applying the WHO causality assessment as requested by PRAC, out of the 497 cases there was 1 probable related, 22 possible related, 90 unlikely related and 384 unassessable cases. Routine statistical reports did not reveal an emerging statistical signal for all vaccine formulations.

The totality of data does not provide sufficient evidence to conclude that vaccination with BNT162b2 and variant formulation is causally related with vaccination, there is no need to update the Product Information nor the European Risk Management Plan. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Rapporteur assessment comment:

Acceptable. There is currently insufficient evidence to support a causal relationship between BNT162b2 and small fiber neuropathy.

The MAH will monitor this topic through routine pharmacovigilance and present in future PSURs only if

²² Terkelsen AJ, Karlsson P, Lauria G, et al. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. *Lancet Neurol.* 2017;16(11):934-44.

any significant new information is identified.

2.3.4. Evaluation of special population

2.3.4.1. Use in paediatric subjects

The MAH performed a review of cases reported among paediatric patients. The MAH provided separate evaluations for the following paediatric age groups: "<5 years of age", "≥5 years and ≤11 years of age", "≥12 to ≤17 years of age" in PSUR section "16.3.5.1. Use in Paediatric Subjects". For each of these paediatric age categories, the MAH provided separate data on cases received in a clinical trial setting and post marketing cases. These evaluations are not replicated in this assessment report.

The MAH stated that among the 1,746 cases involving paediatric subjects, 451 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (251 cases) and/or underlying medical history (282 cases). The MAH reviewed literature during this reporting period and did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

The MAH described that 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.

The MAH concluded that 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.

Rapporteur assessment comment:

"Use in paediatric subjects" is not considered missing information in the BNT162b2 RMP. Paediatric formulations of BNT162b2 (from 6 months of age onwards) are available. Safety information specifically for paediatric age groups is included in the currently approved BNT162b2 product information.

During this reporting period, the MAH also completed paediatric clinical studies C4591007 (assessed in procedure EMEA/H/C/005735/P46/070: no new safety concern was identified) and C4591057 (as per MAH no new safety concerns).

The MAH concluded that no new significant safety information was identified regarding safety in the paediatric population, which is endorsed. Monitoring of this topic under routine pharmacovigilance activities is considered sufficient. The MAH is requested to discuss this topic in the PSUR only when there are changes in the reporting pattern or when new information arises.

2.3.4.2. Use in pregnancy and while breast feeding [Missing information]

The MAH presented a review of safety data relevant for BNT162b2 use in pregnancy or during lactation (PSUR section 16.3.5.2. Use in Pregnant/Lactating Women). The evaluation is summarised below:

The MAH stated that there were no pregnancy or lactation cases in the clinical trial dataset in this reporting period.

Use in pregnant women

The MAH retrieved 371 pregnancy cases during this reporting period. Most of these cases (298) were reported following exposure to the monovalent original vaccine. These 371 cases represent 314 unique pregnancies including 262 'mother cases' and 82 'baby/foetal cases'.

Of the 262 mother cases, 93 cases reported exposure to vaccine in utero without the occurrence of any clinical event. There were 169 mother cases of which 102 were serious and 67 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. Additional pregnancy related events [in addition to exposure only] reported in these cases (>10 occurrences) were coded to the PTs "Abortion spontaneous" (30). Other frequently reported clinical events (≥ 10 occurrences) were coded to PTs "COVID-19" (17), "Headache" (13), "Fatigue" (10).

The MAH also provided an evaluation of 82 baby/foetal cases (79 serious and 3 non-serious) according to pregnancy outcome. These included:

- Live birth with congenital anomaly (45 cases reporting 80 congenital anomalies)
- Spontaneous abortion (4 cases)
- Elective termination (3 cases due to foetal defects)
- Stillbirth (6 cases, including 1 case reporting a foetal defect, 5 without foetal defect)
- Live birth without congenital anomaly (24 cases)

Most reported pregnancy cases (239) during this reporting period were retrospectively reported. Of the prospective 93 pregnancy cases, 83 cases reported a live birth without congenital anomaly.

The MAH further stated that in almost all reported cases (in any pregnancy outcome category) there was limited information regarding mother's medical/obstetric history and/or trimester of exposure which precluded meaningful causality assessment. The trimester of exposure is mostly unknown in both prospective and retrospective pregnancy cases: only in the category "Live birth with congenital anomaly" trimester exposure is mostly available (exposure in first trimester in 4/7 prospective cases and 55/82 retrospective cases).

Use in lactating women

The MAH retrieved 27 cases reporting exposure during breastfeeding: 24 baby cases [16 without additional adverse event] and 3 mother cases. 23 of these 27 cases were reported after exposure to the monovalent original BNT162b2 vaccine.

Overall

The MAH stated that review of the literature did not identify any new safety information regarding the use of BNT162b2 in pregnant/lactating women.

The MAH concluded that 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:

"Use in pregnancy and while breast feeding" is included as area of missing information in the BNT162b2 RMP. The current BNT162b2 product information states that BNT162b2 can be used during pregnancy and breastfeeding.

The BNT162b2 product information was updated regarding use in pregnant women in variation procedure EMA/VR/0000224683 based on final clinical study results of study C4591015: No new safety concern was

identified in this study population.

Study C4591022 is currently the primary RMP study investigating safety of BNT162b2 in pregnant women. The third interim study report of C4591022 dated 4 January 2024, appended to the PSUR, was assessed in procedure EMEA/H/C/005735/MEA/054.2: based on the provided data no safety concerns could be identified for the pregnancy and infant outcomes.

From the cases reported during the reporting period, the MAH concluded that no new safety information was identified. Based on the presented evaluation, it is agreed that no further action is considered warranted at this stage. The most frequently reported adverse outcomes concern relatively common adverse pregnancy outcomes (spontaneous abortion, atrial/ventricular septal defect) and no pattern of congenital anomalies or other events, including breastfeeding events, was identified. In addition, the MAH clarified that in the vast majority of cases only limited information was available about the mother's obstetric and/or medical history, which further limits causality assessment.

Monitoring of this topic under routine pharmacovigilance activities is considered sufficient. The MAH is requested to discuss this topic in the PSUR only when there are changes in the reporting pattern or when new information arises.

Other missing information topics in the PSUR and/or RMP safety specification include:

- Use in immunocompromised patients
- Use in frail patients with comorbidities (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

The MAH stated that upon review of the incremental data of cases reported in frail patients with comorbidities and/or interactions with other vaccines, no new safety issues/signals or reporting pattern changes were detected. The MAH referred to PSUR section "16.4.2 Description of Missing information" regarding summarised information on immunocompromised patients and of patients with autoimmune or inflammatory disorders. In the same PSUR section (16.4.2) the MAH states that 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 regarding long term safety data.

Rapporteur assessment comment:

The MAH was previously requested to only discuss "Use in frail patients with comorbidities (e.g. Chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)" and "Interaction with other vaccines" if the reporting pattern changes and/or there is a safety issue/signal – The MAH declared that this is not the case for these safety topics.

Regarding "Use in immunocompromised patients" and "Use in patients with autoimmune or inflammatory disorders" the MAH provided an updated risk characterisation in section 16.4 of the PSUR mostly based on post marketing data. Based on this risk characterisation no further action is considered warranted at this stage: the most frequently reported adverse events are known adverse reactions to BNT162b2 or represent events associated with COVID-19 (the most frequently reported event in both populations).

Regarding use in immunocompromised patients: the MAH also completed study C4591024 during this reporting period. No new safety concerns were identified in immunocompromised subjects following final clinical study report of study C4591024 assessed in procedure EMA/VR/0000224683.

As described in the BNT162b2 RMP – which no longer includes “Interaction with other vaccines” – all missing information safety concerns (except for vaccine interactions) are addressed through multiple ongoing additional pharmacovigilance studies.

2.4. Characterisation of risks

The MAH provided a characterisation of the important risks and areas of missing information. The MAH stated that no new safety concerns (for inclusion in the EU-RMP) were identified during the reporting period. The MAH proposes to remove “Interaction with other vaccines” from the list of the safety concerns in future PSURs based on the clinical trial data of study C4591030 and that “Interaction with other vaccines” was already removed from the list of safety concerns in the RMP (in procedure EMEA/H/C/005735/II/0201).

Rapporteur assessment comment:

No new RMP or PSUR safety concerns were identified during this PSUR assessment.

The MAH proposed to remove “Interaction with other vaccines” from the PSUR list of safety concerns. This is acceptable: this safety concern was removed from the RMP list of safety concerns following the results of study C4591030 (assessed in procedure EMEA/H/C/005735/II/0201). In addition, the MAH was already requested in previous PSUSAs to only discuss this topic if the reporting pattern changes and/or there is a safety issue/signal. Finally, based on the presented risk characterisation in section 16.4 of the PSUR, post authorisation data received during this reporting period is very limited: there were only 6 relevant cases during this reporting period (out of ~35,000 total post marketing cases during this reporting interval). As part of routine pharmacovigilance activities, the MAH should still discuss this topic if there is a related safety issue/signal.

As discussed in previous assessment comments, the MAH is requested to only discuss the topics “Use in Paediatric Subjects” and “Use in Pregnant/Lactating Women” when there are changes in the reporting pattern or when new information arises.

3. Benefit evaluation

The MAH provided a benefit evaluation. Newly identified information on efficacy and effectiveness included:

- C4591015: Clinical study data for BNT162b2 in pregnant participants ≥18 years of age
- C4591024: Clinical study data for BNT162b2 in immunocompromised participants ≥2 years of age
- C4591054 sub study A, sub study B: Clinical study data for Omicron XBB.1.5-adapted vaccines in individuals ≥12 years of age
- C4591048 sub study C: Clinical study data in children 6 months through <5 years of age
- Real world data for Omicron-adapted vaccines (publications in Table 50 of the PSUR). The MAH summarised as follows:

These fifteen studies found the XBB.1.5-adapted BNT162b2 vaccine was effective against COVID-19-associated medically-attended and emergency department/urgent care visits. Vaccine effectiveness tended to be higher against more severe endpoints such as COVID-19-associated hospitalisation, intensive care unit admission, and death. Vaccine effectiveness tended to be higher during XBB predominance and lower during JN.1 predominance, though confidence intervals within studies overlapped. There were mixed findings about potential differences in vaccine effectiveness by age

group across the studies. Only one study reported vaccine effectiveness for the XBB.1.5-adapted vaccine among children in which vaccine effectiveness was reported for a composite endpoint of emergency department/urgent care visit or hospitalisation.

Rapporteur assessment comment:

Based on the presented data no benefit concern is identified.

Information from completed clinical studies C4591015 and C4591024 is reflected in the BNT162b2 product information (both study results assessed in procedure EMA/VR/0000224683). Studies C4591054 and C4591048 are ongoing studies investigating variant-adapted vaccines, of which C4591048 is included in the RMP (most recent interim study report assessed in EMEA/H/C/005735/MEA/057.5).

The presented publications on real world data concern BNT162b2 XBB.1.5 and may therefore be less relevant considering currently circulating SARS-CoV-2 sub variants and that the vaccines were further adapted (after XBB.1.5) and are already authorised (JN.1 or KP.2 adapted vaccines).

4. Benefit-risk balance

The risks have been evaluated in the context of the benefits of the vaccine. No additional changes to the BNT162b2 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 BNT162b2 PSUR, the benefit-risk balance of BNT162b2 Original (tozinameran), BNT162b2 Original/Omicron BA.1 (tozinameran/riltozinameran), BNT162b2 Original/Omicron BA.4-5 (tozinameran/famtozinameran), and BNT162B2 Omicron XBB.1.5 (raxtozinameran) remains unchanged.

The MAH should continue to review the safety of BNT162b2, 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.

Considering no new safety information has been identified both in the current and the previous reporting period, there are no conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II), the PRAC Rapporteur proposes to amend the PSUR frequency from 1 year to 2 years (see section 5).

5. Rapporteur Request for supplementary information

None.

6. Comments from Member States

MS1 comment

We fully endorse the PRAC Rapp assessment, and support the proposed change in frequency from 1 to 2 years.

MS2 comment

We fully endorse the PRAC Rapp assessment, and have no further comments.

MS3 comment

We overall agree and thank the rapporteur for the assessment, we have a further comment on the topic regarding small fiber neuropathy:

According to the MAH:

“Out of the 497 cases there was 1 probable related, 22 possible related, 90 unlikely related and 384 unassessable cases”

and also

"Possible related cases:

22 cases ([...]) were conservatively judged as possibly related to vaccination due to the temporal relationship to vaccination, however the overwhelming majority of those cases had confounding factors that likely contributed to the development of small fiber neuropathy such as Hypothyroidism, Vitamin B12 deficiency, Autoimmune thyroiditis, Hypertension, Hyperlipidaemia, Gout, Metabolic syndrome, Psoriatic arthritis, Naloxone treatment indication alcohol or opioid use disorder, Lewy body dementia, Neurodermatitis, confounded by Covid vaccination with Sinopharm, concurrent Epstein-Barr infection, very long latency of 500 days or confounded by Covid infection."

However, there is a discrepancy because we reported in the last PSUSA (EMEA/H/C/PSUSA/00010898/202312), at least 9 cases which were medically confirmed by a neurologist, with positive skin biopsy and with no other etiological causes retrieved.

We also noticed that a study report "Small fiber neuropathy associated with COVID-19 infection and vaccination: A prospective case-control study" by V. Donadio et al. October 2024, published during the PSUR period has not been discussed by the MAH.

Considering that small fiber neuropathy is a recent clinical entity, that knowledge is still accumulating and in light of above information, we suggest to continue to closely monitor this topic for the next PSUR.

Rapporteur assessment comment:

The endorsement and further comments on small fibre neuropathy (SFN) are appreciated.

A medical confirmed skin biopsy of SNF does not automatically point in the direction of a causal relation with BNT162b2 vaccination. With a skin biopsy the diagnosis of SFN is confirmed, but the cause that triggered SFN should still be investigated. The 9 cases presented by the MS in the last PSUR were included in the cumulative review and assessed according to WHO causality standards by the MAH and by the PRAC assessor in the current PSUR period. The discrepancy as identified by the member state can be explained by the following: In 2 cases ([REDACTED], [REDACTED]) skin biopsy confirmed small fiber neuropathy, of which one also confirmed Guillain Barré syndrome. In some of these 9 cases relevant medical history was reported, such as gestational diabetes ([REDACTED]), HIV infection ([REDACTED]), Intervertebral disc disorder ([REDACTED]), Intervertebral disc protrusion ([REDACTED]) and COVID-19 infection ([REDACTED] - RS20221519, [REDACTED], [REDACTED]), which could provide an alternative explanation for the occurrence of small fiber neuropathy.

Indeed, the MAH did not discuss the study report “Small fiber neuropathy associated with COVID-19 infection and vaccination: A prospective case–control study” by V. Donadio et al. October 2024 which was published during the reporting period. From this study is it not clear if and when the BNT-162b2 vaccinated SNF patients also experienced Covid-19 infection, no detailed patients characteristics are provided. As the authors indicate, the study has some limitations, e.g. a control group of Covid-19 or vaccinated subjects without SFN symptoms is lacking. Furthermore, the study was actually designed to

study skin innervation in detail with the aim of verifying the possibility of SFN and to elucidate if there is a common pathophysiological mechanism. However, the study was methodologically not designed to evaluate a causal association with COVID-19 vaccination, eg, about half of the cases selected for this case control study were selected based on exposure to the vaccine. The study of Donadio et al is suggestive that Covid-19 infection and BNT126b2 vaccination could possibly contribute to the aetiology of SFN in patients with pre-existing auto-immune disorders, but no causal relation between BNT162b2 vaccination of Covid-19 infection and small fiber neuropathy is identified.

It is recognized that SFN is a fairly new clinical entity, but at this point in time and with the data currently available, routine pharmacovigilance is considered sufficient to monitor the topic of SFN.

7. APPENDIX 1

PRAC QUERY

The EMA is aware of the following recently published paper regarding long-term sequelae of myocarditis after mRNA COVID-19 vaccine administration,

Myocardial injury safety signal for mRNA COVID-19 vaccines (MACiV study findings)

Background:

*Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13.
<https://doi.org/10.1016/j.eclim.2024.102809>*

The next PSUR DLP is due this month. As this article will be covered in the reporting interval for the upcoming PSURs, the PRAC expects its inclusion, together with the reflection/discussion from the MAH on it.

MAH RESPONSE

Background

With its technical benefits of localizing regional dysfunction and matching tissue characterization, cardiac magnetic resonance (CMR) imaging has become the primary imaging tool for diagnosis and to characterize myocarditis disease severity and planning of patient management. The Lake Louise criteria had established the current recommended diagnostic criteria incorporating early gadolinium enhancement (LGE), and T2-weighted imaging for oedema detection. However, prognostic evidence using CMR for patients with suspected myocarditis currently remains limited¹ and was derived from studies on myocarditis in adult patients and acute setting that found the negative predictive value of LGE presence in the acute episode is substantially better than its positive predictive value.²

LGE by CMR was initially validated in animal models of myocardial infarction, with extensive comparisons demonstrating a nearly exact relationship between the size and shape of infarcted myocardium by LGE to that of histopathology. LGE presence in the acute phase of myocarditis is not necessarily synonymous with irreversible damage, as it can be caused by all conditions that enlarge interstitial space, such as replacement fibrosis, oedema, and proteins overload (amyloidosis), and consequently, increase the volume of distribution of gadolinium in myocardium, causing a much slower wash-out. In the case of acute myocarditis, interstitial space could be increased by replacement fibrosis, but also by the presence of oedema and inflammatory cell infiltration, or gadolinium might be incorporated into phagosomes, or its wash-out be delayed by obstruction of lymphatic vessels with inflammatory cells. LGE is not specific for myocardial inflammation, as it only reflects changes in extracellular space, and cannot reliably differentiate between a more recent or an older episode of myocarditis. Finally, myocardial hyperemia, which is a common finding in myocarditis, may increase the amount of gadolinium that arrives at the involved myocardial segments. Whatever the cause is, in the acute setting of myocarditis in the presence of coexisting oedema, expert consensus is that LGE is not considered a definitive marker of irreversible myocardial damage, in opposition to myocardial infarction, where LGE is always associated with irreversible myocardial damage.^{3,4,5,6}

Regarding relevant studies, in a study of the clinical and prognostic role of 6-month repetition of CMR in adult patients with acute myocarditis (N = 187) and preserved EF, from the ITAMY (ITALian study in MYocarditis) registry, Aquaro et al,⁴ found that at follow-up CMR, LGE disappeared completely in only

10% (n = 18) of the patients; the extent of LGE segments decreased in 87 (46%) patients, remained unchanged in 58 (30%), and increased in 26 (14%). Twenty (11%) patients presented with a complete recovery from oedema and LGE, 30 (16%) patients presented with oedema and LGE, and 137 (73%) presented with LGE without oedema. Authors also found that patients with a decreased or unchanged LGE had a better prognosis and 7-year survival than those with increased LGE. Similarly, in their follow-up CMR study in adult patients with acute myocarditis, Bohbot *et al*,⁷ found that the presence of LGE during the acute phase of AM is not necessarily indicative of fibrosis and irreversible myocardial damage and that beyond LGE extent, dynamic changes of LGE may be more accurate for risk stratification. Of the 204 patients in the study, authors found that at follow-up CMR (mean 5.7 months) LGE persisted in 175 patients (85.8%) and the estimated 7-year event-free survival was 96% ± 2% for patients with ≥50% LGE decrease, 89% ± 3% for patients with <50% LGE decrease, and only 66% ± 10% for patients with LGE increase at follow-up CMR. Ammirati *et al*,⁸ colleagues analysed the follow-up CMR (median 148 days) in 49 patients with myocarditis and found there were no significant variations in left ventricular ejection fraction (LVEF) as to reflect the cardiac function at a median of 148 days and a significant decrease of LGE of 42% compared with baseline. Authors concluded LGE appears one of the CMR parameters with larger relative variations in the first months after acute myocarditis.

In children with acute myocarditis, information on LGE on follow-up is only derived from very small studies or case series. In a recent study involving 28 pediatric patients with non-COVID-19-vaccine related myocarditis, at a median follow-up CMR of 6 months, 24 (85.7%) patients had LGE.⁹ In their study of 34 children with acute myocarditis, Dubey *et al*.¹⁰ found that only 12 patients had a follow-up CMR imaging, and of these 12 patients, LGE was detected in 10 out of 12 patients on baseline CMR and persisted in all on follow-up CMR imaging. In contrast, this LGE persistence was not correlated with other indicators of cardiac function, as normalisation of cardiac enzymes and inflammatory markers was noted for all acute myocarditis subjects on follow-up testing, and recovery of biventricular function was seen in all except for one patient. Malek *et al*,¹¹ reports from a study of 18 adolescents with acute myocarditis who received a follow-up CMR at 7 months that despite normalisation of other routinely assessed parameters (including LVEF), there is a high prevalence of persistent magnetic resonance imaging (MRI) changes at follow-up. Between the initial and second MRI, the number of segments with visible LGE decreased in 13 patients (72%), remained unchanged in 2 patients (11%, both with healed myocarditis), and increased in 3 patients (16%): 2 with ongoing disease and in one with healed myocarditis. Finally, in the study of 143 paediatric patients (<21 years) with acute myocarditis, Banka *et al*,¹² found the CMR parameters at presentation associated with persistent LV dysfunction were larger LV end diastolic volume and lower left and right ventricular ejection fraction but not abnormal LGE (follow-up median 7.1 months).

Brief article Summary

In this longitudinal retrospective observational cohort multicenter study across 38 hospitals in the United States, 333 patients with COVID-19 vaccine-associated myocarditis (C-VAM) were compared with 100 patients with multisystem inflammatory syndrome in children (MIS-C). The initial clinical course in C-VAM was more likely to be mild (80% vs. 23%, p < 0.001) and cardiac dysfunction was less common (17% vs. 68%, p < 0.0001), when compared to MIS-C. However, LGE on cardiac MRI was more prevalent in C-VAM (82% vs. 16%, p < 0.001), indicating myocardial injury. The authors stated that mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (interquartile range [IQR] 114–285 days) were reassuring. No cardiac deaths or heart transplantations were reported until the time of submission of this report for all groups.

Article discussion

The marketing authorisation holder (MAH) acknowledges that *Jain et al*, published an interesting article on long-term sequelae of myocarditis after mRNA COVID-19 (coronavirus disease 2019) vaccine administration.

The MAH would like to reflect on the following points:

1. The presence of late gadolinium enhancement in longer term follow-up data of vaccine-induced myocarditis is not a new finding¹³

Several publications described longer term follow up (3-6 months) of patients with myocarditis that described clinical resolution and observations of residual LGE on CMR in some patients. For example, Kracalick *et al*¹³, reported on a follow up surveillance study of Vaccine Adverse Event Reporting System (VAERS) that collected data for 519 (62%) of 836 eligible patients who were at least 90 days post-myocarditis onset. The study found that after at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, most individuals in the cohort were considered recovered by health-care providers, and quality of life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age. Most patients had improvements in cardiac diagnostic marker and testing data at follow-up, including normal or back-to-baseline troponin concentrations (181 [91%] of 200 patients with available data), echocardiograms (262 [94%] of 279 patients), electrocardiograms (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients). An abnormality was noted among 81 (54%) of 151 patients with follow-up cardiac MRI; however, evidence of myocarditis suggested by the presence of both LGE and oedema on cardiac MRI was uncommon (20 [13%] of 151 patients). At follow-up, most patients were cleared for all physical activity (268 [68%] of 393 patients).

2. The clinical outcomes are favorable and do not correlate with LGE findings

Jain *et al*, stated that mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (IQR 114–285 days) were reassuring. The initial clinical course in C-VAM was more likely to be mild (80% vs. 23%, $p < 0.001$) and cardiac dysfunction was less common (17% vs. 68%, $p < 0.0001$), when compared to MIS-C. No cardiac deaths or heart transplantations were reported until the time of submission of this report for all groups.

3. Imaging parameters may not be enough to drive decision making

Medical decision making based on a sole diagnostic imaging parameter is, in general, against the principles of rational medical judgement.¹⁴ To avoid cognitive errors, one should also consider clinical history and course.¹⁵ In the study of Jain *et al*, patient-centered (and hence, important) outcomes, such as clinical course and cardiac dysfunction were more likely to be mild in C-VAM as opposed to MIS-C, as highlighted in point #2 above. Therefore, the main study finding is clinically ambiguous (i.e., abnormal LGE enhancement but with a favorable clinical outcome) and may point towards an uncertainty about the applicability of research evidence on clinical practice.

Furthermore, as noted in the background section, for follow-up CMR investigations the degree and speed of LGE resolution in patients with acute myocarditis has not been firmly established. Few studies have evaluated follow-up CMR in myocarditis. These were mostly in adult patients and it was shown that LGE persists in a high proportion of patients but its persistence (unchanged or decreasing) is not associated with worse prognosis or survival.

Only increased LGE in follow-up CMR demonstrated worse survival free from cardiac events than those with unchanged/decreased LGE. *Jain et al*, focused mainly on persistence of LGE findings rather than their

trajectory (increased, decreased, unchanged), which may be a significant limitation of the study. In fact, an improvement was demonstrated at LGE imaging follow-up, as presented in Figure 2 of the study.

4. A study with larger population and longer follow-up points towards a favorable prognosis of post-COVID-19 mRNA vaccination myocarditis

A 2024 study published by *Semenzato et al.*¹⁶ on JAMA, reports on cardiovascular complications of post-COVID-19 mRNA vaccination myocarditis and other types of myocarditis over an 18-month follow-up. The study recruited patients of various ages, including patients in the paediatric population. In total, 4635 individuals were hospitalized for myocarditis and comprised the 3 groups of the study: 558 with postvaccine myocarditis, 298 with post-COVID-19 myocarditis, and 3779 with conventional myocarditis. *Semenzato et al.*, focused on clinical outcomes (hospital readmission for myopericarditis, other cardiovascular events, all-cause death, and a composite outcome of these events) rather than imaging parameters, as was observed in the study of *Jain et al.* The study by *Semenzato et al.*, found that patients with post-vaccine myocarditis, contrary to those with post-COVID-19 myocarditis, present a more favorable prognosis when compared to conventional myocarditis.

MAH Conclusion

In conclusion, long term outcomes and CMR findings have been subject to close monitoring for myocarditis. The article by Jain et al, does not meet the requirements for a new safety signal, as it does not provide a new aspect of the myocarditis association with BNT162b2 (as discussed on point #1). Importantly, the authors stated that patient-centered clinical outcomes are reassuring (as discussed on point #2). Additionally, this study focuses on a primary outcome (i.e., abnormal imaging finding) that has an uncertain applicability on clinical practice, and hence, on the overall benefit-risk profile of the product (as discussed on point #3). Finally, a larger study with longer follow-up reporting on clinical (rather than imaging) outcomes has been recently published.¹⁶ In this study, the authors found that patients with post-vaccine myocarditis, contrary to those with post-COVID-19 myocarditis, present a more favorable prognosis when compared to conventional myocarditis (as discussed on point #4).

Overall, myocarditis is an ADR of the vaccine that is listed in the label of BNT162b2, an important risk in the European risk management plan and is subject to close monitoring using routine and additional pharmacovigilance activities. To further elucidate the long term outcomes, the MAH currently conducts a low-interventional study using primary data from the Pediatric Heart Network, a National Institutes of Health-funded consortium of leading research hospitals across the United States, Canada, and other countries that conducts research in cardiovascular disease, to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period (C4591036). The MAH will continue to closely monitor this topic.

Rapporteur assessment comment:

The MAH's response including a discussion on long-term outcomes and cardiac magnetic resonance [CMR] findings reported by the publication Jain *et al.* is accepted.

[A **typo** is suspected in the MAH response, background section which states: *The Lake Louise criteria had established the current recommended diagnostic criteria incorporating **early** gadolinium enhancement (LGE), and T2-weighted imaging for oedema detection.*

The paper's authors state that: '*The primary outcome was presence of myocardial **Late gadolinium enhancement (LGE)** at initial presentation. Secondary outcomes included the following variables during follow-up: presence of myocardial LGE; presence of cardiovascular symptoms including chest pain, palpitations, shortness of breath, syncope; ventricular or supra-ventricular tachycardias; frequent premature ventricular contractions; second- or third-degree atrioventricular conduction block; LVEF <55% on echocardiogram; listing for heart transplantation; re-hospitalization and/or*

death attributable to cardiac causes.]

In this longitudinal retrospective observational cohort multicenter study across 38 hospitals in the United States, 333 patients with COVID-19 vaccine-associated myocarditis (C-VAM) were compared with 100 patients with multisystem inflammatory syndrome in children (MIS-C). The initial clinical course in C-VAM was more likely to be mild (80% vs. 23%, $p < 0.001$) and cardiac dysfunction was less common (17% vs. 68%, $p < 0.0001$), when compared to MIS-C. However, LGE on cardiac MRI was more prevalent in C-VAM (82% vs. 16%, $p < 0.001$), indicating myocardial injury. The authors stated that mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (interquartile range [IQR] 114–285 days) were reassuring. No cardiac deaths or heart transplantations were reported until the time of submission of this report for all groups.

In summary the MAH noted that the findings in the paper do not identify new safety information based on the following:

- The presence of **late gadolinium enhancement** in longer term follow-up data of vaccine-induced myocarditis is not a new finding.
- The clinical outcomes are favourable and do not correlate with LGE findings
- Imaging parameters may not be enough to drive decision making
- A study with larger population and longer follow-up points towards a favorable prognosis of post-COVID-19 mRNA vaccination myocarditis

The MAH's commitment is endorsed to continue to closely monitor this topic, *e.g.* within the context of the ongoing low-interventional study C4591036 using primary data from the Pediatric Heart Network (PHN), to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period.

The study protocol of study C4591036 has been agreed within procedure EMEA/H/C/005735/MEA/041.7.

According to the agreed milestones, data collection has started 21 Nov 2022 and will continue until 21 Nov 2030 [estimated]. Annual progress reports are planned from 30 Jun 2025 onwards, through 30 Jun 2030. Final Study Report is due 28 Feb 2031 [estimated].

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PERIODIC SAFETY UPDATE REPORT #7
for

ACTIVE SUBSTANCE: COVID-19 mRNA vaccine (BNT162b2)¹

**BNT162b2 Monovalent Original – BNT162b2 Bivalent Omicron BA.1 – BNT162b2
Bivalent Omicron BA.4/BA.5 – BNT162b2 Monovalent Omicron XBB.1.5 – BNT162b2
Monovalent Omicron JN.1 – BNT162b2 Monovalent Omicron KP.2**

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SIGNATURE: _____ **Date: 17 February 2025**

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

² Earliest conditional approval date.

EXECUTIVE SUMMARY

This is the 7th 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 Bivalent Omicron BA.1 (tozinameran/riltozinameran),⁴ BNT162b2 Bivalent Omicron BA.4/BA.5 (tozinameran/famtozinameran),⁵ BNT162b2 Omicron XBB.1.5 (raxtozinameran),⁶ BNT162b2 Omicron JN.1 (bretovameran)⁷ or BNT162b2 Omicron KP.2 (mRNA encoding KP.2) covering the reporting interval 19 December 2023 through 18 December 2024.

COMIRNATY[®] approved presentations and strengths are reported in the table below.

Age Range of Recipient	Monovalent Presentations	Bivalent Presentations	
	BNT162b2 Original BNT162b2 Omicron XBB.1.5 BNT162b2 Omicron JN.1 BNT162b2 Omicron KP.2	BNT162b2 Bivalent BA.4/BA.5	BNT162b2 Bivalent BA.1
	Strength per dose in micrograms (mcg)		
6 months through 4 years	3 mcg	1.5/1.5 mcg (3 mcg total)	N/A
5 through 11 years	10 mcg	5/5 mcg (10 mcg total)	N/A
12 years and older	30 mcg	15/15 mcg (30 mcg total)	15/15 mcg (30 mcg total)

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).

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.

The excipients for all presentations are: ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315); 2-[(polyethylene glycol)-2000]-N,N-

³ Also referred to as Pfizer-BioNTech COVID-19 vaccine in other Company's documents and as Original, Monovalent original or Wild Type (WT) in this document.

⁴ Also referred as bivalent BNT162b2 (original/Omi BA.1), BNT162b2 bivalent (WT/Omi BA.1) or Bivalent BA.1.

⁵ Also referred as bivalent BNT162b2 (original/Omi BA.4/BA.5), BNT162b2 bivalent (WT/Omi BA.4/BA.5) or Bivalent BA.4/BA.5.

⁶ Also referred to as "2023-2024 formula", Monovalent Omicron XBB.1.5.

⁷ Also referred to as "2024-2025 formula", Monovalent Omicron JN.1 and KP.2, respectively.

ditetradecylacetamide (ALC-0159); 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); cholesterol; tromethamine; tromethamine hydrochloride; sucrose; water for injections.

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 the available formulations and presentations in the approved populations.

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Color or Pre-Filled Syringe)	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 BA.4/BA.5 - Omicron XBB.1.5 - Omicron JN.1
	Yellow	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	- Omicron XBB.1.5 - Omicron JN.1 - Omicron KP.2
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 BA.4/BA.5 - Omicron XBB.1.5 - Omicron JN.1
	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 - Omicron JN.1 - Omicron KP.2
	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 - Omicron JN.1 - Omicron KP.2
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 BA.1 - Bivalent BA.4/BA.5 - Omicron XBB.1.5 - Omicron JN.1 - Omicron KP.2
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	- Original (Wildtype) - Bivalent BA.4/BA.5 - Omicron XBB.1.5 - Omicron JN.1 - Omicron KP.2
	Pre-filled syringe	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	- Omicron XBB.1.5 - Omicron JN.1 - Omicron KP.2

Cumulatively, it is estimated that 72,486^{8,9} participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with:

- 65,513 participants exposed to BNT162b2 original;
- 11,836 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 bivalent (original/Omi), BNT162b2 bivalent [original/Omi BA.1 (B.1.1.529)], BNT162b2 bivalent (original/Omi BA.4/BA.5), BNT162b2 Omi XBB.1.5, BNT162b2 (Omi JN.1), BNT162b2 (Omi KP.2), BNT162b5 bivalent (original/Omi BA.2), BNT162b5 bivalent (original/Omi BA.4/BA.5), BNT162b6 bivalent (original/Omi BA.4/BA.5), BNT162b7 monovalent (Omi BA.4/BA.5), and BNT162b7 bivalent (original/Omi BA.4/BA.5);
- 522 participants exposed to other early development candidates (including BNT162a1, BNT162b1,¹⁰ BNT162b3 and BNT162c2), and
- 6524 participants received placebo.

BNT162b2 is also being utilised in 4 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026,¹¹
- 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)/bIRV/QIV/, bivalent BNT162b2 (original/Omi BA.4/BA.5)/tIRV in the clinical study C5261001,¹² as a study vaccine.

⁸ Participants to more than one clinical trial (e.g., extension study) are counted once when receiving the same treatment in the parent study.

⁹ From the total number of participants to the BNT162b2 clinical development, those accounted to the study BNT162-21 receiving bivalents BNT162b2 are 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.

¹⁰ The decrease in number for BNT162b1 with respect to the previous PSUR #6 (N=411) is due to Study C4591001, where 111 subjects were erroneously attributed to BNT162b1. Of note, 78 out of 300 participants also received BNT162b2 (this is noted under treatment arm 'BNT162b1/ BNT162b2' in Appendix 2.3)

¹¹ 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.

¹² 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.

In CTs C5261002¹³ and C5261023,¹⁴ 8750 and 1247 participants received blinded therapy, respectively.

- C548: 772 participants received BNT162b2 as a study vaccine in combination with QIV/RSVpreF (312) or RSVpreF/placebo (310) or placebo (150); 301 other participants received placebo/RSVpreF (152) or placebo/QIV (149) in study C5481001.¹⁵
- C568: 641 participants received blinded therapy in study C5681001.¹⁶

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 BNT162-21.¹⁷

Previously publicly available regional information on vaccine doses administered is no longer consistently available for estimation of cumulative worldwide exposure. The best estimate of the post-marketing exposure is based on the worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group reported in the shipment tracker from 01 December 2020¹⁸ through 22 December 2024. Approximately 5,032,571,025 doses of BNT162b2 (monovalent and bivalent presentations) were shipped from BioNTech and Pfizer worldwide. Out of the cumulative number of shipped doses, 3,946,055,525 were monovalent original vaccine (including PBS and Tris/Sucrose), 717,702,100 were bivalent vaccines and 368,813,400 were monovalent Omicron presentations (of which 237,508,600 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); there were 4,546,909,545 doses for adult¹⁹ presentations and 485,661,480 doses for paediatric²⁰ presentations. Overall, 2,588,253,585

¹³ A phase 3, randomized, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a combined modified RNA vaccine candidate against COVID-19 and influenza in healthy individuals.

¹⁴ A phase 1/2, randomized, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of combined vaccine candidates against influenza and COVID-19 in healthy individuals.

¹⁵ 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.

¹⁶ A Phase 1/2 Randomized Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA COVID-19 Vaccine and a Recombinant Influenza Vaccine Administered as a Single Injection in Healthy Adults 50 Years of Age or Older.

¹⁷ An exploratory phase 1, 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.

¹⁸ BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the United Kingdom (UK) on this date.

¹⁹ Approved for 12 years of age and older.

²⁰ Approved for 6 months through <12 years.

doses of BNT162b2 (monovalent and bivalent presentations) were shipped to rest of world (ROW).²¹

During the interval 18 December 2023 through 22 December 2024²², approximately 179,315,700 doses of BNT162b2 monovalent and bivalent presentations were shipped worldwide. Out of the doses shipped during the reporting period, 949,220 were monovalent original vaccine (Tris/Sucrose), 2,140,020 were bivalent vaccines and 176,226,460 were monovalent Omicron vaccines (of which 44,921,660 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); there were 169,235,820 doses for adult¹⁹ presentations and 10,079,880 doses for paediatric²⁰ presentations. Overall, 69,537,760 doses of BNT162b2 (monovalent and bivalent presentations) were shipped to ROW.²¹

Additionally, as per data provided by contractual party (CP) in Hong Kong, Macau, and Taiwan, 32,553,932 doses of monovalent (original and Omicron XBB.1.5 and Omicron JN.1) and bivalent Omicron BA.4/BA.5 vaccine presentations were administered cumulatively and 206,479 doses were administered in the interval reporting period.

The marketing authorisation holders (MAHs) of BNT162b2 monovalent and bivalent presentations in different countries/regions are the following: BioNTech, Pfizer, the local Ministry of Health (MoH), the local Government, and the CP Fosun Pharma.

During the reporting period,

- the European Medicines Agency (EMA) approved the deletion of BNT162b2 Original (tozinameran), BNT162b2 Bivalent BA.1 (tozinameran/riltozinameran) and BNT162b2 Bivalent BA.4/BA.5 (tozinameran/famtozinameran) presentations for BNT162b2 at the request of the MAH for commercial reasons only;
- in other countries the licenses (EUA or full MA) expired, or have been cancelled or were replaced or withdrawn (for commercial reasons).

A summary of number of countries/regions where BNT162b2 is currently approved is provided below.

Number of Countries/Regions by MAH where BNT162b2 Monovalent and Bivalent Vaccine Presentations are currently Approved

Marketing Authorisation Holder	Number of Countries/Regions where the Marketing Authorisation is Held					
	BNT162b2 Original	BNT162b2 Bivalent BA.1	BNT162b2 Bivalent BA.4/BA.5	BNT162b2 Omicron XBB.1.5	BNT162b2 Omicron JN.1	BNT162b2 Omicron KP.2
BioNTech	13	0	8	40	35	34
Pfizer	14	2	13	19	10	0

²¹ Non-EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa.

²² The shipment processing operation is set up to calculate shipment by week (Monday to Sunday) rather than by day and therefore the start date was Monday 18 December 2023.

Number of Countries/Regions by MAH where BNT162b2 Monovalent and Bivalent Vaccine Presentations are currently Approved

Marketing Authorisation Holder	Number of Countries/Regions where the Marketing Authorisation is Held					
	BNT162b2 Original	BNT162b2 Bivalent BA.1	BNT162b2 Bivalent BA.4/BA.5	BNT162b2 Omicron XBB.1.5	BNT162b2 Omicron JN.1	BNT162b2 Omicron KP.2
Fosun Pharma	0	0	1	1	1	0
Local MoH	2 ^a	0	0	0	0	0
Local Government	1 ^b	0	1	0	0	0
All	30	2	23	60	46	34

a. Moldova and Kenya

b. Ghana.

In addition, World Health Organization (WHO) had approved the transition from the Emergency Use Listing (EUL) to Prequalification (PQ) 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 29.0 dated 27 November 2024, in effect at the end of the reporting period. Four (4) previous CDS versions (version 25.0 dated 26 January 2024, version 26.0 dated 03 April 2024, version 27.0 dated 01 July 2024 and version 28.0 dated 09 September 2024) were also in effect during the reporting period.

During the reporting period, safety related changes were included in the sections below:

- Section 4.4 Special warnings and precautions for use (CDS version 28.0)
- Section 4.5 Interaction with other medicinal products and other forms of interaction (CDS version 29.0)
- Section 4.6 Fertility, pregnancy and lactation (CDS version 28.0)
- Section 4.8 Undesirable effects (CDS versions 25.0, 27.0, 28.0 and 29.0)
- Section 4.9 Overdose (CDS version 26.0)
- Appendix A and Appendix B (CDS versions 25.0, 27.0 and 28.0)

Migraine, Transverse myelitis, Subacute thyroiditis, Erectile dysfunction, Hypertension, Giant cell arteritis, Exacerbation of diabetes mellitus, Exacerbation of adrenal insufficiency, Tongue discolouration, Sciatica, Tonsillitis, Erysipelas, Angina bullosa haemorrhagica, Polycystic ovaries, Cerebral amyloid angiopathy, Cough, Aphasia, Disturbance in attention, Myocardial necrosis marker increased, Pelvic pain, and Paralysis were new safety signals opened during the reporting period, while Pulmonary embolism and Post-menopausal haemorrhage were ongoing signals. Following evaluation, all these signals were closed as signals determined not to be risks.

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]. The requests are summarised in the table below.

Regulatory Authority Procedure Number (if applicable)	Request(s) <i>PSUR Section(s) addressing the Request</i>
PRAC	The MAH is requested to include and provide a reflection/discussion on the recently published paper regarding long-term sequelae of myocarditis after mRNA COVID-19 vaccine administration, in the next PSUR, due for submission by 26 February 2025. Myocardial injury safety signal for mRNA COVID-19 Vaccines (Maciv Study Findings) <i>Please refer to Section 11 Literature and to Appendix 5.1.</i>
EMA PSUR #6 Final AR EMEA/H/C/PSUSA/ 00010898/202312	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. <i>Please refer to Section 15 Other Safety Topics Not Considered Signals and to Appendix 5.2.</i>
	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. <i>Please refer to Section 15 Other Safety Topics Not Considered Signals and to Appendix 5.3.</i>
	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. <i>Please refer to Section 15 Other Safety Topics Not Considered Signals and to Appendix 5.4.</i>

Regulatory Authority Procedure Number (if applicable)	Request(s) <i>PSUR Section(s) addressing the Request</i>
EMA <i>PSUR #5 Final AR EMA/H/C/PSUSA/ 00010898/202306</i>	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. <i>Please refer to Section 16.3.3 Evaluation of Other Risks (not categorised as important).</i> 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. <i>Please refer to Section 16.3.4 Evaluation of Special Situations.</i>
Health Canada	<i>BioNTech Manufacturing GmbH</i> 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. <i>Please refer to Section 15 Other Safety Topics Not Considered Signals and to Appendix 5.3.</i>
EMA <i>PSUR #4 AR EMA/H/C/PSUSA/ 00010898/202212</i>	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. <i>Please refer to Section 16.3.3 Evaluation of Other Risks (not categorised as important).</i> 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. <i>Please refer to Section 16.3.3 Evaluation of Other Risks (not categorised as important).</i> 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. <i>Please refer to Section 16.3.4 Evaluation of Special Situations.</i> 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. <i>Please refer to Section 16.3.5 Update on Special Patient Populations.</i> The MAH should continue to report on the administered 1st, 2nd, 3rd, 4th, etc. doses of Comirnaty as presented in future PSURs. <i>Please refer to Section 5.2 Cumulative and Interval Patient Exposure from Marketing Experience.</i>

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Regulatory Authority Procedure Number (if applicable)	Request(s) <i>PSUR Section(s) addressing the Request</i>
EMA PSUR #4 AR EMA/H/C/PSUSA/ 00010898/202212 Cont'd	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%. <i>Please refer to Section 6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources.</i>
EMA PSUR #3 AR EMA/H/C/PSUSA/ 00010898/202206 ²³	For future PSURs 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. <i>Please refer to Section 16.3.3 Evaluation of Other Risks (not categorised as important).</i> 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. <i>Please refer to Section 16.3.4 Evaluation of Special Situations.</i> 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. <i>Please refer to Section 16.3.5 Update on Special Patient Populations.</i>
WHO	Pregnancy outcome in clinical trials. <i>Please refer to Section 16.3.5.2 Use in Pregnant/Lactating Women.</i>
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. <i>Please refer to Section 8 Findings From Non-Interventional Studies, Appendix 5.5 and Appendix 5.6.</i>
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. <i>Please refer to Section 6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources and to Appendix 2.2.9.</i>

²³ In addition, concerning hearing loss, the MAH was requested in future reviews of cases reporting hearing loss to conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss, if applicable. The MAH acknowledges; this topic has been monitored using routine pharmacovigilance and since no significant new information was identified it is not presented in the current PSUR.

Regulatory Authority Procedure Number (if applicable)	Request(s) <i>PSUR Section(s) addressing the Request</i>
Medsafe (New Zealand) <i>AR of PSUR#3</i>	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. <i>Please refer to Section 16.3.5.1 Use in Paediatric Subjects.</i>
EMA/PRAC 202255/2022 13 th <i>Summary Safety Report</i>	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. <i>Please refer to Section 11 Literature.</i>

The European Union Risk Management Plan (EU-RMP) in effect at the beginning of the reporting period is version 11.0 adopted on 26 October 2023 (Procedure number EMEA/H/C/005735/II/0188). The safety concerns in the EU-RMP for BNT162b2 are:

- Important identified risk: Myocarditis and Pericarditis.
- Important potential risk: 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,²⁴ Long term safety data.

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

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 monovalent (original, Omicron XBB.1.5, Omicron JN.1 and Omicron KP.2) and bivalent vaccines (Omicron BA.1 and Omicron BA.4/BA.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.

²⁴ The missing information “Interaction with other vaccines” was removed from the list of safety concerns in the EU-RMP version 12.0, based on the C4591030 final study report and the non-interventional effectiveness data from a large retrospective cohort study of commercially insured US adults conducted by the MAH supported by the results from 15 prospective study publications describing the effect of coadministration of COVID-19 vaccine dose(s) with an influenza vaccine on immune responses and safety. The EU-RMP version 12.0 approved with procedure EMEA/H/C/005735/II/0201 and EC decision on 03 July 2024.

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LIST OF ABBREVIATIONS

Abbreviation	Term
20vPnC	pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)
3V	trivalent
4V	quadrivalent
ABH	angina bullosa haemorrhagica
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC-0159	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ALC-0315	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
aPV	additional pharmacovigilance
AR	assessment report
ARDS	acute respiratory distress syndrome
ATC	anatomical therapeutic chemical
BC	blood culture
bIRV	bivalent influenza modRNA vaccine
BMJ	British Medical Journal
BUD	beyond use date
CAA	cerebral amyloid angiopathy
CDC	Centers for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMI	cell-mediated immunity
CMR	cardiac (or cardiovascular) magnetic resonance
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-NET	COVID-19 Hospitalization Surveillance Network
CP	(SDEA) contractual party
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial
DART	developmental and reproductive toxicity
DLP	data lock point
DNA	deoxyribonucleic acid
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EB05	lower 5% confidence interval of the Empirical Bayes Geometric Mean

Abbreviation	Term
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECMO	extracorporeal membrane oxygenation
ED	emergency department; erectile dysfunction
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
EPITT	European pharmacovigilance issues tracking tool
ESND	(France) National Health Insurance database
EU	European Union
EUA	emergency use authorisation
EUL	emergency use listing
EURD	European Union reference date
EU-RMP	European Union risk management plan
FDA	(US) Food and Drug Administration
GCA	giant cell arteritis
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
GVP	good pharmacovigilance practices
HA	Health Authority
HBV	hepatitis B virus
HCP	healthcare professional
HCRU	characteristics and healthcare resource use
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLGT	(MedDRA) High Level Group Term
HLH	haemophagocytic lymphohistiocytosis
HLT	(MedDRA) High Level Term
HPV	human papillomavirus
HRU	healthcare resource utilization
IB	investigator's brochure
IBD	international birth date
ICDH	International Classification of Headache Disorder
ICH	International Council for Harmonisation
ICSR	individual case safety report
ICU	intensive care unit
ID	Identifier
IgG	immunoglobulin G
IIM	idiopathic inflammatory myopathies
IM	intramuscular/intramuscularly
IMP	investigational medicinal product
inact	inactivated
IR	incident rate

Abbreviation	Term
IV	intravenous/intravenously
JAK	Janus kinase
JAMA	Journal of American Medical Association
LMIC	low- and middle-income country
LNP	lipid nanoparticles
LoS	length of stay
MAA	marketing authorisation application
MACiV	myocarditis after COVID vaccination
MAH	marketing authorisation holder
MC	medically confirmed
ME	medication error
MEA	additional pharmacovigilance activity in the risk-management plan
MedDRA	Medical Dictionary for Regulatory Activities
Medsafe	(New Zealand) Medicines and Medical Devices Safety Authority
MHPD	Marketed Health Products Directorate
MHRA	(UK) Medicines and Healthcare Products Regulatory Agency
MIS-C	multisystem inflammatory syndrome in children
MoH	ministry of health
MRI	magnetic resonance imaging
mRNA	messenger RNA
N/A	not applicable; not available
NAAT	nucleic acid amplification test
NEC	not elsewhere classified
NHS	National Health Service
NIH	National Institute of Health
NIS	non-interventional study
NMC	non-medically confirmed
NOS	not otherwise specified
NR	not reported
NSCLC	non-small cell lung cancer
NT50	50% neutralising titer
O/E	observed versus expected
Omi	omicron
ONS	Office for National Statistics
OR	odds ratio
PASS	post-authorisation safety study
PB	pharmacovigilance branch
PBRER	periodic benefit-risk evaluation report
PBS	phosphate-buffered saline
PE	pulmonary embolism
PHEIC	public health emergency of international concern
PHN	Pediatric Heart Network
PI	product information
PM	post-marketing

Abbreviation	Term
PMH	post-menopausal haemorrhage
PQ	prequalification
PRAC	Pharmacovigilance Risk Assessment Committee
preF	prefusion F
PSUR	periodic safety update report
PSUSA	periodic safety update single assessment
PT	(MedDRA) Preferred Term
PV	pharmacovigilance
PVP	pharmacovigilance plan
PY	person-year
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QPPV	qualified person for pharmacovigilance
RGE	recombinant glycoprotein E
RMP	risk management plan
RNA	ribonucleic acid
ROW	rest of world
RSI	reference safety information
RSV	respiratory syncytial virus
RSVpreF	respiratory syncytial virus vaccine
RT-PCR	reverse transcriptase-polymerase chain reaction
S	spike
SAE	serious adverse event
sag	surface antigen
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAT	subacute thyroiditis
SBSR	summary bimonthly safety report
SD	standard deviation
SFDA	Saudi Food and Drug Authority
SFN	small fiber neuropathy
SIIV	seasonal inactivated influenza vaccine
SmPC	summary of product characteristics
SMQ	Standardised MedDRA Query
SMSR	summary monthly safety report
SOC	(MedDRA) System Organ Class
split	split virus
SR	seroconversion rate
SSA	Substudy A
SSB	Substudy B
SSD	Substudy D
SSE	Substudy E
SSR	summary safety report
TGA	(Australia) Therapeutic Goods Administration
tIRV	trivalent influenza modRNA vaccine

Abbreviation	Term
Tris	tromethamine buffer or (HOCH ₂) ₃ CNH
TTH	tension-type headache
UC	urgent care
UK	United Kingdom
UKHSA	(United Kingdom) Health Security Agency
UMC	Uppsala Monitoring Centre
US	United States
USA	United States of America
USG	United States Government
VE	vaccine effectiveness
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WT	wild type

1. INTRODUCTION

This is the 7th PSUR for the COVID-19 mRNA vaccine, COMIRNATY[®], also referred to as BNT162b2 Original (tozinameran),³ BNT162b2 Bivalent Omicron BA.1 (tozinameran/riltozinameran),⁴ BNT162b2 Bivalent Omicron BA.4/BA.5 (tozinameran/famtozinameran),⁵ BNT162b2 Omicron XBB.1.5 (raxtozinameran),⁶ BNT162b2 Omicron JN.1 (bretovameran)⁷ or BNT162b2 Omicron KP.2 (mRNA encoding KP.2) covering the reporting interval 19 December 2023 through 18 December 2024.

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]),²⁵ and Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance version 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.

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK²⁶ on 01 December 2020.

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

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Color or Pre-Filled Syringe)	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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1

²⁵ The corePSUR19 guidance, was discontinued on 30 March 2023.

²⁶ Conditional marketing authorisation approval was also granted in the UK on 01 January 2021 and converted to standard marketing authorisation on 09 November 2022.

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Color or Pre-Filled Syringe)	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 <i>Cont'd</i>	Yellow	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	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 • Omicron JN.1 • Omicron KP.2
	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 • Omicron JN.1 • Omicron KP.2
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 BA.1 • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Pre-filled syringe	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2

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(ies) 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

Table 1. List of PSURs

PSUR Number	Reporting Period
4	19 June 2022 through 18 December 2022
5	19 December 2022 through 18 June 2023
6	19 June 2023 through 18 December 2023

2. WORLDWIDE MARKETING APPROVAL STATUS

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK²⁶ 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.

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.

Overall, BNT162b2 (any vaccine presentation) received marketing authorisation approval in 104 countries/regions and is currently approved in 87 countries/regions.

BNT162b2 original received marketing authorisation approval in 104 countries/regions and is currently approved in 30 countries/regions. This vaccine presentation was prequalified by the WHO in 2024.

In 2022, to address the emergence of Omicron variants, bivalent formulations were developed. Bivalent Omicron BA.1 and bivalent BA.4/BA.5 received marketing authorisation approval in 46 and 73 countries/regions, respectively and are currently approved in 2 and 23 countries/regions, respectively. In 2024, the bivalent BA.4/BA.5 vaccine was prequalified by the WHO.

In 2023, to address the emergence of new Omicron variant (XBB.1.5), an adapted monovalent formulation was developed. The monovalent XBB.1.5 vaccine, first authorized in the EU countries on 31 August 2023, has received marketing authorisation and is currently approved in 60 countries/regions and has been prequalified by the WHO.

In 2024, to address the emergence of SARS-CoV-2 variants with multiple mutations (i.e. JN.1, KP.2), two adapted monovalent variant vaccine constructs were developed. The BNT162b2 Omicron JN.1-adapted monovalent COVID-19 vaccine (COMIRNATY JN.1) was first authorized in the EU countries on 03 July 2024 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. The JN.1-

adapted monovalent COVID-19 vaccine received marketing authorization approval and is currently approved in 46 countries/regions. It was prequalified by the WHO.

On 26 September 2024, the European Commission granted marketing authorization for Omicron KP.2-adapted monovalent COVID-19 vaccine (COMIRNATY KP.2) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

On 22 August 2024, the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application for individuals 12 years of age and older (COMIRNATY® (COVID-19 Vaccine, mRNA)), and granted emergency use authorization for individuals 6 months through 11 years of age (Pfizer-BioNTech COVID-19 Vaccine) of the companies' Omicron KP.2-adapted 2024-2025 Formula COVID-19 vaccine. The KP.2-adapted monovalent variant vaccine received marketing authorization approval and is currently approved in 34 countries/regions.

The formulations and presentations available for use in different age groups are reported in Table 2.

Table 2. Available Presentations of Monovalent and Bivalent Vaccine Variants

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Colour or Pre-Filled Syringe)	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for BNT162b2 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 (Wild type) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	Yellow	Concentrate for dispersion for injection. Must Dilute. IM	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
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 BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1
	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 • Omicron JN.1 • Omicron KP.2
	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 • Omicron JN.1 • Omicron KP.2

Table 2. Available Presentations of Monovalent and Bivalent Vaccine Variants

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Colour or Pre-Filled Syringe)	Pharmaceutical Form, Dilution Requirement and Route of Administration	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for BNT162b2 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 BA.1 • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Light grey	Dispersion for injection. Do not dilute. IM	Single dose vial (0.48 mL) contains one 0.3 mL dose	• Original (Wildtype) • Bivalent BA.4/BA.5 • Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2
	Pre-filled syringe	Dispersion for injection. Do not dilute. IM	Single dose prefilled syringe contains one 0.3 mL dose	• Omicron XBB.1.5 • Omicron JN.1 • Omicron KP.2

During the reporting period,

- the European Medicines Agency (EMA) approved the deletion of BNT162b2 Original (tozinameran), BNT162b2 Bivalent BA.1 (tozinameran/riltozinameran) and BNT162b2 Bivalent BA.4/BA.5 (tozinameran/famtozinameran) presentations for BNT162b2 at the request of the MAH for commercial reasons only;
- in other countries the licenses (EUA or full MA) expired, or have been cancelled or were replaced or withdrawn (for commercial reasons).

The MAHs and the number of countries/regions where BNT162b2 is currently approved are presented in Table 3.

Table 3. Number of Countries/Regions by MAH where BNT162b2 Monovalent and Bivalent Vaccine Presentations are currently Approved

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held					
	BNT162b2 Original	BNT162b2 Bivalent BA.1	BNT162b2 Bivalent BA.4/BA.5	BNT162b2 Omicron XBB.1.5	BNT162b2 Omicron JN.1	BNT162b2 Omicron KP.2
BioNTech	13	0	8	40	35	34
Pfizer	14	2	13	19	10	0
Fosun Pharma	0	0	1	1	1	0
Local MoH	2 ^a	0	0	0	0	0
Local Government	1 ^b	0	1	0	0	0

All	30	2	23	60	46	34
a. Moldova, Kenya.						
b. Ghana.						

In addition, World Health Organization (WHO) had approved the transition from the Emergency Use Listing (EUL) to Prequalification (PQ) of BNT162b2.

During the reporting period, the European Medicines Agency (EMA) approved the deletion of BNT162b2 Original (tozinameran), BNT162b2 (Original and Omicron Bivalent BA.1) (tozinameran/riltozinameran) and BNT162b2 (Original and Omicron Bivalent BA.4/BA.5) (tozinameran/famtozinameran) presentations for BNT162b2 at the request of the MAH for commercial reasons only.

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.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID-19 mRNA vaccine CDS version 29.0 dated 27 November 2024, in effect at the end of the reporting period and included in Appendix 1.

Four (4) previous CDS versions (version 25.0 dated 26 January 2024, version 26.0 dated 03 April 2024, version 27.0 dated 01 July 2024 and version 28.0 dated 09 September 2024) in effect during the reporting period, are included in Appendix 1.2, Appendix 1.3, Appendix 1.4 and Appendix 1.5, respectively.

The following safety-related changes were made during this reporting interval:

- Section 4.4 Special warnings and precautions for use (CDS version 28.0)
- Section 4.5 Interaction with other medicinal products and other forms of interaction (CDS version 29.0)
- Section 4.6 Fertility, pregnancy and lactation (CDS version 28.0)
- Section 4.8 Undesirable effects (CDS versions 25.0, 27.0, 28.0 and 29.0)
- Section 4.9 Overdose (CDS version 26.0)
- Appendix A and Appendix B (CDS versions 25.0, 27.0 and 28.0)

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

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 72,486^{8,9} participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

BNT162b2 original: 65,513 participants of which

- 35,589²⁷ received BNT162b2 original only (of which 167 were exposed *in utero*);
- 22,813 had received BNT162b2 original post-unblinding and had received placebo before (22,060) or vice-versa (753);
- 5393 received BNT162b2/placebo²⁸;
- 564 received BNT162b2/SIIV as first dose and placebo as second dose²⁹;
- 564 received placebo/SIIV as first dose and BNT162b2 as second dose²⁹;
- 78 received BNT162b2 original and also BNT162b1;
- 590 received BNT162b2 original and also BNT162b2 (B.1.351).³⁰

Variant and variant-adapted vaccines based on BNT162b2: 11,836 participants of which

- 753 received BNT162b2 (B.1.351)^{31,32};
- 372 received BNT162b2 (B.1.617.2);
- 768 received BNT162b2 (B.1.1.7 + B.1.617.2);
- 20 received BNT162b2 (B.1.1.7);
- 72 received BNT162b2 (B.1.1.529);^{27,33}
- 1814 received BNT162b2 Omi;

²⁷ A participant to a BioNTech study, who should have received BNT162b2 original, was erroneously administered with BNT162b2 (B.1.1.529), therefore the treatment group for this participant has been updated to BNT162b2 (B.1.1.529), instead of BNT162b2 original (as in PSUR #6).

²⁸ The increased with respect to PSUR #6 is mainly attributable to Study C4591031.

²⁹ The treatment arms for Study C4591030 were updated according to the final CSR, where participants in the coadministration and in the separate-administration groups were equally distributed (564 each).

³⁰ This includes participants who may have first been exposed to BNT162b2 and afterwards BNT162b2SA and vice versa. Many of these participants had several booster vaccinations with a different sequential exposure of BNT162b2 and BNT162b2SA (these are noted under treatment arm 'BNT162b2/BNT162b2SA' in Appendix 2.3).

³¹ Out of the total 753 participants who received BNT162b2 (B.1.351), 590 also received BNT162b2 (this is noted under treatment arm 'BNT162b2/ BNT162b2SA' in Appendix 2.3).

³² BNT162b2 (B.1.351), which is also referred to as BNT162b2s01 and BNT162b2sA.

³³ BNT162b2 (B.1.1.529) is a monovalent vaccine, which is also referred to as BNT162b2 Omi BA.1.

- 1814 received BNT162b2 bivalent (original/Omi);
- 102 received BNT162b2 bivalent [original/Omi BA.1 (B.1.1.529)];
- 2797 received BNT162b2 bivalent (original/Omi BA.4/BA.5);
- 2632 received BNT162b2 Omi XBB.1.5;
- 216 received BNT162b2 (Omi JN.1);
- 127 received BNT162b2 (Omi KP.2);
- 104 received BNT162b5 bivalent (original/Omi BA.2);
- 62 received BNT162b5 bivalent (original/Omi BA.4/BA.5);
- 60 received BNT162b6 bivalent (original/Omi BA.4/BA.5);
- 63 received BNT162b7 monovalent (Omi BA.4/BA.5);
- 60 had received BNT162b7 bivalent (original/Omi BA.4/BA.5).

Early development candidates: 522 participants of which

- 30 received BNT162a1;
- 300 received BNT162b1¹⁰;
- 96 received BNT162b3;
- 96 received BNT162c2.

Other treatments: 6524 participants (168 of them were exposed *in utero*) received 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 4 other Pfizer clinical development programs:

- B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026¹¹ [BNT162b2/20vPnC (187) and BNT162b2/placebo (185)];
- 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)/bIRV/QIV/, bivalent BNT162b2 (original/Omi BA.4/BA.5)/tIRV in the clinical study C5261001,¹² as a study vaccine. In CTs C5261002¹³ and C5261023¹⁴, 8750 and 1247 participants received blinded therapy, respectively.
- C548: 772 participants received BNT162b2 as a study vaccine in combination with QIV/RSVpreF (312) or RSVpreF/placebo (310) or placebo (150); 301 other participants received placebo/RSVpreF (152) or placebo/QIV (149) in study C5481001.¹⁵

- C568: 641 participants received blinded therapy in study C5681001.¹⁶

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

Of note, bivalent BNT162b2 (original/Omi BA.4/BA.5) or monovalent Omi XBB.1.5 are 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 BNT162-21.¹⁷

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

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

In the PRAC AR of the PSUR #4 (EMA/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

Previously publicly available regional information on vaccine doses administered is no longer consistently available for estimation of cumulative worldwide exposure. Currently, the ECDC website³⁴ contains data on COVID-19 vaccination in the EU/EEA since September 2023. EU/EEA Member States are requested to report basic indicators (number of individuals receiving one vaccine during the reporting period starting from 01 September 2023, vaccine product) and data by target groups, but not dose number.

5.2.1. Cumulative Exposure

Previously publicly available regional information on vaccine doses administered is no longer consistently available for estimation of cumulative worldwide exposure. The best estimate of the post-marketing exposure is based on the worldwide estimated cumulative number of shipped doses, which is detailed below.

MAH Data

The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group reported in the shipment tracker (Order Book)³⁵ from

³⁴ Data on COVID-19 vaccination in the EU/EEA.

³⁵ 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.

01 December 2020¹⁸ through 22 December 2024 is showed in Table 4. Approximately a total of 5,032,571,025³⁶ doses of BNT162b2 monovalent and bivalent presentations were shipped worldwide. Out of the cumulative number of shipped doses, 3,946,055,525 were monovalent original vaccine (including PBS and Tris/sucrose), 717,702,100 were bivalent vaccines and 368,813,400 were monovalent Omicron presentations (of which 237,508,600 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); cumulatively, there were 4,546,909,545 doses for adult¹⁹ presentations and 485,661,480 doses for paediatric²⁰ presentations. Overall, 2,588,253,585 doses of BNT162b2 (original, bivalent and monovalent) were shipped to ROW.²¹

Table 4. Cumulative Estimated Number of Shipped Doses by Vaccine Presentation, Region and Age Group

Age Group Vaccine Presentation → Region/Country ↓	Paediatrics				Adults			
	Original	Bivalent	Monovalent	Total	Original	Bivalent	Monovalent	Total
EU/EEA, US, Japan	166,965,500	21,606,900	12,548,840	201,121,240	1,519,322,120	478,411,740	245,462,340	2,243,196,200
ROW	276,122,200	2,424,400	5,993,640	284,540,240	1,983,645,705	215,259,060	104,808,580	2,303,713,345
Total	443,087,700	24,031,300	18,542,480	485,661,480	3,502,967,825	693,670,800	350,270,920	4,546,909,545

Table 5 through Table 10 show the worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group.

Table 5. Cumulative Estimated Number of Shipped Doses of 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)	22.3	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	501212015	587341115
US	13	13669300	64199800	433548635	511417735
Canada	1.9	1710000	6550000	67663380	75923380
Central and South America	15.6	24934800	87128300	502158915	614222015
Asia	29.9	15606600	135667000	1028214960	1179488560
Japan	7.1	10017600	16016400	252909540	278943540
Other Countries	22.8	5589000	119650600	775305420	900545020

³⁶ The total includes doses shipped for COVAX, USG Donation and EC Donation programs; it does not include CP data.

Table 5. Cumulative Estimated Number of Shipped Doses of Original by Region Worldwide and Age Group

Region/Country	% of Total Doses ^a	6-month – 4 years	5 – 11 years	≥12 years ^b	All
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	3502967825	3946055525

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 6. Cumulative Estimated Number of Shipped Doses of Bivalent BA.1 by Region Worldwide and Age Group

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

Table 7. Cumulative Estimated Number of Shipped Doses of 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	36.9	0	1814400	215963400	217777800
European Union (27)	33	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	862680	862680
Commonwealth of Independent States	0.9	0	0	5499360	5499360

Table 7. Cumulative Estimated Number of Shipped Doses of 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
North America	23.8	5321400	13278700	121649880	140249980
US	21.3	5321400	12455100	108015120	125791620
Canada	2.5	0	823600	13634760	14458360
Central and South America	11.8	63600	366000	69402600	69832200
Asia	22.9	0	3187200	131925210	135112410
Japan	17.1	0	2016000	98662590	100678590
Other Countries	5.8	0	1171200	33262620	34433820
Oceania	3.8	0	0	22282560	22282560
Australia/New Zealand	3.8	0	0	22245120	22245120
Other Countries	0	0	0	37440	37440
Africa	0.8	0	0	4557600	4557600
Total	100	5385000	18646300	565781250	589812550

Table 8. Cumulative Number of Estimated Shipped Doses of Monovalent 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	42.8	1339200	1817280	98423040	101579520
European Union (27)	34.3	883200	1480320	79123200	81486720
European Economic Area Countries (3)	0.8	9600	14400	1984320	2008320
Switzerland	0.2	0	0	476160	476160
UK	6	446400	250560	13567680	14264640
Other Countries	0.1	0	4800	331200	336000
Commonwealth of Independent States	1.3	0	67200	2940480	3007680
North America	20.4	2870760	2769000	42851200	48490960
US	15.7	2736360	2302440	32333440	37372240
Canada	4.7	134400	466560	10517760	11118720
Central and South America	4	2812800	759840	5918880	9491520
Asia	25.2	539400	1033920	58271040	59844360
Japan	16.6	441600	782400	38203200	39427200
Other Countries	8.6	97800	251520	20067840	20417160
Oceania	3.5	52800	24960	8192160	8269920
Australia/New Zealand	3.5	52800	15360	8131680	8199840
Other Countries	0	0	9600	60480	70080
Africa	4.1	0	14400	9817920	9832320
Total	100	7614960	6419400	223474240	237508600

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Table 9. Cumulative Number of Estimated Shipped Doses of Monovalent JN.1 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	78.9	631680	705600	54276680	55613960
European Union (27)	67.7	369600	570240	46798800	47738640
European Economic Area Countries (3)	1.5	5760	8640	1068480	1082880
Switzerland	0.5	0	8640	337640	346280
UK	9.1	256320	118080	6071760	6446160
Other Countries	0	0	0	0	0
Commonwealth of Independent States	0	0	0	0	0
North America	0	0	0	0	0
US	0	0	0	0	0
Canada	0	0	0	0	0
Central and South America	1.6	0	87840	1020000	1107840
Asia	10.7	4320	15360	7497260	7516940
Japan	2.2	0	0	1573920	1573920
Other Countries	8.4	4320	15360	5923340	5943020
Oceania	8.9	23040	96000	6158880	6277920
Australia/New Zealand	8.9	23040	96000	6158880	6277920
Other Countries	0	0	0	0	0
Africa	0	0	0	0	0
Total	100	659040	904800	68952820	70516660

Table 10. Cumulative Number of Estimated Shipped Doses of Monovalent KP.2 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	34.6	79200	141120	20810880	21031200
European Union (27)	24.3	74880	135360	14584320	14794560
European Economic Area Countries (3)	0.6	4320	5760	325440	335520
Switzerland	0	0	0	0	0
UK	9.7	0	0	5898240	5898240
Other Countries	0	0	0	2880	2880
Commonwealth of Independent States	0	0	0	0	0
North America	65.4	1501380	1222580	37032980	39756940
US	53	1501380	1222580	29467220	32191180
Canada	12.4	0	0	7565760	7565760
Central and South America	0	0	0	0	0
Asia	0	0	0	0	0
Japan	0	0	0	0	0
Other Countries	0	0	0	0	0
Oceania	0	0	0	0	0
Australia/New Zealand	0	0	0	0	0
Other Countries	0	0	0	0	0

Table 10. Cumulative Number of Estimated Shipped Doses of Monovalent KP.2 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Africa	0	0	0	0	0
Total	100	1580580	1363700	57843860	60788140

CP Data

Cumulative CP (Fosun) data on the number of original, bivalent and monovalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 11.

Table 11. Cumulative Administered Doses of Original, Bivalent BA.4/BA.5 and Monovalent Vaccine Presentations – Contractual Party Data

Region Country -Vaccine Presentation	Number of Administered Doses
Asia	32553932
Hong Kong	12235843
<i>Original^a</i>	<i>11451700</i>
- Original 30 mcg PBS and Tris	11407900
- Original 10 mcg Tris	19900
- Original 3 mcg Tris	23900
<i>Bivalent BA.4/BA.5 15/15 mcg^b</i>	<i>615883</i>
<i>Monovalent XBB.1.5^c</i>	<i>166090</i>
- Monovalent XBB.1.5 30 mcg	165085
- Monovalent XBB.1.5 10 mcg	1005
- Monovalent XBB.1.5 3 mcg	
<i>Monovalent JN.1^d</i>	<i>2170</i>
- Monovalent JN.1 30 mcg	2157
- Monovalent JN.1 10 mcg	13
- Monovalent JN.1 3 mcg	
Macau	424389
<i>Original + Bivalent BA.4/BA.5^e</i>	<i>399317</i>
<i>Monovalent XBB.1.5 30 mcg^f</i>	<i>24318</i>
<i>Monovalent JN.1 30 mcg^g</i>	<i>754</i>
Taiwan^h	19893700
<i>Original</i>	<i>19893700</i>
- Original 30 mcg PBS and Tris	17622400
- Original 10 mcg Tris	1931300
- Original 3 mcg Tris	340000

a. Cumulative period: through 15 July 2024.

b. Cumulative period: through 20 April 2024.

c. Cumulative period: through 19 November 2024.

d. Cumulative period: through 29 November 2024.

e. Cumulative period: through 08 February 2024. No discrimination between administration data for original and bivalent BA.4/BA.5 was possible.

f. Cumulative period: through 26 November 2024.

g. Cumulative period: through 14 December 2024.

h. Cumulative period: through 30 August 2023.

5.2.2. Interval Exposure

MAH Data

Approximately a total of 179,315,700³⁶ doses of BNT162b2 monovalent and bivalent presentations were shipped worldwide during the reporting interval from 18 December 2023²² through 22 December 2024, as shown in Table 12. Out of the shipped doses during the reporting period, 949,220 were original vaccine (Tris/sucrose), 2,140,020 were bivalent vaccines and 176,226,460 were monovalent presentations (of which 44,921,660 were XBB.1.5, 70,516,660 were JN.1 and 60,788,140 were KP.2, respectively); there were 169,235,820 doses for adult¹⁹ presentations and 10,079,880 doses for paediatric²⁰ presentations. Overall, 69,537,760 doses of BNT162b2 monovalent and bivalent presentations were shipped to ROW.²¹

Table 12. Interval Estimated Number of Shipped Doses by Vaccine Presentation, Region and Age Group

Age Group Vaccine Presentation → Region/Country ↓	Paediatrics				Adults			
	Original	Bivalent	Monovalent	Total	Original	Bivalent	Monovalent	Total
EU/EEA, US, Japan	0	0	5,523,360	5,523,360	30,500	0	104,224,080	104,254,580
ROW	0	72,000	4,484,520	4,556,520	918,720	2,068,020	61,994,500	64,981,240
Total	0	72,000	10,007,880	10,079,880	949,220	2,068,020	166,218,580	169,235,820

Table 13 and Table 14 show the worldwide estimated interval number of shipped doses by vaccine presentation (original, bivalent BA.4/BA.5 and XBB.1.5)³⁷ region and countries and by age group.

Table 13. Interval Estimated Number of Shipped Doses of 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	0	0	0	0
European Union (27)	0	0	0	0	0
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	0	0	0	0
Commonwealth of Independent States	0	0	0	0	0
North America	3.2	0	0	30500	30500
US	3.2	0	0	30500	30500
Canada	0	0	0	0	0
Central and South America	0	0	0	0	0

³⁷ No doses of bivalent BA.1 were shipped in the reporting period. For the reporting period, the number of doses shipped of monovalent JN.1 and monovalent KP.2 doses overlaps with the cumulative number of doses shipped for these 2 vaccine presentations; please refer to Section 5.2.1 Cumulative Exposure.

Table 13. Interval Estimated Number of Shipped Doses of Original by Region Worldwide and Age Group

Region/Country	% of Total Doses ^a	6-month – 4 years	5 – 11 years	≥12 years ^b	All
Asia	96.8	0	0	918720	918720
Japan	0	0	0	0	0
Other Countries	96.8	0	0	918720	918720
Oceania	0	0	0	0	0
Australia/New Zealand	0	0	0	0	0
Other Countries	0	0	0	0	0
Africa	0	0	0	0	0
Total	100	0	0	949220	949220

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 14. Interval Estimated Number of Shipped Doses of 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	0.5	0	0	10200	10200
European Union (27)	0	0	0	0	0
European Economic Area Countries (3)	0	0	0	0	0
Switzerland	0	0	0	0	0
UK	0	0	0	0	0
Other Countries	0.5	0	0	10200	10200
Commonwealth of Independent States	0	0	0	0	0
North America	0	0	0	0	0
US	0	0	0	0	0
Canada	0	0	0	0	0
Central and South America	36.5	6000	66000	707100	779100
Asia	43.1	0	0	918720	918720
Japan	0	0	0	0	0
Other Countries	43.1	0	0	918720	918720
Oceania	0	0	0	0	0
Australia/New Zealand	0	0	0	0	0
Other Countries	0	0	0	0	0
Africa	20.2	0	0	432000	432000
Total	100	0	66000	2068020	2134020

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

Table 15. Interval Estimated Number of Shipped Doses of Monovalent XBB.1.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses ^a	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	19.1	105600	227520	8247360	8580480
European Union (27)	11.5	100800	149760	4899840	5150400
European Economic Area Countries (3)	0	4800	5760	0	10560
Switzerland	0	0	0	15360	15360
UK	0.1	0	0	63360	63360
Other Countries	0.7	0	4800	328320	333120
Commonwealth of Independent States	6.7	0	67200	2940480	3007680
North America	15.3	874350	489370	5488780	6852500
US	15.3	874350	489370	5488780	6852500
Canada	0	0	0	0	0
Central and South America	19.8	2812800	759840	5302560	8875200
Asia	21.5	1800	136320	9506880	9645000
Japan	0	0	0	17280	17280
Other Countries	21.4	1800	136320	9489600	9627720
Oceania	2.5	52800	24960	1058400	1136160
Australia/New Zealand	2.4	52800	15360	997920	1066080
Other Countries	0.2	0	9600	60480	70080
Africa	21.9	0	14400	9817920	9832320
Total	100	3847350	1652410	39421900	44921660

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, bivalent and monovalent XBB.1.5 doses administered in Hong Kong, Macau and Taiwan, is provided in Table 16 below.³⁸

Table 16. Interval Administered Doses of Original, Bivalent BA.4/BA.5 and Monovalent Vaccine Presentations – Contractual Party Data

Region Country -Vaccine Presentation	Number of Administered Doses
Asia	206479
Hong Kong^a	183778
<i>Original</i>	<i>6400</i>
- Original 10 mcg Tris	1800
- Original 3 mcg Tris	4600
<i>Bivalent BA.4/BA.5 15/15 mcg^b</i>	<i>9118</i>

³⁸ For the reporting period, the number of doses shipped of monovalent JN.1 overlaps with the cumulative number of doses shipped for this vaccine presentation; please refer to Section 5.2.1 Cumulative Exposure.

Table 16. Interval Administered Doses of Original, Bivalent BA.4/BA.5 and Monovalent Vaccine Presentations – Contractual Party Data

Region Country -Vaccine Presentation	Number of Administered Doses
<i>Monovalent XBB.1.5^c</i>	<i>166090</i>
<i>- Monovalent XBB.1.5 30 mcg</i>	<i>165085</i>
<i>- Monovalent XBB.1.5 3 and 10 mcg</i>	<i>1005</i>
Macau	22701
<i>Original + Bivalent BA.4/BA.5^{c,d}</i>	235
<i>Monovalent XBB.1.5 30 mcg</i>	21712
Taiwan	0

- Interval period: 16 December 2023 through 15 July 2024.
- Interval period: 16 December 2023 through 20 April 2024.
- No discrimination between administration data for Original and Bivalent BA.4/BA.5 was possible.
- Interval period: 15 December 2023 through 08 February 2024.
- Interval period: 12 January 2024 through 19 November 2024.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 27.1 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 approved on 19 October 2022 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 2.2.9 displays, for the PM dataset, demographic interval data including ethnicity and race, when available.

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

Response

Please refer to the footnote 40 in this Section.

Appendix 2.2^{39,40} provides the overall (including monovalent [original and Omicron] and bivalent presentations) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. Appendix 2.2.1 through Appendix 2.2.8 provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [monovalent original, bivalent Omicron BA.1, bivalent Omicron BA.4/BA.5, Omicron, Multivalent NOS, Monovalent Omicron XBB.1.5, monovalent Omicron KP.2 and monovalent Omicron JN.1]. 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 2024 and the interval data are from 19 December 2023 to 18 December 2024. 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 2.2.8 totals, due to the fact that Appendix 2.2 through Appendix 2.2.8 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 2.2.9 displays, for the PM dataset, demographic interval data, including ethnicity and race when available.

³⁹ The interval data are notable for a large number of cases of monovalent original vaccine received in the current reporting period (15,186) with known event onset date and describing at least one event occurred in 2020 (21 cases) or in 2021 (10,124 cases) or in 2022 (4009 cases) or in 2023 (1714 cases) or in 2024 (1022 cases).

⁴⁰ During the reporting interval all the cases downloaded through EudraVigilance were included in the PM dataset.

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

Table 17 below summarises the study treatments in the clinical studies by original vaccine or the variant-adapted vaccine.

Table 17. Clinical Trials During the Reporting Period: Study Treatments – Original and Variant-Adapted Vaccines

Original	BNT162b2	C4591007, C4591015, C4591024, C4591031, C4591036 ^a , BNT162-17
Variant-Adapted Vaccines	BNT162b2 (B.1.1.7)	BNT162-17
	BNT162b2 (B.1.1.7 + B.1.617.2)	
	BNT162b2 (B.1.617.2)	
	BNT162b2 (B.1.1.529.1)	
	Original + Omi BA.1	C4591031, C4591036 ^a , C4591044
	Original + Omi BA.2 ^b	C4591044
	Original + Omi BA.4/BA.5	C4591036 ^a , C4591044, C4591048
	Omi BA.1	C4591031
	Omi BA.4/BA.5	C4591044
	Omicron XBB.1.5	C4591048, C4591054
	Omicron JN.1	C4591054
	Omicron KP.2	C4591048, C4591054

a. Low-Interventional.

b. BNT162b5.

7.1. Completed Clinical Trials

Safety Trials (see Appendix 4.1 for a list of completed interventional safety studies):

During the reporting period, there were 2 interventional safety studies (PASS) that were completed with final CSRs (C4591015 and C4591024) and are summarized in Table 18. Appendix 6.4 provides final study reports that became available during the reporting interval for all PASS.

Table 18. Summary of Results from PASS Completed During the Reporting Period

Protocol ID	Protocol Title	Conclusions
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.	BNT162b2 was safe and well-tolerated in maternal and infant participants. Among maternal participants who received BNT162b2, local reactions and systemic events following vaccination were predominantly mild to moderate in severity and short lived (median duration 1.0 to 3.0 days). Reactogenicity after each dose was generally higher among participants in the BNT162b2 group compared to what was observed in the placebo group. The frequency of maternal and infant participants with any AE/SAE reported from Dose 1 to 1 month after Dose 2 of BNT162b2 was similar to what was observed in the placebo group.

Table 18. Summary of Results from PASS Completed During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591015 <i>Cont'd</i>		No maternal participants had any AEs leading to withdrawal and none died. Two infants, 1 in the BNT162b2 group (HIV-positive maternal participant) and 1 in the placebo group, had fatal SAEs that were assessed by the investigator as not related to study intervention. Overall, there were few AESIs reported in infants from birth to 6 months of age. Numerical differences between infant participants with reported congenital anomalies were observed between groups, with anomalies reported in 8/156 participants in the BNT162b2 group and 2/159 in the placebo group. For each anomaly observed, the frequency difference between the BNT162b2 and placebo groups was low with 95% confidence intervals that encompassed zero. Apart from atrial septal defect, all anomalies were single occurrences. The clinical data were reviewed in the context of the available data on background rates of the observed congenital anomalies. Taking this and the low number of events reported in this study into consideration, the findings were not determined to be indicative of a safety risk for infants. There were no reports of myocarditis or pericarditis in maternal or infant participants during the study.
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.	Based on the available safety data from 124 participants (37, 65, 15 and 7 participants 2 to <5 years of age, 5 to <12 years age, 12 to <18 years age, and ≥ 18 years of age, respectively) from study vaccination through end of study, BNT162b2 at the age appropriate 3 μg, 10 μg, and 30 μg dose level was generally well tolerated across all age groups, and disease subsets, with mostly mild or moderate reactogenicity and few reported AEs. The majority of AEs were in the infections and infestations SOC and all AESIs were likely related to participant's underlying condition. There were no deaths and no SAEs assessed as related by the investigator.

Other Trials that Reported New Significant Safety/Efficacy Information

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

Remaining Trials

During the reporting interval, there were 4 completed clinical trials (BNT162-17, C4591007, C4591031, and C4591044) 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 19. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
BNT162-17	A Phase 2 trial to evaluate the safety and immunogenicity of SARS-CoV-2, monovalent and multivalent RNA-based vaccines in healthy participants.	<u>Safety</u> Based on the totality of the safety data, the BNT162b2-based variant vaccines BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.529), and BNT162b2 were generally well tolerated and had acceptable safety profiles in healthy participants at the doses tested. There were no SAEs related to IMP or AEs that led to treatment or study withdrawal. Two events of myocarditis (one SAE that was not related to IMP, and one non-serious AESI [PT: myocarditis; investigator term: probable myocarditis] that was related to IMP [BNT162b2 (B.1.617.2)]), and no events of pericarditis were reported. The safety profiles of the four BNT162b2-based variant vaccines were comparable with BNT162b2. <u>Immunogenicity</u> <i>Part A</i> - SARS-CoV-2 neutralizing antibody responses against the reference strain and B.1.1.7 and B.1.617.2 variants were induced in - BNT162b2-experienced participants administered one dose of 30 µg BNT162b2 (B.1.1.7), 30 µg BNT162b2 (B.1.617.2), or BNT162b2 or one or two doses of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2) and - COVID-19 vaccine-naïve participants administered two or three doses of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). <i>Part B</i> - In BNT162b2-experienced participants administered one dose of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2) or 30 µg BNT162b2 (B.1.617.2), descriptive analyses showed an induction of SARS-CoV-2 neutralizing antibody responses against the B.1.1.7 and B.1.617.2 variants that were higher than SARS-CoV-2 neutralizing antibody responses against the reference strain in BNT162-02 participants administered two doses of 30 µg BNT162b2: - Non-inferiority of both variant immune responses after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain immune response after two doses of BNT162b2 based on GMTs and SR rates were both met.

Table 19. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
BNT162-17 <i>Cont'd</i>		– Non-inferiority of the B.1.617.2 variant immune response after one dose of BNT162b2 (B.1.617.2) to the reference strain immune response after two doses of BNT162b2 based on GMTs and SR rates were both met. • Comparison of the reference strain immune response in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection at 3 weeks post-Dose 1 of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2) with that at 1 month after two doses of 30 µg BNT162b2 in BNT162-02 participants without evidence of infection was performed: Non-inferiority of the reference strain immune response based on GMR was met. – The GMT was substantially higher at 3 weeks post-Dose 1 of BNT162b2 (B.1.1.7 + B.1.617.2) in participants with evidence of prior SARS-CoV-2 infection than at 1 month after two doses of BNT162b2 in participants without evidence of infection. – Non-inferiority of reference strain immune response by SR rate was almost met, missing the non-inferiority margin by 0.04%. • For COVID-19 vaccine-naïve participants administered three doses of BNT162b2 (B.1.1.7 + B.1.617.2), second- and third-dose SARS-CoV-2 neutralizing antibody responses against the reference strain and B.1.1.7 and B.1.617.2 variants were detected. <i>Part C</i> • One dose of 30 µg BNT162b2 (B.1.1.529) or 30 µg BNT162b2 induced SARS-CoV-2 neutralizing antibody responses against the BA.1 variant. Based on the adjusted GMR, NTs were comparable for participants administered BNT162b2 (B.1.1.529) and participants administered BNT162b2. The percentage of participants showing a seroresponse to the BA.1 variant was 59.4% for participants administered one dose of 30 µg BNT162b2 (B.1.1.529) compared to 22.8% for participants administered one dose of 30 µg BNT162b2.
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	Additional safety data analyzed in this final CSR are consistent with previously reported results. There were no confirmed cases of myocarditis/pericarditis in Study C4591007. The low percentage of participants ≥5 to <12 years of age and ≥12 to <16 years of age with elevated troponin I levels at baseline and after vaccination with BNT162b2 in Study C4591007 are not suggestive of increased risk of subclinical myocarditis and pericarditis in individuals >5 to <12 years of age and >12 to <16 years, both male and female, after BNT162b2 vaccination.

Table 19. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
	candidate against COVID-19 in healthy children.	
C4591031	A Phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.	SSD: The tolerability and safety profile of BNT162b2 Omi when administered as a third, fourth, and/or fifth dose was safe and well tolerated and consistent with results previously reported in clinical studies for BNT162b2 30 µg in this age group. SSE: The tolerability and safety profile of monovalent BNT162b2 30 µg, monovalent BNT162b2 60 µg, monovalent BNT162b2 Omi 30 µg, monovalent BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 30 µg, and bivalent BNT162b2 + BNT162b2 Omi 60 µg up to 6 months after vaccination was acceptable and consistent with the known safety profile of BNT162b2 and previously reported AE profile for Omicron BA.1-modified BNT162b2 vaccines.
C4591044	An interventional, randomized, active-controlled, Phase 1/2/3 study to investigate the safety, tolerability, and immunogenicity of BNT162b RNA-based vaccine candidates in COVID-19 vaccine-experienced healthy individuals	Results for combined Cohort 2 and analyses (below) are for participants 18 through 55 (n=313) and >55 years of age (n=306) who received a 30 µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (Dose 4). Cohort 2 and Cohort 3 The safety profile within 6 months after vaccination (Dose 4) with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) at the 30 µg and 60 µg dose level was well tolerated across all age groups, with few reported AEs. The AE profile through 6 months after study vaccination consisted mainly of reactogenicity events, labelled reactions (eg, lymphadenopathy) and other AEs that occur in a general adult population. The incidence of severe and life-threatening events was low. No new or concerning safety findings were noted 6 months after vaccination.

7.2. Ongoing⁴¹ Clinical Trials

During the reporting period, there were 3 ongoing sponsor-initiated clinical trials.

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

- PASS:
 - **Original and Variant-Adapted Vaccines⁴²**
 - 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.
- Other trials where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.

Other Trials that Reported New Significant Safety/Efficacy Information

During the reporting period, there were no ongoing trials that reported new significant safety/efficacy information.

Remaining Trials

There were 2 ongoing CTs with variant-adapted version(s) of the vaccine (C4591048, and C4591054).

- **Variant-Adapted Vaccines⁴²**
 - 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.*

Study C4591048 reported 2 SAEs considered related to the vaccination by the investigator during the reporting period. Substudy A reported an event of pyrexia (1 day post vaccination) and Substudy E reported an event of seizure (12 days post vaccination).

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

⁴¹ Includes ongoing studies as well as studies in which patient enrollment and follow-up have been completed, but the analysis and CSR are in-progress.

⁴² Refer to Table 17 for the study treatments.

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 3 Pfizer-sponsored clinical development programs (C526, C548 and C568) and in another BioNTech-sponsored clinical development program (BNT162b4). See Section 7.5 below for details.

7.5. New Safety Data Related to Fixed Combination Therapies

During the reporting period, BNT162b2 was also administered as study vaccine in other Pfizer-sponsored clinical development programs of combinations with an investigational mRNA influenza vaccine in Study C5261001,¹² C5261002,¹³ C5261023,¹⁴ with QIV and RSV preF vaccines in Study C5481001,¹⁵ and with the recombinant influenza vaccine in Study C5681001.¹⁶

BNT162b2 was also being utilised as study vaccine 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

As per communication dated 26 September 2023 from Health Canada “As noted by the MAH and following the April 2023 PRAC meeting, it was recommended to terminate the Study C4591010 due to low enrollment with no further study reports required. The MAH will be requested to remove Study C4591010 from the Canadian addendum to reflect the updated RMP at the next regulatory opportunity”, no further study reports for study C4591010 is required.

Study C4591010 is no longer a Category 3 commitment in the EU-RMP version 9.0 by request from PRAC (procedure EMEA/H/C/005735/MEA 0.11.8). Thus, no interim/final reports were submitted to EMA during the reporting period. Please refer to Appendix 5.5 and Appendix 5.6 for the interim reports of studies C4591021 and C4591022 submitted in the reporting period, respectively.

Appendix 4.4 provides a list of non-interventional safety studies ongoing during the reporting period.

8.1. Completed Non-Interventional Studies

Safety studies

No safety studies were completed during the reporting period.

Other studies

During the reporting period, the studies C4591042, C4591053, C4591057, and C4591060 were completed.⁴³ No new safety information emerged from these non-interventional studies; the summary of results from these studies is provided in Table 20.

Table 20. Summary of Results from Completed NISs During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591042	Patient characteristics, healthcare resource utilization and costs among patients with COVID-19 in England	This retrospective cohort study quantified COVID-19 HCRU and associated costs in England. Although the burden of COVID-19 has reduced following the roll-out of COVID-19 vaccines in the UK, substantial economic burden due to COVID-19 was observed on the NHS. Importantly, this study showed much of the burden during the study period was driven by COVID-19-related hospitalisations, and that older adults are associated with higher burden. Findings from this study can be used to inform the long-term strategy for resource allocation in the management of COVID-19.
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.	Vaccination against COVID-19 may reduce the risk of long COVID in both immunocompetent and immunocompromised patients. However, no association was found between frequency of primary care visits and vaccination among patients diagnosed in 2021. Future studies with larger sample size, higher vaccine uptake, and longer study periods during the pandemic are needed to further quantify the impact of vaccination on long COVID.

⁴³ In the reporting period of the latest PSUR (19 June 2023 through 18 December 2023), the NIS C4591050 “*Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance*” was completed. No new safety information emerged from this study.

Study C4591066 “*Patient characteristics, healthcare resource utilization and costs associated with long covid in France: an observational study using general practitioner electronic health records*” has been removed from the list of NIS because this study was brand agnostic and did not capture any COVID vaccine or vaccination information.

Table 20. Summary of Results from Completed NISs During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591057	Special investigation for booster immunization in children aged 6 months to 4 years	Booster immunization with Comirnaty is well-tolerated in children aged 6 months to 4 years. Based on the results of this study, there are no new safety concerns or risks were identified in this study.
C4591060	HRU and costs associated with COVID - 19 in Colombia: a retrospective large database study.	Most COVID patients were treated only in an outpatient setting mirroring low-cost expenses. However, for severe and critical COVID cases the total healthcare costs were substantially higher due to the LoS in general ward and ICU.

8.2. Ongoing Non-Interventional Studies

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

- PASS: Non-interventional studies C4591009,⁴⁴ C4591010,⁴⁵ C4591021,⁴⁴ C4591022,⁴⁴ C4591038,⁴⁴ C4591049,⁴⁶ C4591051,⁴⁷ C4591052, C4591055,⁴⁸ and C4591062⁴⁹ are PASS. No clinically important information has emerged from PASS. Summary of the interim report of the NISs C4591021 and C4591022 submitted during the reporting period is available in Appendix 5.5 and Appendix 5.6, respectively.⁵⁰

⁴⁴ Studies C4591009, C4591021, C4591022, and C4591038 are requirements by the US FDA and are Category 3 commitments in the EU-RMP version 13.2. For study C4591009, an interim CSR was submitted to the US FDA and EMA 30 April 2024 (no new safety information reported); final CSR will be submitted by 31 March 2026.

⁴⁵ Study C4591010 is no longer a Category 3 commitment in the EU-RMP version 9.0 by request from PRAC (procedure EMEA/H/C/005735/MEA 0.11.8). Thus, no interim/final reports were submitted to EMA during the reporting period.

⁴⁶ Study C4591049 is a voluntary study designed to provide real-world safety information on a cohort of people receiving the Pfizer-BioNTech COVID-19 vaccine. Interim report 1 was submitted to FDA (28 February 2024) during the reporting period.

⁴⁷ Study C4591051 is no longer a Category 3 commitment in the EU-RMP 13.1 as agreed upon by PRAC (procedure EMEA/H/C/005735 MEA/064.3).

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

⁴⁹ The interim CSR was submitted to the US FDA on 28 June 2024.

⁵⁰ Interim CSR was published in March 2024 for study C4591021 and in January 2024 for study C4591022.

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

Other Studies

There were 8 ongoing non-interventional studies:

- C4591014,⁵¹ *Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- C4591025,⁵² *A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.*
- C4591034, *Patient-Reported Outcomes Associated With COVID-19 and Influenza: A Prospective Survey Study on Outpatient Symptomatic Adults with Test-Confirmed Illness in the United States.*
- C4591059, *Use and Effectiveness of COVID-19 Vaccines using state vaccine registries and insurance claims data.*
- C4591065, *Effectiveness of BNT162b2 formulations using state vaccine registry and insurance claims data.*
- C4591068, *Estimated Vaccine Effectiveness (VE) and Durability of Pfizer/BioNTech 2024–2025 COVID-19 (Coronavirus Disease 2019) Vaccine.*
- C4591071, *COENZA: Study on COVID-19 and Influenza vaccinations based on a sample of the French National Health Insurance database (ESND).*
- C4591072, *Korean Post Marketing Surveillance for Comirnaty Injection.*

An interim report from Study C4591062 was completed during the reporting period. This non-interventional study used US commercial claims data from the Optum pre-adjudicated medical and adjudicated pharmacy claims database and included 113,459 individuals who received the COMIRNATY 2023-2024 Formula between 11 September 2023 and 15 January 2024. The interim report did not identify any new safety signals associated with vaccination with the COMIRNATY 2023-2024 Formula, although the study may be underpowered due to a short accrual period and a small number of events. Among individuals who received a seasonal influenza vaccination on the same day as the COMIRNATY 2023-2024 Formula, there was a non-significant increased incidence of non-febrile convulsions/seizures (relative incidence in the risk window compared to the control window: 3.18; 95% CI: 0.93–14.32), although this estimate is based on few events.

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

⁵¹ PAM-MEA-013.

⁵² Study C4591025 is a committed study, which was requested by the Ministry of Food and Drug Safety in Korea.

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-MAH sponsored clinical trials/studies.

9.2. Medication Errors

Analysis of the safety database

Cases potentially indicative of medication errors⁵³ that occurred in the reporting period are summarised below.

Of the 6238 cases, 596⁵⁴ 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 504 cases.
- 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 92 cases.

Clinical Trial Data

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

⁵³ Medication errors search criteria: MedDRA (version 27.1): *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; 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 additional condition for nonprescription use; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Issue with additional condition for nonprescription use; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product knowledge deficit; 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; 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.

⁵⁴ Among the 596 cases, 42 cases involved paediatric subjects 6 months to 4 years and 207 cases involved children 5 through 11 years.

Post-Authorisation Data

- Number of cases: 5642 cases reporting 15,019 events (16.2% of 34,843 cases, the total PM dataset) indicative of potential medication errors were retrieved in the current 1-year reporting period compared to 7880 relevant cases (7.4%) analysed in the PSUR #6 covering a 6-month period. An increased reporting rate in medication errors has been observed in this reporting period, however the interval data are notable for a large number of cases (1009) of monovalent original vaccine received in the current reporting period with known medication error onset date and describing at least one medication error occurred in 2020 (5 cases) or in 2021 (960 cases) or in 2022 (168 cases) or in 2023 (56 cases) or in 2024 (20 cases).
- The 5642 relevant medication error cases originated ($\geq 2\%$ of cases) from the following countries: US (2489), Japan (681), Germany (477), UK (406), Australia (372), France (283), Canada (223), Norway (172), and Sweden (113).
- The most frequently reported ($\geq 2\%$) medication error PTs included Poor quality product administered (3181),⁵⁵ Product administration error (2418), Inappropriate schedule of product administration (1081), Product temperature excursion issue (631), Expired product administered (363), Incorrect route of product administration (241), Product preparation error (234), Underdose (227), Wrong product administered (183), Incorrect dose administered (153), Product preparation issue (118).
- Clusters of medication errors were reported in three instances. The medication error cases (>300) were identified and coded to the PTs Poor quality product administered, Product administration error, and Product temperature excursion issue. No cases demonstrated harm, and none had co-reported events: in 371 cases (US), it was reported that the provider administered BNT162b2 for 12 years and older single dose vials given past BUD, in 341 cases (Japan) it was reported that BNT162b2 was accidentally stored frozen (-18 centigrade) was thawed and used for vaccination and in 301 cases (Australia), expired vaccine was administered.

9.2.1. Medication Errors Categorisation

Among the medication error cases (5642 cases), compared to 7880 medication errors in the PSUR #6, 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)]: 278 cases (4.9%) compared to 303 cases (3.8%) in the PSUR #6. The clinically relevant co-reported

⁵⁵ Of the 3181 cases reporting the PT Poor quality product administered, the PT was reported as non-serious occurrence in all but 1 event. In this serious case the lot number was unknown, and no product investigation was performed. Product investigation was reported in 36 cases non-serious cases. No related quality issues were identified during the investigation. There is no impact on product quality, regulatory, validation, stability.

events (≥ 10) were coded to the PTs Vaccination site pain (45), Pain in extremity (44), Headache (41), Fatigue, Arthralgia (26 each), Myalgia (21), Dizziness, Pyrexia, Nausea (19 each), Dyspnoea, Pain (15 each), Vaccination site erythema, Malaise (11 each), Palpitations, Back pain and Asthenia (10 each).

- Medication errors without harm [i.e., not resulting in adverse reaction(s)]: 5357 cases (94.9%) compared to 7571 (96.1%) in the PSUR #6.
- Potential medication errors: 5 cases (0.1%) compared to 6 cases (0.1%) in the PSUR #6.
- Intercepted medication errors: 2 cases (0.04%) compared to no cases in the PSUR #6.

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

Cases are clustered in monovalent original or bivalent or multivalent NOS or monovalent Omicron XBB.1.5 or Omicron JN.1 or Omicron KP.2 according to the vaccine formulation administered as last suspect dose.

9.2.2. Medication Errors in Subjects aged 6 Months through <5 Years⁵⁶

- Number of relevant cases: 336.
- Country/region of incidence: US (326), Japan (7), Canada, (3).
- Number of relevant events: 570.
- Relevant event seriousness: non-serious (570).
- Relevant medication errors PTs most frequently reported (≥ 10): Poor quality product administered (156), Product preparation error (128), Product administration error (104), Product preparation issue (57), Underdose (56), Expired product administered (24), Product temperature excursion issue (19), Inappropriate schedule of product administration (10).

Table 21 describes for each ME category the top 3 medication errors by vaccine presentation in individuals aged 6 months through <5 years.

Table 21. 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	Inappropriate schedule of product administration	0	1	1
	Bivalent BA.1	-	0	0	0

⁵⁶ Cases where the age was reported as “Infant” (78 cases) were evaluated in this age group.

Table 21. 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 <i>Cont'd</i>	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	Product preparation error	0	3	3
		Incorrect dose administered	0	2	2
		Product preparation issue	0	1	1
	Omicron JN.1	-	0	0	0
	Omicron KP.2	Product preparation error	0	3	3
		Product preparation issue	0	1	1
		Poor quality product administered	0	1	1
Medication Errors without harm	Original	Incorrect dose administered	0	3	3
		Inappropriate schedule of product administration	0	3	3
		Poor quality product administered	0	3	3
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	Wrong product administered	0	2	2
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	Poor quality product administered	0	104	104
		Product administration error	0	82	82
		Underdose	0	46	46
	Omicron JN.1	Product preparation error	0	1	1
	Omicron KP.2	Product preparation error	0	76	76
		Poor quality product administered	0	49	49
		Expired product administered	0	21	21
Potential Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0
Intercepted Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0

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9.2.3. Medication Errors in Subjects aged 5 through <12 Years⁵⁷

- Number of relevant cases: 401.
- Country/region of incidence: US (380), Canada (5), Australia and UK (4 each), Argentina, Brazil, Japan (2 each), Belgium and Germany (1 each)
- Number of relevant events: 766.
- Relevant event seriousness: non-serious (766).
- Relevant medication errors PTs most frequently reported (>10): Poor quality product administered (326), Product administration error (240), Product temperature excursion issue (66), Expired product administered (59).

Table 22 describes for each ME category the top 3 medication errors that occurred by vaccine presentation in individuals aged 5 through <12 years.

Table 22. 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	Accidental exposure to product by child	0	1	1
		Exposure via skin contact	0	1	1
		Incorrect route of product administration	0	1	1
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0
Medication Errors without harm	Original	Expired product administered	0	12	12
		Inappropriate schedule of product administration	0	5	5
		Poor quality product administered	0	3	3
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	Wrong product administered	0	3	3
		Product administration error	0	1	1
		Medication error	0	1	1
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	Poor quality product administered	0	244	244
		Product administration error	0	191	191
		Product temperature excursion issue	0	54	54

⁵⁷ Cases where the age was reported as “Child” (283 cases) were evaluated in this age group.

Table 22. 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 <i>Cont'd</i>	Omicron JN.1	Product administration error	0	4	4
		Poor quality product administered	0	4	4
	Omicron KP.2	Poor quality product administered	0	74	74
		Product administration error	0	41	41
		Expired product administered	0	20	20
Potential Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0
Intercepted Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0

9.2.4. Medication Errors in Subjects aged 12 Years and Older⁵⁸

- Number of cases: 2458.
- Country/region of incidence ($\geq 2\%$): US (505), Germany (442), UK (255), France (219), Japan (204), Canada (172), Norway (166), Sweden (109), Argentina (66).
- Number of relevant events: 3223.
- Relevant event seriousness: non-serious (3180), serious (43).
- Relevant medication errors PTs most frequently reported (>10): Inappropriate schedule of product administration (1000), Poor quality product administered (643), Product administration error (568), Incorrect route of product administration (216), Expired product administered (160), Wrong product administered (151), Incorrect dose administered (110), Underdose (92), Product temperature excursion issue (66), Medication error (48), Accidental exposure to product (27), Product administered at inappropriate site (21), Accidental overdose (16), Product storage error (13), Product

⁵⁸ Cases where the age was reported as: “Adolescent” (4 cases), “Adult (161 cases) or “Elderly” (188 cases) were evaluated in this age group.

label issue, Product preparation issue, Vaccination error, Wrong technique in product usage process (12 each).

Table 23 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 23. 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	Incorrect route of product administration	0	62	62
		Inappropriate schedule of product administration	0	46	46
		Wrong product administered	9	2	11
	Bivalent BA.1	Product administered at inappropriate site	0	3	3
		Wrong product administered	3	0	3
		Product administration error	0	1	1
	Bivalent BA.4/BA.5	Wrong product administered	11	3	14
		Incorrect route of product administration	1	3	4
		Product administration error	0	2	2
	Multivalent NOS	Wrong technique in product usage process	0	1	1
	Omicron XBB.1.5	Incorrect route of product administration	1	16	17
		Incorrect dose administered	0	17	17
		Wrong product administered	7	2	9
	Omicron JN.1	Incorrect route of product administration	0	6	6
		Incorrect dose administered	0	5	5
		Product administration error	0	4	4
	Omicron KP.2	Incorrect route of product administration	0	6	6
		Incorrect dose administered	0	3	3
		Product administration error	0	1	1
Medication Errors without harm	Original	Inappropriate schedule of product administration	1	939	940
		Incorrect route of product administration	0	86	86
		Wrong product administered	42	8	50
	Bivalent BA.1	Wrong product administered	8	0	8
		Inappropriate schedule of product administration	2	2	4
		Vaccination error	0	2	2
	Bivalent BA.4/BA.5	Wrong product administered	52	18	70
		Medication error	1	30	31
		Incorrect dose administered	0	8	8
	Multivalent NOS	Vaccination error	0	1	1
		Inappropriate schedule of product administration	0	1	1

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Table 23. 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 <i>Cont'd</i>	Omicron XBB.1.5	Poor quality product administered	1	530	531
		Product administration error	1	489	490
		Expired product administered	0	132	132
	Omicron JN.1	Poor quality product administered	0	66	66
		Product administration error	0	55	55
		Incorrect route of product administration	0	24	24
	Omicron KP.2	Underdose	0	51	51
		Poor quality product administered	1	46	47
		Product temperature excursion issue	0	26	26
Potential Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	Circumstance or information capable of leading to medication error	0	1	1
	Omicron JN.1	Circumstance or information capable of leading to medication error	0	1	1
	Omicron KP.2	-	0	0	0
Intercepted Error	Original	-	0	0	0
	Bivalent BA.1	-	0	0	0
	Bivalent BA.4/BA.5	-	0	0	0
	Multivalent NOS	-	0	0	0
	Omicron XBB.1.5	-	0	0	0
	Omicron JN.1	-	0	0	0
	Omicron KP.2	-	0	0	0

9.2.5. Medication Errors in Subjects with Unknown Age

- Number of cases: 2447.
- Country/region of incidence ($\geq 2\%$): US (1278), Japan (468), Australia (337), UK (147), France (64).
- Number of relevant events: 4585.
- Relevant event seriousness: non-serious (4581), serious (4).
- Relevant medication errors PTs most frequently reported ($>2\%$): Poor quality product administered (2056), Product administration error (1506), Product temperature excursion

issue (480), Expired product administered (120), Product preparation error (90), Underdose (71), Inappropriate schedule of product administration (65).

Table 24 below describes for each ME category the top 3 medication errors occurred by vaccine presentation when the vaccine presentation is unknown age.

Table 24. 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	2
		Inappropriate schedule of product administration	2
		Product administered at inappropriate site	1
	Bivalent BA.1	Wrong product administered	1
	Bivalent BA.4/BA.5	Incorrect dose administered	1
	Multivalent NOS	Wrong product administered	1
		Inappropriate schedule of product administration	1
	Omicron XBB.1.5	Product administration error	2
		Poor quality product administered	2
		Incorrect dose administered	1
	Omicron JN.1	Product administered at inappropriate site	1
	Omicron KP.2	Product administered at inappropriate site	1
		Poor quality product administered	1
		Incorrect dose administered	1
Medication Errors without harm	Original	Poor quality product administered	651
		Product temperature excursion issue	343
		Product administration error	307
	Bivalent BA.1	Wrong technique in product usage process	1
		Wrong product administered	1
	Bivalent BA.4/BA.5	Poor quality product administered	7
		Expired product administered	6
		Product administration error	4
	Multivalent NOS	Expired product administered	2
	Omicron XBB.1.5	Poor quality product administered	1209
		Product administration error	1109
		Expired product administered	89
	Omicron JN.1	Poor quality product administered	60
		Product administration error	52
		Accidental underdose	21
	Omicron KP.2	Poor quality product administered	133
		Product temperature excursion issue	66
		Product preparation error	43
Potential Error	Original	-	0
	Bivalent BA.1	-	0
	Bivalent BA.4/BA.5	-	0
	Multivalent NOS	-	0
	Omicron XBB.1.5	Circumstance or information capable of leading to medication error	2
		Product label confusion	1
	Omicron JN.1	Circumstance or information capable of leading to medication error	1
	Omicron KP.2	-	0

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Table 24. Medication Error Categories: Top 3 Medication Errors in Unknown Age Group by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Total
Intercepted Error	Original	-	0
	Bivalent BA.1	-	0
	Bivalent BA.4/BA.5	-	0
	Multivalent NOS	-	0
	Omicron XBB.1.5	Intercepted product selection error	1
	Omicron JN.1	Product prescribing error	1
		Intercepted product prescribing error	1
	Omicron KP.2	-	0

Conclusion

Overall, among the 5642 relevant PM medication error cases, 278 cases (0.8% of the total interval cases, 4.9% 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.

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.*

On 12 December 2024, the PRAC requested the MAH *to include and provide a reflection/discussion on the recently published paper regarding long-term sequelae of myocarditis after mRNA COVID-19 vaccine administration, in the next PSUR, due for submission by 26 February 2025.*

Myocardial injury safety signal for mRNA COVID-19 vaccines (MACiV study findings)
Background:

Reference – Jain SS, Anderson SA, Steele JM, et al. *Cardiac manifestations and outcomes of*

COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13.

Response

Please refer to the content of Appendix 5.1 for the full assessment; the MAH conclusion is reported below.

MAH Conclusion

Long term outcomes and CMR findings have been subject to close monitoring for myocarditis. Jain et al, does not meet the requirements for a new safety signal, as it does not provide a new aspect of the myocarditis association with Comirnaty. Importantly, the authors stated that patient-centered clinical outcomes are reassuring. Additionally, this study focuses on a primary outcome (i.e., abnormal imaging finding) that has an uncertain applicability on clinical practice, and hence, on the overall benefit-risk profile of the product. Finally, a larger study with longer follow-up reporting on clinical (rather than imaging) outcomes has been recently published (Semenzato et al, in the Clinical subsection below). In this study, the authors found that patients with post-vaccine myocarditis, contrary to those with post-COVID-19 myocarditis, present a more favorable prognosis when compared to conventional myocarditis.

Overall, myocarditis is an ADR of the vaccine that is listed in the label of Comirnaty, an important identified risk in the RMP and is subject to close monitoring using routine and additional PV activities. To further elucidate the long term outcomes, the MAH currently conducts a low-interventional study using primary data from the Pediatric Heart Network (PHN), a NIH-funded consortium of leading research hospitals across the US, Canada, and other countries that conducts research in cardiovascular disease, to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period (C4591036). The MAH will continue to closely monitor this topic.

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 4 clinical studies that presented relevant safety findings on myocarditis cases after vaccination with any BNT162b2 vaccine presentation. The first one of these publications is the one for which the PRAC asked the

MAH to discuss it, while the other 3 provide important information characterising the known myocarditis risk and are presented below.

1. Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. *Lancet*. 2024;76:1-13. <https://doi.org/10.1016/j.eclim.2024.102809>

Please refer to Appendix 5.1 for the full assessment.

2. Semenzato L, Le Vu S, Botton J, et al. Long-Term Prognosis of Patients With Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies. *JAMA*. 2024;332:1367-77.

Importance: Although patients with myocarditis after COVID-19 mRNA vaccination appear to have a good prognosis near hospital discharge, their longer-term prognosis and management remain unknown.

Objective: To study the cardiovascular complications of post-COVID-19 mRNA vaccination myocarditis and other types of myocarditis during an 18-month follow-up, as well as disease management based on a study of the frequency of medical procedures and drug prescriptions.

Design, setting, and participants: In this cohort study based on the French National Health Data System, all individuals aged 12 to 49 years hospitalised for myocarditis in France between December 27, 2020, and June 30, 2022, were identified.

Exposure: Individuals were categorized as having postvaccine myocarditis (within 7 days after COVID-19 mRNA vaccine), post-COVID-19 myocarditis (within 30 days of SARS-CoV-2 infection), or conventional myocarditis.

Main outcomes and measures: The occurrence of clinical outcomes (hospital readmission for myopericarditis, other cardiovascular events, all-cause death, and a composite outcome of these events) over the 18 months following hospital admission were analyzed using weighted Cox models to standardize the comparisons with the conventional myocarditis group. Also, medical management after hospital discharge was longitudinally assessed using generalized estimated equation models.

Results: In total, 4635 individuals were hospitalised for myocarditis: 558 with postvaccine myocarditis, 298 with post-COVID-19 myocarditis, and 3779 with conventional myocarditis. Patients with postvaccine myocarditis were younger than those with post-COVID-19 and conventional myocarditis (mean [SD] age of 25.9 [8.6], 31.0 [10.9], and 28.3 [9.4] years, respectively) and were more frequently men (84%, 67%, and 79%). Patients with postvaccine myocarditis had a lower standardized incidence of the composite clinical outcome than those with conventional myocarditis (32/558 vs 497/3779 events; weighted hazard ratio, 0.55 [95% CI, 0.36-0.86]), whereas individuals with post-COVID-19 myocarditis had similar results (36/298 events; weighted hazard ratio, 1.04 [95% CI, 0.70-1.52]). The standardized frequency of medical procedures and

drugs prescribed in patients with postvaccine myocarditis or post-COVID-19 myocarditis followed a similar trend in the 18 months following hospital discharge to that of patients with conventional myocarditis.

Conclusions and relevance: Patients with post-COVID-19 mRNA vaccination myocarditis, contrary to those with post-COVID-19 myocarditis, show a lower frequency of cardiovascular complications than those with conventional myocarditis at 18 months. However, affected patients, mainly healthy young men, may require medical management up to several months after hospital discharge.

3. Choi Y, Lee JS, Choe YJ, et al. Myocarditis and Pericarditis are Temporally Associated with BNT162b2 COVID-19 Vaccine in Adolescents: A Systematic Review and Meta-analysis. *Pediatr Cardiol.* 2024 Oct 15. doi: 10.1007/s00246-024-03618-2.

The incidence of myocarditis and pericarditis has been documented in adolescents after COVID-19 vaccinations. This study aims to assess the risk of myopericarditis in adolescents following COVID-19 vaccination, using a meta-analysis of the published cases. A comprehensive literature search of the following databases on July 5, 2023: MEDLINE, EMBASE, PubMed, and the Cochrane Library was performed. The authors performed a meta-analysis using a random-effects model to estimate the incidence of myopericarditis per million of administered COVID-19 vaccine doses or COVID-19 infections. A total of 33 studies were included in the meta-analysis. The incidence of myopericarditis per million COVID-19 infections (1583.9 cases, 95% CI 751.8-2713.8) was approximately 42 times higher than that for COVID-19 vaccine administrations (37.6 cases, 95% CI 24.2-53.8). The risk of myopericarditis after COVID-19 vaccination was particularly high among the 16-19 age group (39.5 cases per million, 95% CI 25.8-56.0), males (43.1 cases per million, 95% CI 21.6-71.9), and those who received the second dose (47.7 cases per million, 95% CI 22.2-82.2). There were no significant differences in the incidence of myopericarditis per million COVID-19 vaccine administrations between Europe, the Western Pacific, and the Americas ($p = 0.51$). Adolescents faced a potential risk of myopericarditis after COVID-19 vaccination, but this risk is less harmful than that of myopericarditis following COVID-19 infection.

4. Albertson TE, Hansen C, Bihari S, et al. Serum Troponin I Assessments in 5- to 30-Year-Olds After BNT162b2 Vaccination. *Infect Dis Ther.* 2024;13(4):699-714.

Introduction: Rare myocarditis and pericarditis cases have occurred in coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine recipients. Troponin levels, a potential marker of myocardial injury, were assessed in healthy participants before and after BNT162b2 vaccination.

Methods: Vaccine-experienced 12- to 30-year-olds in phase 3 crossover C4591031 Substudy B (NCT04955626) who had two or three prior BNT162b2 30- μ g doses were randomized to receive BNT162b2 30 μ g followed by placebo, or placebo followed by BNT162b2 30 μ g, 1 month apart. A participant subset, previously unvaccinated against COVID-19, in the phase 3 C4591007 study (NCT04816643) received up to three vaccinations (BNT162b2 10 μ g or placebo [5- to 11-year-olds]) or open-label BNT162b2

30 µg (12- to 15-year-olds). Blood samples collected pre-vaccination, 4 days post-vaccination, and 1-month post-vaccination (C4591031 Substudy B only) were analyzed. Frequencies of elevated troponin I levels (male, > 35 ng/l; female, > 17 ng/l) were assessed.

Results: Percentages of 12- to 30-year-olds (n = 1485) in C4591031 Substudy B with elevated troponin levels following BNT162b2 or placebo receipt were 0.5% and 0.8% before vaccination, 0.7% and 1.0% at day 4, and 0.7% and 0.5% at 1 month, respectively. In Study C4591007 (n = 1265), elevated troponin I levels were observed in 0.2, 0.4, and 0.2% of 5- to 11-year-old BNT162b2 recipients at baseline and 4 days post-dose 2 and 3, respectively; corresponding values in 12- to 15-year-olds were 0.4, 0.4, and 0.7%. No 5- to 11-year-old placebo recipients had elevated troponin levels. No myocarditis or pericarditis cases or deaths were reported.

Conclusions: Among 5- to < 30-year-olds in both studies, troponin levels were rarely elevated ($\leq 1.0\%$) and similar before and post-vaccination; troponin levels were also similar between BNT162b2 and placebo in 12- to 30-year-old and 5- to 11-year-old recipients in the respective studies. No myocarditis or pericarditis cases were reported. These findings did not provide evidence that BNT162b2 causes troponin elevations. No utility of routine measurement of troponin levels in asymptomatic BNT162b2 recipients was identified.

Myocarditis is an important identified risk; please refer to Section 16.3.1.1.1 *Important Identified Risks – Myocarditis* for the cases retrieved in the reporting period and for the evaluation of this important identified risk.

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.

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 EU-RMP version 14.0 was submitted for upversioning of RMP version 13.2 following positive CHMP Opinion, dated 16 January 2025, for the grouped Type II variation EMA/VR/0000231586.

This grouped Type II variation included an updated RMP (based on version 13.0) to remove the following studies/milestones from Part III.2 Part V, Part VI and Annexes as applicable: C4591007, C4591015, C4591024, C4591031 (SSE), C4591044, C4591014, WI255886 and C4591051. New milestone, key objectives, design and study population of study C4591048 were aligned according to protocol amendment #5. A new milestone for CSR submission of study C4591021 was also proposed due to the need to collect all necessary data and conduct analyses and quality control checks for the final study report. Whereas all data were extracted, and variables created, the end of data collection requires further time to be completed for the reasons outlined in the corresponding justification document which was provided in the approved EMA/VR/0000231586 procedure (CHMP Opinion received 16 January 2025).

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

Signal Overview

New signals detected, signals with ongoing evaluations, and signals that were closed during the reporting interval are presented below in Table 25. 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 monovalent (original, Omicron XBB.1.5, Omicron JN.1, Omicron KP.2), and bivalent (Omicron BA.1 and Omicron BA.4/BA.5) vaccine presentations.

Table 25. Overview of Signals (at DLP 18 December 2024)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Migraine	New and Closed	Enquiry from a Regulatory Authority (Australia TGA)	Not a risk	N/A
Transverse myelitis	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Subacute thyroiditis	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Erectile dysfunction	New and Closed	Enquiry from a Regulatory Authority (Rwanda FDA)	Not a risk	N/A
Hypertension	New and Closed	Enquiry from a Regulatory Authority (Rwanda FDA)	Not a risk	N/A
Giant cell arteritis	New and Closed	Enquiry from a Regulatory Authority (Rwanda FDA)	Not a risk	N/A

Table 25. Overview of Signals (at DLP 18 December 2024)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Exacerbation of diabetes mellitus	New and Closed	Enquiry from a Regulatory Authority (Rwanda FDA)	Not a risk	N/A
Exacerbation of adrenal insufficiency	New and Closed	Enquiry from a Regulatory Authority (Rwanda FDA)	Not a risk	N/A
Tongue discolouration	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Sciatica	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Tonsillitis	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Erysipelas	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Angina bullosa haemorrhagica	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Polycystic ovaries	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Cerebral amyloid angiopathy	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Cough	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Aphasia	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Disturbance in attention	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Myocardial necrosis marker increased	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Pelvic pain	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Paralysis	New and Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Pulmonary embolism	Closed	Enquiry from a Regulatory Authority (SFDA)	Not a risk	N/A
Post-menopausal haemorrhage	Closed	Enquiry from a Regulatory Authority (EMA/PRAC)	Not a risk	EPITT No. 19989

* 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

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUSA/00010898/202312), the following request was made: *The MAH was requested to 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-ratios⁵⁹ were*

⁵⁹ On 06 November 2024, the MAH received the positive EMA feedback about the request to discontinuing O/E analysis for Comirnaty. On 29 November 2024, the MAH received the MHRA feedback that was aligned with the EMA position on discontinuing O/E analysis for Comirnaty.

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.

Response

Please refer to the HLH subsection for the summary and conclusion of the evaluation and to Appendix 5.2 Hemophagocytic Lymphohistiocytosis for the full evaluation.

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.

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUSA/00010898/202312), the following request was made: 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.

Response

Please refer to the IIM/Autoimmune Myositis, and IIM Flares subsection for the summary and conclusion of the evaluation and to Appendix 5.3 IIM/Autoimmune Myositis, and IIM Flares for the full evaluation.

In the PRAC AR of the PSUR #6 (EMA/H/C/PSUSA/00010898/202312), the following request was made: 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.

Response

Please refer to the Small Fiber Neuropathy subsection for the summary and conclusion of the evaluation and to Appendix 5.4 Small fiber neuropathy for the full evaluation.

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 Hemophagocytic Lymphohistiocytosis (HLH), Idiopathic Inflammatory Myopathies (IIM)/Autoimmune Myositis and IIM flares and Small fiber neuropathy.

HLH

To date, no plausible biological mechanism has been identified to support the development of HLH in patients vaccinated with BNT162b2, nor is there evidence to suggest that vaccination with BNT162b2 directly causes HLH. Data from pivotal clinical trials and placebo-controlled follow-up assessments did not reveal any cases of HLH. Safety follow up beyond 6 months after dose 2, identified a single report in a 51-year-old male. Similarly, in Study C4591006, a required non-interventional post-authorization clinical study, adverse events of PTs Liver disorder and HLH were reported in a 50-year-old female and were assessed as unrelated to the vaccination. A comprehensive literature review did not provide evidence of a causal relationship. The review of the 130 post-marketing cases from the safety database indicated that the majority (56.9%) were females, with a mean age of 49.3 years. When applying the WHO causality assessment framework, one case was classified as “probably related”, 31 cases as “possibly related”, 58 as “unlikely related”, 39 as “unassessable” cases and one as a duplicate case. Routine statistical reports did not reveal an emerging statistical signal for BNT162b2.

Overall, the totality of evidence does not substantiate a causal relationship between BNT162b2 and HLH. Consequently, there is no need to update the Product Information or

RMP at this time. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

IIM/Autoimmune Myositis, and IIM Flares

Non-clinical studies in rats have not shown any evidence of autoimmune myositis, and no long-term inflammation as would be expected in such an autoimmune response. No new cases were retrieved in MAH-run clinical trials. The majority of literature studies, including but not limited to large ones, actively support the safety of BNT162b2 on individuals with IIMs and have not associated BNT162b2 with any new-onset IIMs. Post-marketing data showed a very small number of 6 subjects (7 cases) out of a total of 220 in the reporting period that were well documented, had a reasonable temporal relationship and no apparent alternative explanation. Four subjects corresponded to dermatomyositis, one to antisynthetase syndrome and one to anti-HMG-CoA immune-mediated necrotizing myopathy. In two cases of dermatomyositis, a screening for malignancy was not mentioned, despite dermatomyositis being associated with malignancies (paraneoplastic syndrome). Routine statistical reports showed that the EB05 (product specific Bayesian Multi-Item Gamma Poisson Shrinker) is less than the EB05 >2 threshold, thus indicating no emerging statistical signal for the selected PTs and each vaccine variant (including but not limited to the new JN.1 and KP.2 vaccine variants). Overall, there is no new evidence to support a causal relationship between vaccination and the development of IIM and IIM flares. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Small Fiber Neuropathy

There is no biologic plausibility that vaccination with BNT162b2 can lead to the development of SFN. No potential mechanism has been established and up to 50% of cases of SFN remain idiopathic even in the absence of vaccination. Clinical data does not indicate any causal relationship with vaccination. The very limited literature did not provide any evidence for a causal relationship. A review of the 497 post-marketing reports revealed a younger population with a mean age of 44 years, the majority (74%) were female. When applying the WHO causality assessment as requested by PRAC, out of the 497 cases there was 1 probable related, 22 possible related, 90 unlikely related and 384 unassessable cases. Routine statistical reports did not reveal an emerging statistical signal for all vaccine formulations. The totality of data does not provide sufficient evidence to conclude that vaccination with BNT162b2 and variant formulation is causally related with vaccination, there is no need to update the Product Information nor RMP. This topic will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Product Lots and AE Reports

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

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16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 26 summarizes the important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU-RMP version 11.0 adopted on 26 October 2023 (Procedure number EMEA/H/C/005735/II/0188).

Table 26. 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 ^a
	Long-term safety data

a. The MAH, based on the results of study C4591030, had removed the missing information “Interaction with other vaccines” from the list of safety concerns in the EU-RMP version 12.0. This version was approved with procedure EMEA/H/C/005735/II/0201 and EC decision on 03 July 2024). The MAH proposes to remove the missing information from the list of safety concerns in the future PSURs.

During the reporting period, the MAH submitted the versions of the EU-RMP reported in the table below:

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
EMEA/H/C/005735/II/0201 - Final CSR C4591030 - C4591030 aPV milestone deletion - Removal of missing information regarding interactions with other vaccines	11 Dec 2023	RMP version 11.1 Submitted: - Gateway: 11 Dec 2023 Consolidated RMP v11.4 (II-0201 RMP v11.1 tracked on clean approved IB-0210 RMP v11.3): Submitted: - Eudralink: 10 May 2024 - Gateway: 11 Jul 2024	- CHMP Opinion: 30 May 2024 - EC decision: 03 Jul 2024
		Up-versioned RMP v12.0, content-wise similar to consolidated RMP v11.4 (II-0201 RMP v11.1 tracked on clean approved IB-0210 RMP v11.3) Submitted: - Eudralink: 15 May 2024 - Gateway: 11 Jul 2024	

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Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
EMA/H/C/005735/II/0206/G - RMP study/milestone commitments following submission of its final CSR - aPV update regarding protocol amendments of studies C4591052 (PA #1 and PA#2) - aPV update regarding C4591021 PA #4 - other minor RMP changes.	22 Dec 2023	RMP version 11.2 Submitted: Gateway: 22 Dec 2023	- CHMP Opinion: 13 Jun 2024 - EC decision: n/a
		Consolidated RMP v13.0 (II-0206/G RMP v11.2 tracked on clean approved II-0201 RMP v12.0) Submitted: - Eudralink: 03 Jun 2024 - Gateway: 25 Jun 2024	
EMA/H/C/005735/IB/0210 aPV milestone updates for: - C4591048 - C4591009 - C4591044	26 Feb 2024	RMP version 11.3 Submitted: Gateway: 26 Feb 2024	- CHMP Opinion: 03 Apr 2024 - EC decision: n/a
EMA/VR/0000231586 (Internal: II-0228/G) - C4591044 Final CSR - C4591048 PA#5 - RMP v13.1 - C4591021 milestone extension justification - RMP v13.2	30 Sep 2024	RMP version 13.1 Submitted: Gateway: 30 Sep 2024	- CHMP Opinion: 16 Jan 2025 - EC decision: n/a
		Consolidated RMP version 13.2 (RMP v13.1 and RMP v13.2 tracked on clean approved II-0206/G RMP 13.0) Submitted: Gateway: 15 Nov 2024	

16.2. Signal Evaluation

Please refer to Table 25 for signals that were closed during the reporting interval. There were no ongoing signals.

16.2.1. Evaluation of Closed Signals

Table 27 provides summary evaluations of the signals closed during the reporting period. Routine signal detection continues.

Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined Not to be Risks	
Migraine	On 25 January 2024, the MAH received a request from TGA to make safety-related changes to the Australia PI for COMIRNATY. The TGA's PB has recently assessed the risk of migraine with COVID-19 vaccines. The TGA assessment concluded that there are sufficient safety grounds to update the Australian PI for COMIRNATY to adequately communicate the risk to healthcare practitioners. This is based on evidence from published literature and reported cases of migraine with significant rates of ED assessment or hospital admission required as well as the distinct presentation of migraine compared to tension-type headaches. In response to the TGA's request, an evaluation of COMIRNATY and migraine was conducted, including various data sources such as clinical trial data, MAH safety

Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Migraine <i>Cont'd</i>	database data, disproportionality analyses, literature review and observed to expected analyses. Despite uncertainty regarding the mechanism of post-vaccination headache, it is nonetheless a well-recognized post-vaccination systemic reactogenicity event that is collected in the MAH COVID-19 vaccine clinical trials. Commensurate with this observation, headache is one of the most frequent spontaneously reported AEs following COMIRNATY vaccination; and is noted as an adverse reaction in the core data sheet and product labeling documents. Migraine as a specific medical condition had not previously been identified by the MAH as a safety signal for COMIRNATY. AE reports of migraine from the placebo-controlled portions of the largest pivotal COMIRNATY clinical trial (C4591001) was more frequent in vaccinated participants compared to placebo participants, however, overall reports of migraine were very low (<1% regardless of group) with overlapping incidence confidence intervals. At the time of evaluation, the global safety database contained 2,040,800 AE reports for BNT162b2 vaccines, of which 17,634 reports contained the event migraine (reporting rate: 0.86%). The spontaneous reports were of variable quality and most did not contain clinical detail that would clearly support migraine diagnoses based on ICDH-3 criteria. Approximately half of the cases in each of the analysed groups were found to be confounded either by medical conditions or medications known to be associated with migraines or headaches. Overall, the majority of the cases co-reported several events along with migraine, precluding a meaningful causality assessment for BNT162b2 and the isolated migraine component. The medical literature is supportive of headache as an expected vaccine reaction and the logical expectation that individuals prone to headache (i.e., individuals with known headache disorders such as TTH or migraine) are more likely to experience post-COVID-19 vaccine headaches than individuals without headache disorders. There is not a substantial body of post-vaccination literature differentiating migraine as a headache subtype or consistently describing post-vaccination headaches as having typical migraine characteristics or features. O/E analyses were <1 except for females in the younger age group (<5 years) which is likely due to the very low number of reported cases in that age group. Overall, the analyses are not supportive of higher-than-expected reporting of cases of new migraine. While this review supports the known causal association between vaccination with COMIRNATY and headache, there is insufficient mechanistic and clinical information to support that there is a causal relationship between COMIRNATY and migraine. Therefore, the MAH considers that no update to the core data sheet or product labeling is warranted at this time. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored by routine pharmacovigilance.
Transverse myelitis	The MAH received a query from SFDA on 05 January 2024 regarding COMIRNATY and a potential signal of transverse myelitis. Transverse myelitis is a neurological disorder causing segmental bilateral acute spinal cord injury and motor, sensory and/or autonomic symptoms as a result of acute inflammation involving both gray and white matter (including neurons, axons, oligodendrocytes and myelin). While transverse myelitis has been reported with vaccinations, causation has not been established. This evaluation of transverse myelitis coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, literature review, and observed to expected analyses. The placebo-controlled clinical trial data did not provide supportive evidence of a causal association between COMIRNATY and transverse myelitis, although it is acknowledged that rare AEs may not occur in a clinical trial, even when participants may number in the thousands. A cumulative search of Pfizer's global safety database was conducted through 31 December 2023 as of date: 07 January 2024) to identify all BNT162b2 AE reports coded with the MedDRA (version 26.1) PT Myelitis transverse. The search yielded 378 cases out of a total of 2,003,153 cases reported for the BNT162b2 vaccines. The reporting rate for the

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Transverse myelitis <i>Cont'd</i>	event is 0.019%. All cases were categorized as serious, 319 (84.4%) were spontaneous in origin, 57 (15.1%) were from literature sources and 2 (0.5%) were reported from clinical studies. Countries reporting ≥ 10 cases were: US (78), UK (57), Germany (43), Saudi Arabia (22), Japan (20), Netherlands (18), Australia (15), France (11), New Zealand and Spain (10 each). There were 227 (60.1%) cases reported in females, 124 (32.8%) in males and 27 (7.1%) with no sex specified. Most post-authorization cases reported to the safety database did not include diagnostic or clinical detail supporting the diagnosis of transverse myelitis. In the cases that did include enough detail to be categorized as BC Levels 2 and 3, many also contained confounding factors and potential alternative causes of transverse myelitis other than vaccination with COMIRNATY. The large population published studies from various geographic regions are overall unsupportive of an association between vaccination for COVID-19 and the occurrence of transverse myelitis. The O/E analysis is also unsupportive. In summary, there is not sufficient evidence to conclude that COMIRNATY administration causes transverse myelitis and therefore, the product labeling does not warrant changes. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored with routine pharmacovigilance.
Subacute thyroiditis	The MAH received a query from SFDA on 05 January 2024 regarding COMIRNATY and a potential signal of subacute thyroiditis. Subacute thyroiditis, also known as De Quervain's thyroiditis or granulomatous thyroiditis, is the most common cause of painful thyroiditis. SAT, presumed to be caused by viral infections or post-viral inflammatory responses, generally develops 2 to 8 weeks following viral upper respiratory tract infections and cases tend to increase during virus outbreaks. It has been hypothesized that viral antigens in vaccines may trigger inflammation in the thyroid, similar to an infectious agent. This evaluation of subacute thyroiditis coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, literature review, and observed to expected analyses. The placebo-controlled clinical trial data did not provide supportive evidence of a causal association between COMIRNATY and SAT, although it is acknowledged that uncommon AEs may not occur in clinical trials, even when participants number in the thousands. A cumulative safety database search of the Pfizer global safety database through 31 Dec 2023 (as of 07 Jan 2024) was conducted using MedDRA (Version 26.1) to identify cases with PT: Thyroiditis subacute. A total of 349 cases (0.017% of total 2,003,153 cases for BNT162b2 vaccines) were retrieved. Out of these 349, (286, 81.9%) were spontaneous, (61, 17.5%) were literature, and 1 each were solicited and clinical study cases. Cases included females (260, 74.5%) and males (84, 24.1%) and sex unknown/no data (5, 1.4 %). The patients ranged in age from 23-95 years (mean = 47.9 years). Of these 349, there were 212 serious cases (60.7%) and 137 (39.3%) cases were nonserious. The number of reported post-authorization SAT cases that did not include alternative explanations or confounding factors was relatively low (72 cases) when taking into consideration the unprecedented number of doses of COMIRNATY that have been administered worldwide and the number of AEs reported to the safety database. While the large population study of AESIs in >1.3 million individuals was not designed to compare the incidence of SAT between non-vaccinated individuals and those vaccinated with BNT162b2, the low number of SAT reports following BNT162b2 administration (1 per 100,000 doses after dose 1, 0 per 100,000 after Dose 2) is reassuring even though it does not prove a lack of association. Likewise, the smaller cohort studies did not provide comparative incidences of SAT in vaccinated vs unvaccinated cohorts, rather they provided clinical descriptions of SAT presentation and course. The disproportionality analysis in the published literature was inconsistent with that in the MAH's safety database, although limitations of this signal detection exercise, such as potential masking of signals, is acknowledged. The O/E analyses and interim results of the non-interventional PASS (C4591021) are also not supportive of a

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Subacute thyroiditis <i>Cont'd</i>	relationship between COMIRNATY and SAT. In summary, there is not sufficient evidence to conclude that COMIRNATY administration causes SAT and, therefore, no product labeling changes are warranted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored with routine pharmacovigilance.
Erectile dysfunction	On 09 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of Erectile dysfunction. Erectile dysfunction can be classified as organic (ie, vasculogenic, neurogenic, cavernous factors, hormonal, drug induced), psychogenic or mixed. This evaluation of erectile dysfunction coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. In the blinded placebo-controlled follow-up period of the pivotal C4591001 study, ED was observed in 6 participants; 1 participant in the BNT162b2 group (considered unrelated by the investigator) and 5 participants in the placebo group. The literature on ED and BNT162b2 is limited; 2 small studies suggest that COVID-19 vaccination has either no effect, or a beneficial effect on erectile function. ED has not met threshold for statistical disproportionate reporting within the MAH's global safety database. ED has multiple potential etiologies including psychosocial factors which are not only poorly reported in spontaneous post-marketing data but were potentially exacerbated by a global pandemic. It is noted that 40.5% of the reports in this dataset were received in 2021. A search of the safety database cumulatively through 31 January 2024 was conducted for all BNT162b2 vaccines for cases coded with the MedDRA version 26.1 PTs: Erectile dysfunction, Psychogenic erectile dysfunction, Organic erectile dysfunction. A total of 625 relevant cases (0.03% of the 2,030,113 cases with BNT162b2 as the suspect drug). These 625 cases reported a total of 3361 events. The majority of cases (605, 96.8%) are spontaneous reports. A total of 116 cases were confounded and the majority of the remaining cases lacked information on the patient's medical history or concomitant medications. Given that 8 of the 12 most commonly prescribed drugs list ED as a side effect and it is estimated 25% of cases of ED are due to medications, the lack of concomitant medication information is an important potential confounder. Almost half of the cases reported an onset either the same day as vaccination or within 3 days of vaccination; from a perspective of biological plausibility, it seems unlikely that a pathological process (vascular, neurological, local) could be initiated and have end-organ effect in such a short time frame. ED is common and the occurrence coincidental to vaccination is possible. To conclude, the totality of the data does not provide sufficient evidence to conclude that vaccination with BNT162b2 causes ED, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this this topic will be monitored using routine pharmacovigilance.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Hypertension	On 09 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of Hypertension. Hypertension has been reported as an adverse reaction after administration of the oral cholera vaccine, while the product labels of other vaccines routinely administered to people of advanced age, such as the quadrivalent influenza vaccine or the Herpes zoster vaccine, do not note hypertension as an adverse reaction. This evaluation of hypertension coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Large clinical studies did not show a difference in the incidence of hypertension compared to placebo. The scientific literature did not reveal convincing evidence that vaccination with BNT162b2 causes hypertension, most studies had several limitations or were small and without comparator groups. Post-marketing reports revealed a large amount of hypertension events in individuals (38178 cases out of a total of 2,047,788 cases in the safety database, i.e., 1.86% of total cases) who received BNT162b2, however, the lack of a control group and incomplete information are major limitations of spontaneous reporting and the multitude of potential confounding factors affecting blood pressure make conclusions based on spontaneous reports difficult. Hypertension is one of the most common medical conditions worldwide and there is a high prevalence of undiagnosed and uncontrolled hypertension. In addition, Hypertension (SMQ narrow) has not met a threshold for statistically significant disproportionate reporting within the MAH's global safety database. Given the totality of the available information, a causal association of hypertension after vaccination with BNT162b2 is not supported and no changes to the product information are warranted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Giant cell arteritis	On 09 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of Giant cell arteritis. Regarding background data, there has been recognition of clinical overlap in the presenting symptoms and signs of COVID-19 and GCA and there have been suggestions of a potential association between influenza vaccine and the development of GCA in some publications presenting case reports. This evaluation of giant cell arteritis coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Large scale clinical trials did not report any cases of GCA in either the BNT162b2 or placebo groups. There was relatively little in the published medical literature on COVID-19 vaccines and giant cell arteritis. One group performed a disproportionality analysis for GCA on Vigibase data and found that COVID-19 vaccines were associated with an increased reporting in GCA. All other literature data were case series or case reports. Overall, the available literature did not provide evidence of a causal association between BNT162b2 and GCA. The O/E analyses revealed ratios <1, suggesting that the number of reports of GCA are lower than would be expected based on the background rate of GCA in an unvaccinated population. Finally, there was a relatively low number of GCA spontaneous reports (394 cases out of a total of 2,040,800 cases in MAH's safety database, i.e., 0.02% of total cases). They were of varying quality, with most lacking information that would allow the confident attribution of GCA to the vaccine. Given the totality of the available information, a causal association of GCA after vaccination with BNT162b2 is not supported and no changes to the product information are necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will be monitored using routine pharmacovigilance.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Exacerbation of diabetes mellitus	On 09 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of Exacerbation of diabetes mellitus. Diabetes mellitus is estimated to affect approximately 530 million adults worldwide, with a global prevalence of 10.5% among adults aged 20 years to 79 years. A mechanism by which COMIRNATY vaccination could cause diabetes mellitus exacerbation has not been elucidated. There has been speculation of how SARS-CoV-2 infection may lead to glucose alteration. This evaluation of exacerbation of diabetes mellitus coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. The nonclinical and clinical trial data are unresponsive of a causal association between BNT162b2 and exacerbation of diabetes mellitus. In the MAH's global safety database, exacerbation of diabetes mellitus was not identified as a statistical signal. A total of 223 cases were retrieved from the MAH safety database (out of a total of 2,047,746 cases, i.e., 0.01% of total cases). Seventy-nine cases reported glycemic alteration in the context of significant medical conditions such as acute infection, and ischemic events, thereby confounding a thorough assessment of the role of vaccination. Glycemic control in patients with diabetes mellitus is often difficult to consistently achieve. Eight cases of glycemic alteration following >1 dose of vaccine did not consistently provide sufficient information for complete assessment, as in some cases glucose values, latency from vaccination to event or complete information on concomitant medication and pre vaccination glucose values were not provided. The medical literature revealed a small number of differently designed studies and had inconsistent findings. The medical literature consisting of large population data was not supportive of changes in blood glucose following vaccination. To conclude, in the context of the unprecedented use of BNT162b2 (hundreds of millions of doses) and the large number of AE reports received from around the world, the totality of the data does not allow a conclusion that vaccination with BNT162b2 causes exacerbation of diabetes mellitus, therefore no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Exacerbation of adrenal insufficiency	On 09 February 2024 the MAH received the request from Rwanda FDA to investigate the safety signal of Exacerbation of adrenal insufficiency. Adrenal insufficiency is a relatively rare but potentially serious condition characterized by reduced production of glucocorticoids and/or mineralocorticoids and adrenal androgens due to the destruction of the adrenal gland or lack of its stimulation. HCPs who have published cases describing adrenal crises in patients with adrenal insufficiency following COVID-19 vaccination, have theorized that they may have been caused by a strong immune response, including the release of proinflammatory cytokines, following vaccination. This evaluation of exacerbation of adrenal insufficiency coincident with COMIRNATY vaccination provided information from several data sources, such as nonclinical data, clinical trial data, MAH safety database data, disproportionality analyses, and literature review. There were no signs of adrenal insufficiency in the nonclinical repeat-dose studies or DART study. No AEs of acute adrenal insufficiency were reported in clinical trial data. The literature review revealed a limited number of articles that were mostly case reports. Two small studies (<90 and <170 participants, respectively) looked at the use of additional glucocorticoid following COVID-19 vaccination in patients with adrenal insufficiency and concluded that prophylactic administration of glucocorticoids in such patients was not needed. Sixty-eight cases were retrieved from the global safety database for the MAH COVID-19 vaccine (out of a total of 2,047,746 cases in the database, reporting rate 0.003%). Although there are a small number of cases (24 cases) with no clear explanation of the cause of adrenal insufficiency exacerbation, given the context of the extensive vaccine exposure that has occurred with the MAH COVID-19 vaccine, this is not

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Exacerbation of adrenal insufficiency <i>Cont'd</i>	unexpected. There was no emerging statistical signal of disproportionality for acute adrenal insufficiency based on EB05 scores. Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and the exacerbation of adrenal insufficiency. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Tongue discolouration	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Tongue discoloration. The tongue can often provide clinical clues to systemic conditions and demonstrate a number of conditions unrelated to other systemic diseases. This evaluation of tongue discolouration coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. During the placebo-controlled period of Study C4591001, 21,926 participants ≥ 16 years of age received BNT162b2 and 21,921 participants ≥ 16 years of age received placebo. One participant in the placebo group reported tongue discolouration, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0-0.1 versus 0 participants in the BNT162b2 group (IR/100 PY 0.0, 95% CI: 0.0-0.0). No relevant literature was retrieved. Tongue discolouration has multiple potential triggers which are poorly reported in spontaneous post-marketing data. A total of 116 cases were retrieved from the MAH's global safety database for the MAH COVID-19 vaccine (out of 2,051,801 cases in the database, reporting rate 0.005%). Most cases of tongue discolouration in the MAH global safety database had either insufficient information for a proper evaluation or an alternative potential trigger for tongue discolouration. Given the context of the extensive vaccine exposure that has occurred with the MAH COVID-19 vaccine, few cases of tongue discolouration are not unexpected. On cumulative review of the relevant PT in MAH's global safety database, the EB05 scores were less than the EB05>2 threshold, thus indicating no emerging statistical signal for the selected PT. Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and tongue discolouration. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Sciatica	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Sciatica. This evaluation of Sciatica coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Sciatica is a very common condition with a lifetime incidence between 10% to 40% and an annual incidence of 1% to 5%. In large scale clinical trials, there were similar numbers of participants reporting sciatica in the vaccine group (n = 14) and the placebo group (n = 11). There were no relevant articles in the published medical literature on BNT162b2 and sciatica. Safety database search yielded 1069 cases reporting sciatica (out of a total of 2,051,801 cases present in the database, reporting rate 0.05%); 1020 were spontaneous reports, 39 were solicited reports and 10 were from a clinical study. Only 22 out of the 1069 cases were considered as relevant. Also, there was no emerging statistical signal of disproportionality for sciatica based on EB05 scores. Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and sciatica. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Tonsillitis	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Tonsillitis. Tonsillitis is the inflammation of tonsils. It is a common condition, making up approximately 1.3% of outpatient visits. It is generally caused by infections, which may be viral or bacterial, with viral etiologies being the most common. This evaluation of Tonsillitis coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, Pfizer safety database data, disproportionality analyses, and literature review. The pathogenesis of erysipelas begins with a disruption of the skin barrier (such as ulcers, trauma etc.), allowing the infective agent to enter. Tonsillitis is a common condition making up approximately 1.3% of outpatient visits. In large scale clinical trials, there was a greater number of reports of tonsillitis in the placebo group (n = 8) compared to the vaccine group (n = 2). There were no relevant articles in the published medical literature on BNT162b2 and tonsillitis. The safety database search yielded 792 cases reporting tonsillitis (out of a total of 2,051,801 cases present in the database, i.e., 0.4% of total cases); 738 were spontaneous reports, 44 were solicited reports, 9 were from a clinical study and 1 was from the literature. Of the 792 cases, only 323 had any information on medical history. Of them, 179 had a reported time to onset between 0 to 14 days for the PT tonsillitis. Of the 179 cases, only 46 were medically confirmed and were further analyzed. Most cases (n = 40) had confounding factors or an alternative explanation. Also, there was no emerging statistical signal of disproportionality for tonsillitis based on EB05 scores. Based on the totality of available data, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and tonsillitis. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Erysipelas	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Erysipelas. Erysipelas is an acute bacterial infection of the dermis, hypodermis and its reticular lymphatic vessels and is considered to be a specific type of cellulitis. This evaluation of Erysipelas coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Within the Phase 2/3 part of study C4591001, 21,926 participants ≥16 years of age received BNT162b2 and 21,921 participants ≥16 years of age received placebo: 2 participants in the BNT162b2 group reported erysipelas, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0-0.1 versus 0 patients in the placebo group (IR/100 PY 0.0, 95% CI: 0.0-0.0). There was no relevant literature. In MAH's global safety database, erysipelas was not identified as a statistical signal. The safety database retrieved a total of 475 cases out of 2,051,801 AE reports (0.02%). There is a relatively small number of post-authorization reports of erysipelas shortly following COVID-19 vaccine administration, in which erysipelas was reported to have developed at the vaccination site. It is conceivable that erysipelas may occur at the vaccination site as a result of aseptic vaccine administration technique, however, the spontaneous reports did not clearly describe this scenario. Some cases had insufficient information about the medical history and concomitant medications, preventing confidence in the diagnosis and assessment of the clinical context and none of the reported cases performed diagnostic examination to confirm an infectious origin. Moreover, some, as per description, were more suggestive of a local reaction or swelling of the injected limb. To conclude, in the context of the unprecedented use of BNT162b2 (hundreds of millions of doses) and the large number of AE reports received from around the world, the totality of the data does not allow a conclusion that vaccination with BNT162b2 causes erysipelas, therefore no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Angina bullosa haemorrhagica	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Angina bullosa haemorrhagica (ABH). ABH is a benign, self-limited condition characterized by the sudden onset of blood-filled blisters in the oral cavity. The etiology of this oral pathology is unknown, and it is considered to occur in susceptible patients following trauma in the oral cavity. This evaluation of ABH coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. ABH is a rare event, no adverse events were reported in the clinical trials and there was no relevant literature. Post-marketing reports revealed a small number of ABH events (10 cases) in individuals who received BNT162b2, with most cases being confounded. Routine statistical reports did not reveal disproportional reporting. In the context of hundreds of millions of doses of BNT162b2 administered worldwide, the totality of the available information does not support a causal association between ABH and vaccination with BNT162b2. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Polycystic ovaries	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Polycystic ovaries. Polycystic ovary syndrome is one of the most common conditions in reproductive aged women affecting 8-13% of all women of reproductive age. The etiology of polycystic ovary syndrome is a complex trait arising from the interaction of genetic and environmental factors. This evaluation of Polycystic ovaries coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Within the blinded placebo-controlled period of Study C4591001 21,926 participants ≥ 16 years of age received BNT162b2 and 21,921 participants ≥ 16 years of age received placebo; 1 participant in the vaccine group reported polycystic ovaries, corresponding to 0.0 IR/100 PY with a 95% CI of 0.0-0.1 versus 0 participants in the placebo group (IR/100 PY 0.0, 95% CI: 0.0-0.0). There was no relevant literature. A cumulative search of the MAH's global safety database was conducted through 31 March 2024 to identify all cases that reported Original BNT162b2, Bivalent (BNT162b2/BNT162b2 Omicron BA.1) and Bivalent (BNT162b2/BNT162b2 Omicron BA.4/BA.5) vaccine, Multivalent NOS and Monovalent Omi XBB.1.5 presentations. as the suspect drug reporting the event coded with the MedDRA Version 26.1 PTs Polycystic ovarian syndrome and Polycystic ovaries. A total of 156 cases were retrieved from the MAH's global safety database out of 2,051,801 total cases (reporting rate 0.007%). The cases have been reported after BNT162b2, BNT162b2 Omicron BA.1, BNT162b2 Omicron BA.4/BA.5, BNT162b2 XBB 1.5 or BNT162b2 multivalent NOS administration. Although there are a small number of medically confirmed, serious cases, most of them had either insufficient information to confirm the diagnosis or had polycystic ovary syndrome as medical history or had underlying comorbidities considered a trigger of polycystic ovary syndrome. Additionally, the number of reports is relatively low given the extensive MAH COVID-19 vaccine exposure worldwide. Routine statistical reports did not reveal disproportional reporting. Overall, the totality of available information does not allow a conclusion that vaccination with BNT162b2 causes polycystic ovaries. Therefore, no label changes are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Cerebral amyloid angiopathy	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Cerebral amyloid angiopathy. CAA is usually an age-related degenerative condition caused by deposition of beta amyloid in the walls of cerebral small vessels. Different genetic risk factors have been identified. Additionally, non-genetic factors are thought to contribute to the risk of CAA. For example, uncontrolled hypertension has been reported to be more prevalent among CAA patients. This evaluation of Cerebral amyloid angiopathy coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. CAA was not reported by participants in either the vaccine (N = 21,926) or placebo (N = 21,921) groups during the placebo-controlled period of the MAH-run pivotal clinical trial C4591001 in participants 12 years and older, nor in participants 16 years and older in the placebo-controlled period of booster study C4591031 SSA, nor in the placebo controlled period of the MAH-run pivotal clinical trial in participants 6 months to <12 years of age, C4591007. There was no relevant literature. A total of 28 cases were retrieved from the MAH's global safety database, out of a total of 2,051,801 (0.001%) cases in the MAH database for the MAH COVID-19 vaccine. Many cases describing an uncertain CAA diagnosis, and most patients having multiple underlying comorbidities that may contribute to the presence of CAA. In addition, CAA has not met the threshold for statistical disproportionate reporting within the MAH's global safety database. To conclude, the totality of the data does not provide sufficient evidence to conclude that vaccination with BNT162b2 causes CAA, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Cough	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Cough. Other than the rare context of anaphylaxis, in which an allergic reaction to the vaccine could affect the lower respiratory tract, there is no known biological mechanism by which vaccination with BNT162b2 may cause cough. This evaluation of cough coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. In the placebo-controlled stages of the pivotal studies, cough was not commonly reported. When reported, the incidences did not differ significantly between the vaccine and placebo recipients. At the time of evaluation, the MAH's global safety database contained 2,051,801 AE reports for BNT162b2 vaccines, of which 34,402 reports contained the event cough (reporting rate: 1.68%). The spontaneous reports were of variable quality, and majority did not contain adequate clinical information for a meaningful assessment of the event cough. Cough was very often reported in the context of infections or potential hypersensitivity reactions involving multiple organ systems. Overall, in all the cases with adequate clinical information, cough could be attributed to an alternative etiology. While medical literature capturing acute post-vaccination AEs may report cough, its incidence is relatively low across the reviewed studies, and it does not emerge as a notable vaccine-associated event by the authors. The data across these studies, involving tens of thousands of reports and multiple pharmacovigilance databases, do not depict a strong association between COMIRNATY and reports of cough. Overall, there is insufficient mechanistic information and a lack of clear and consistent data to support a conclusion of a causal relationship between COMIRNATY and cough. Therefore, the MAH considers that no update to the core data sheet or product labeling is warranted at this time. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Aphasia	On 7 May 2024 the MAH. received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Aphasia. Aphasia is delineated as “the loss of ability to communicate orally, through signs, or in writing, or the inability to comprehend such communications; the loss of language usage ability.” This condition can be precipitated by a myriad of cerebral pathologies, with cerebrovascular accident being the predominant etiology. This evaluation of Aphasia coincident with COMIRNATY vaccination provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Clinical trial data in large randomized-placebo-controlled studies did not show a difference in the occurrence of aphasia between BNT162b2 and placebo. There was no published literature describing an association between vaccination with BNT162b2 and aphasia. A cumulative search of MAH’s global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA Version 27.0 PT Aphasia. The search yielded 3121 cases reporting aphasia (out of a total of 2,060,299 cases, i.e., 0.15% of total cases); 3023 were spontaneous reports, 71 were solicited reports, 5 were from literature and 22 were from clinical studies. There are a number of medically confirmed serious cases that did not provide clear alternative explanations for aphasia; however, this is not sufficient to conclude a causal association between aphasia and the MAH COVID-19 vaccine. There was no emerging statistical signal of disproportionality for aphasia based on EB05 scores in the global safety database. Overall, the totality of available information is not supportive of a causal relationship between the vaccine and aphasia. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Disturbance in attention	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Disturbance in attention. Broadly, attention is defined as the set of processes that allow us to process certain information to the (relative) exclusion of other information. Given the great complexity of information available to our senses at any given time, attention is crucial for sorting out relevant information and limiting the amount of information that gains access to further processing. A disturbance in attention is a sign or symptom that may occur in association with a variety of medical conditions. This evaluation provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. In the blinded placebo-controlled follow-up period of the pivotal C4591001 study, disturbance in attention was reported in 4 participants in the BNT162b2 group and no participant in the placebo group. None of the participants of the C4591031 SSA reported disturbance in attention. During the placebo-controlled Study C4591007, 1 participant in the BNT162b2 group reported disturbance in attention. The medical literature on disturbance in attention and BNT162b2 was limited. One relevant article was identified that assessed short term AEs reported via an electronic questionnaire and noted a small percentage ($\leq 1.8\%$) of reports of lack of concentration after second and third doses of the MAH COVID-19 vaccine and without a significant difference between the doses. Disturbance in attention has multiple potential etiologies which are poorly reported in the spontaneous post-marketing data. A cumulative search of MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT Disturbance in attention. A total of 11,260 AE reports (containing 113,925 events) were retrieved using the above search criteria in the context of 2,060,299 total AE reports in the MAH safety database for the MAH COVID-19 vaccine (reporting rate 0.5%). Most cases described medical histories or co-reported events that provided more likely explanations for attention disturbances than the vaccine itself. There was no emerging statistical signal of disproportionality for disturbance in attention based on EB05 scores.

Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Disturbance in attention <i>Cont'd</i>	Overall, the available information on disturbance of attention and COMIRNATY is not sufficient to conclude a causal association. The MAH considers this signal refuted and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Myocardial necrosis marker increased	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Myocardial necrosis marker increased. An increase in myocardial necrosis marker in serum is a sign of an underlying cardiac condition. Cardiac AESIs that may be associated with increases in myocardial necrosis markers (including myocardial infarction, myocarditis/pericarditis) have been monitored closely and included in aggregate safety reports for regulatory authorities by the MAH since the initial authorization of BNT162b2. Myocarditis and pericarditis are identified risks for BNT162b2 vaccines and as such are discussed in product labeling. This evaluation provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. The PT Myocardial necrosis marker increased was not reported as an AE in the placebo-controlled portions of the large BNT162b2 clinical trials. There is no relevant literature, describing an association between vaccination with BNT162b2 and myocardial necrosis marker increased, except for articles reporting increased myocardial necrosis markers in the context of myocarditis. There was no signal of disproportionality for the AE in the global safety database. A cumulative search of MAH's global safety database was conducted through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT Myocardial necrosis marker increased. A total of 175 AE reports (containing 1488 events) were retrieved using the search criteria mentioned above in the context of 2,060,299 total AE reports in the MAH global safety database received for the MAH COVID-19 vaccine (reporting rate 0.008%). There are a small number of serious cases with no clear explanation, however given the context of the unprecedented vaccine exposure and the known rare risk of myocarditis, this is not unexpected. The MAH considers this signal refuted, and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Pelvic pain	On 7 May 2024 the MAH. received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Pelvic pain. Acute pelvic pain is a nonspecific symptom that may occur in association with many medical conditions. It is generally defined as pain in the anatomic region of the pelvis that has lasted <3 months. The pain can be sharp or dull, focal or diffuse, sporadic or constant. Pain that is exclusive to the mid or upper abdomen, and low back is not considered pelvic pain. Importantly, a patient with chronic pelvic pain can present with an acute process arising de novo or a pain exacerbation that is related to the chronic condition. Over one-third of reproductive-aged women will experience non-menstrual pelvic pain at some point. While most acute pelvic pain is caused by reproductive, urinary, or gastrointestinal tract disorders, abnormalities of musculoskeletal, vascular, and neurologic processes can contribute as well. Because multiple organ systems are contained within the pelvis, a broad differential diagnosis exists for patients with acute pelvic pain. This evaluation provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. In clinical studies of 21,926 participants ≥16 years of age in the BNT162b2 group of Study C4591001, 3 reported PT Pelvic pain (for an incidence rate of 0.0 per 100 PY). Of 21,921 participants in the placebo group, 3 reported PT Pelvic pain (for an incidence rate of 0.0 per 100 PY). There was no relevant medical literature. A cumulative search of the MAH's global safety database was conducted

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Pelvic pain <i>Cont'd</i>	through 30 April 2024 to identify all cases that reported BNT162b2 as the suspect drug and events coded with the MedDRA version 27.0 PT Pelvic pain. A total of 1660 cases, reporting 10,619 AEs, were retrieved from the MAH's global safety database; 1639 were spontaneous reports, 17 were solicited reports, and 4 were from clinical studies. Contextually, the total number of AE reports for BNT162b2 vaccines in the safety database is 2,060,299 (reporting ratio of 0.08%). The majority of the spontaneous reports of pelvic pain also co-reported potential causes of the pain, given that pelvic pain may originate from any of several anatomic systems. There was no clear and consistent trend pointing toward a disorder that is known to be caused by the vaccine. There was no emerging statistical signal of disproportionality for pelvic pain based on EB05 scores. Overall, the available information is not supportive of a causal association between pelvic pain and COMIRNATY. The MAH considers this signal refuted, and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Paralysis	On 7 May 2024 the MAH received a request from Saudi FDA to provide a signal assessment report for COMIRNATY and Paralysis. Paralysis is a loss of motor function in 1 or more muscles. It may be temporary or permanent, proximal, distal or combined, asymmetric or symmetric, acute, subacute or chronic. It may be progressive or episodic. The potential causes of paralysis vary but include demyelinating conditions such as Guillain-Barré syndrome, neurologic conditions such as transverse myelitis or stroke, infectious diseases such as poliomyelitis, poisoning such as consumption of tetrodotoxin, autoimmune conditions such as myasthenia gravis, metabolic myopathies and genetic conditions such as hyperkalemic periodic paralysis or trauma and nerve injury. The variety of potential causes is reflected in the plethora of diagnostic investigations that can be applied. Apart from patient history and clinical examination, they may include laboratory parameters, imaging studies such as MRI, electrodiagnostic testing, invasive procedures such as lumbar puncture or muscle biopsy, or genetic testing. This evaluation provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Large scale clinical trials did not report any cases with the PT Paralysis in either the BNT162b2 or placebo groups. Overall, the available literature did not provide evidence of a causal association between BNT162b2 and paralysis in general. The safety database was searched for all cases reporting PT: Paralysis for the BNT162B2 vaccine through 30 April 2024 (MedDRA version 27.0). The search yielded 1847 cases reporting paralysis; 1831 were spontaneous reports, 6 were solicited reports, 4 were from the literature, and 6 were from a clinical study. Contextually, the total number of AE reports for BNT162b2 vaccines in the safety database is 2,060,299. They were of varying quality, with most lacking information that would allow the confident attribution of paralysis to the vaccine and many with confounders or more plausible alternative explanation. There was no signal of disproportionality for the AE in the global safety database. Overall, the available information on paralysis and COMIRNATY is not sufficient to conclude a causal association. The MAH considers this signal refuted and no changes to the product information are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Pulmonary embolism	A request was received from SFDA on 22 October 2023 pertaining to the occurrence of pulmonary embolism following vaccination with the MAH COVID-19 Vaccine (COMIRNATY). Pulmonary embolism refers to obstruction of the pulmonary artery or 1 of its branches by material (eg, thrombus, tumor, air, or fat) that originated elsewhere in the body. The source

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Pulmonary embolism <i>Cont'd</i>	of most emboli is the lower extremity proximal veins and >50 percent of patients with proximal deep vein thrombosis have concurrent pulmonary embolism at presentation. Most pulmonary embolisms move beyond the bifurcation of the main pulmonary artery to lodge distally in the main lobar, segmental, or subsegmental branches of a pulmonary artery. Pulmonary embolism can be bilateral or unilateral, depending on whether they obstruct arteries in the right, left, or both lungs. Smaller thrombi that are located in the peripheral segmental or subsegmental branches are more likely to cause pulmonary infarction and pleuritis. The occurrence of pulmonary embolism is not uncommon, and the incidence rises with increasing age, such that pulmonary embolism has an incidence of >500 per 100,000 after the age of 75 years. Case-fatality rate increases with increasing age. Men have a higher risk for pulmonary embolism compared to women. Other risk factors include genetic conditions (eg, factor V Leiden mutation) and acquired factors, including recent surgery/trauma, immobilization, malignancy, pregnancy, obesity, and smoking. This evaluation provided information from several data sources, such as clinical trial data, MAH safety database data, disproportionality analyses, and literature review. Within the blinded placebo-controlled follow-up period of both adult studies (defined as from first vaccine received to unblinding date), out of a total of 28,095 participants exposed to BNT162b2 (23,041 from Study C4591001 and 5054 from Study C4591031 Sub-study A) and 28,056 exposed to placebo (23,040 from Study C4591001 and 5016 from Study C4591031), 21 AEs were reported under the aforementioned PTs (18 from Study C4591001 and 3 from Study C4591031). Of these 21 AEs, 8 were reported in the BNT162b2 group (all from Study C4591001) and the remaining 13 were reported in the placebo group (10 from Study C4591001 and 3 from Study C4591031). There were no events reported in Study C4591007. The extensive literature review of the Original and Bivalent BNT162b2 vaccines did not demonstrate strong support for a causal relationship between pulmonary embolism and vaccination with BNT162b2. A cumulative search of MAH's global safety database was conducted through 15 October 2023 to identify all the cases that reported BNT162b2 including BNT162b2 Bivalent Omicron BA.1 and BA.4/BA.5 as well as BNT162b2 XBB1.5 as the suspect drug with events coding to the PTs Pulmonary embolism, Pulmonary infarction, Pulmonary microemboli, Pulmonary thrombosis, Pulmonary artery occlusion, Pulmonary artery thrombosis. Safety database search retrieved a total of 8753 cases, corresponding to 0.46% of all the cases (1,914,175) with BNT162b2 as the suspect drug. Of the 8753 cases, 4153 were male patients, 4452 female patients, and the gender was unknown in 148 cases. The age of the patients ranged from 12 years to 102 years (n = 8371), with a mean age of 59.7 years. In 42.9% cases (n = 3754), the age was equal to or over 65 years. The countries reporting the highest number of cases (top 5) were Germany (1913), France (1573), UK (768), US (477), Italy (412). All 8753 cases were assessed as serious. Case outcome was reported as fatal (731), resolved/resolving (4315), or not resolved (2592). In 1115 cases, the outcome was unknown. Of the 8753 cases, 9165 relevant PTs were reported (1 case may report >1 relevant PT): Pulmonary embolism (8368), Pulmonary thrombosis (390), Pulmonary infarction (334), Pulmonary artery thrombosis (49), Pulmonary microemboli (16), Pulmonary artery occlusion (8). All these relevant PTs were assessed as serious. Of the 8753 cases, the clinical outcome of the relevant events was reported as fatal (672), resolved/resolving (4516), not resolved (2153), or unknown (1845). In 16 cases, the relevant PTs occurred before the patients received BNT162b2. In 3930 out of the remaining 8737 cases, there were significant confounding factors, eg, presence of co-suspect drugs or concomitant drugs known to cause pulmonary embolism such as oral contraceptives, JAK inhibitors, anti-VEGF therapy; pre-existing common risk factors for pulmonary embolism such as pulmonary embolism history, deep vein thrombosis, bedridden, hypercoagulation, obesity; present co-reported events associated with thromboembolism, such as COVID-19, pneumonia/pneumonitis, atrial fibrillation, sepsis, disseminated intravascular coagulation.

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Pulmonary embolism <i>Cont'd</i>	In 4113 out of the remaining 4807 cases, information important for a medically meaningful assessment of pulmonary embolism (eg, medical history, concomitant drugs, and/ or latency from vaccination) was not reported. Of the remaining 694 cases, 231 cases were not medically confirmed. In 250 out of the remaining 463 cases, the diagnosis of pulmonary embolism was confirmed by imaging studies (eg, angiogram, computerized tomogram, MRI) or autopsy. Of these 250 cases with confirmatory diagnostic studies, the age of the patients ranged from 17 years to 98 years. In 55.6% cases (n = 138), the age of the patients was ≥ 65 years. Of the 250 cases, 264 relevant PTs were reported: Pulmonary embolism (249), Pulmonary infarction (10), Pulmonary thrombosis (5). Of the 250 cases, the latency between the dose of BNT162b2 to the occurrence of pulmonary embolism ranged from <1 day to 297 days, with a mean of 19.6 days and a median of 11 days. In 83.6% cases (n = 209), the latency was ≤ 30 days. However, a temporal association of the AEs following BNT162b2 administration in these reports does not necessarily mean a causal relationship with administration of BNT162b2 and may represent temporally coincidental events. The clinical outcome of the 264 relevant PTs was reported as fatal (10), resolved/resolving (179), not resolved (42) and unknown (33). The most frequently reported medical history (>15 times) included hypertension (96), Tobacco user (22), Depression (20), Dyslipidaemia (20), Asthma (18). The most frequently reported concomitant drugs (>15 times) included acetylsalicylic acid (26), hydrochlorothiazide (23), levothyroxine (23), atorvastatin (20), bisoprolol (20), paracetamol (18), omeprazole (17). Of the 10 cases with fatal outcome, 3 cases were reported from France, and the remaining 7 cases were reported from UK, Japan, Spain, Ireland, Norway, Denmark, Argentina (1 each). The age of the patients ranged from 40 to 98 years. In 5 cases, the age was ≥ 65 years. In 9 out of the 10 cases, the patients had major risk factors for atherothrombotic disease including hypertension, diabetes mellitus, or hypercholesterolaemia. In the remaining case, the patient had been breathless for 2 weeks before administration of BNT162b2, and the patient also had medical history of chest pain which was treated as pericarditis and pneumonia. The reporting physician noted that it is possible that the patient had a previous undiagnosed pulmonary embolism. No significant findings were identified for these cases with fatal outcome. In summary, upon review of these confirmed cases of pulmonary embolism, the available information is inconclusive to ascertain whether pulmonary embolism was causally related to vaccination or just temporally coincidental in these cases, considering the limitations of individual case reports. Routine statistical reports did not reveal an emerging statistical signal. In the Observed to expected ratio, based on the selected background rates and the estimated number of exposure person-years calculated using the number of the MAH vaccine doses through 05 October 2023 in the EEA and the length of risk windows, O/E ratios were below 1 overall for risk windows of 21 days and 42-days. The O/E ratios were below 1 for the 14-day risk window with the exception of the 12 to 17-year age group. However, the result was not statistically significant. This suggests that the number of observed cases of pulmonary embolism is not higher than expected in the absence of the MAH COVID-19 vaccines overall and within the queried strata. In summary, based on clinical data, literature data, routine statistical reports, safety database review, an O/E analysis as well as review of post-authorization safety studies, there is insufficient evidence to conclude a causal relationship between vaccination with BNT162b2 and the development of pulmonary embolism. The MAH considers this safety signal refuted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance.
Post-menopausal haemorrhage	The EMA PRAC signal assessment report on postmenopausal haemorrhage with COMIRNATY COVID-19 vaccine was received on 26 October 2023 [(EPITT ref. No. 19989) EMA/PRC/470614/2023]. Postmenopausal (bleeding) haemorrhage is not uncommon and occurs in approximately 4-11% of postmenopausal women with the incidence inversely related to the time since

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Table 27. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Post-menopausal haemorrhage <i>Cont'd</i>	menopause. There are many possible mechanisms of postmenopausal haemorrhage that can be theorized following COVID-19 vaccination, but there seems to be an absence of strong evidence for any mechanistic pathway. This evaluation provided information from several data sources, such as preclinical data, clinical trial data, MAH safety database data, disproportionality analyses, and literature review. In animal model studies of BNT162b2, no clinical signs of bleeding or haemorrhage were observed. In clinical trials, out of a total of 13857 female participants exposed to BNT162b2 and 13,958 exposed to placebo, 3 AEs of postmenopausal haemorrhage were reported, 1 in the BNT162b2 group and 2 in the placebo group. Ongoing clinical trials have incorporated more detailed questionnaires for participants reporting menstrual abnormalities. Literature data on postmenopausal haemorrhage were limited and did not provide evidence of a causal association with vaccination. In routine statistical reports, no statistical signal of disproportionality was identified for postmenopausal haemorrhage with the BNT162b2 vaccines. The majority of ICSRs in the global safety database were reported in women in the early postmenopausal period, when the incidence of postmenopausal haemorrhage is expectedly higher. Due to the nature of spontaneous case reports the needed clinical information for a meaningful assessment was often missing or incomplete with the main reason for classification as “possibly related based on WHO-UMC criteria” being only limited to a reasonable temporal relationship to vaccination. The conclusions that can be drawn are limited. In the O/E analysis, the number of observed cases of postmenopausal haemorrhage was not higher than expected based on background rates in the absence of the MAH COVID-19 vaccines for either of the risk windows. To conclude, the totality of the data does not provide enough evidence to conclude that vaccination with BNT162b2 causes postmenopausal haemorrhage, therefore no label amendments or RMP updates are considered necessary. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored using routine pharmacovigilance. On 11 March 2024, PRAC Final Assessment Report was received. PRAC agreed there is insufficient evidence to establish a causal association between Comirnaty and PMH and to continue to monitor through routine PV.
Important Risks	
None	
Risks Not Categorised as Important	
None	

16.2.2. Signal Evaluation Plan for Ongoing Signals

During the reporting period there were no ongoing signals.

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 589 potentially relevant cases of myocarditis and pericarditis: 393 cases reported myocarditis, and 233 cases reported pericarditis (in 37 of these 589 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, relevant safety information on myocarditis was reviewed. Please refer to Section 11 *Literature* for details. There was no significant new safety data on pericarditis 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”.⁶⁰
- 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 version 11.0 adopted on 26 October 2023.

⁶⁰ Myocarditis and pericarditis are listed in Section 4.8 of the EU-SmPC and in Section 4.8 of the RSI.

16.3.1.1.1. Important Identified Risks – Myocarditis

Search criteria⁶¹ - SMQ Noninfectious myocarditis/pericarditis (Narrow search).

Overall – All Ages

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 393 (monovalent original [325], monovalent Omicron XBB.1.5 [43], monovalent Omicron JN.1 [10], bivalent Omicron BA.4/BA.5 [9], bivalent Omicron BA.1 [4], monovalent Omicron KP.2 [2]; 1.1% of 34,843 cases, the total PM dataset), compared to 482 cases (0.5%) retrieved in the PSUR #6. Upon review of the 325 cases reported with monovalent original, the earliest event onset of the myocarditis related events occurred in 2021 (89 cases), in 2022 (67 cases), in 2023 (19 cases) and in 2024 in 9 cases.
- Country/region of incidence (≥ 10): Germany (107), UK (50), Japan (38), France (33), Sweden (26), US (25), Austria (16), and Australia (12).
- MC cases (213), NMC cases (180).
- Subjects' gender: female (157), male (219) and unknown (17).
- Subjects' age in years: $n = 343$, range: 7 – 95, mean: 43.8, median: 42.0.
- Medical history ($n = 166$); the most frequently (≥ 10) reported medical conditions included Hypertension (34), Drug hypersensitivity, Tobacco user (13 each), Hypercholesterolaemia, Hypothyroidism (10 each).
- COVID-19 Medical history ($n = 27$): COVID-19 (19), Suspected COVID-19 (6), Coronavirus infection, COVID-19 immunisation (1 each).
- Co-suspect medications (≥ 2): Elasomeran, Influenza vaccine inact sag 4V, pembrolizumab (4 each), Influenza vaccine inact split 4V (3), COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19) (2).

⁶¹ The SMQ (narrow) Noninfectious myocarditis/pericarditis that became available upon the up versioning to MedDRA version 25.0 is used as search criteria. In the up-versioning to MedDRA to 27.1, a new PT was added to the SMQ (Myocarditis-myositis-myasthenia gravis overlap syndrome) and is now included in the evaluation of myocarditis. The relevant PTs are: Autoimmune myocarditis; Carditis; Chronic myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune mediated myocarditis; Myocarditis; Myocarditis-myositis-myasthenia gravis overlap syndrome; Myopericarditis.

- Number of relevant events: 399.
- Relevant event seriousness: serious (399).
- Reported relevant PTs: Myocarditis (334), Myopericarditis (49), Carditis (8), Eosinophilic myocarditis, Giant cell myocarditis (3 each), Chronic myocarditis and Hypersensitivity myocarditis (1 each).
- Relevant event outcome: fatal (21), resolved/resolving (131), resolved with sequelae (40), not resolved (84), unknown (123).

- Risk factors:

Of the 393 cases reporting events indicative of myocarditis, 213 cases (54.2%) were MC. Of the 393 cases, in 93 cases (23.7% 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 131 cases (33.3%) 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 316 cases (80.4%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

*Age-stratified data*⁶²

Subjects aged 6 months through <5 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: none; 1 case (0.001%) was retrieved in the PSUR #6.

⁶² Cases where the age was reported only as:

- "Adolescent" (8 cases) were evaluated in the overall and in the 16-17 years age groups, and
- "Adult" (9 cases) were evaluated in the overall and in the 'Age Unknown' age group;

Subjects aged 5 through <12 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 1 (monovalent original [1]; 0.003% of 34,843 cases, the total PM dataset, 0.1% of the 716 subjects aged 5-11 years), compared to 4 cases (0.004 %) retrieved in the PSUR #6.
- Country/region of incidence: Brazil.
- Subjects' age in years: 7.
- Medical history: not reported.
- COVID-19 Medical history: not reported.
- Co-suspect medications: none.
- Most frequently co-reported PTs: Cardiac failure, Pericarditis, and Pulmonary oedema.

Myocarditis relevant data in this subgroup of subjects are summarised in Table 28.

Table 28. Myocarditis in Subjects Aged 5 through <12 years (N = 1)

Characteristics		Gender		
		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 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	Unknown	0	1	0
Event Outcome	Fatal	0	1	0
Duration of event ^b n = 0	Not Applicable			

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1):

A 7-year-old male subject,⁶³ dose 1 (monovalent original), MC, Brazil:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Cardiac failure, Myocarditis, Pericarditis, and Pulmonary oedema.
- Time to onset (myocarditis and pericarditis): unknown.
- Causes of death: Cardiac failure; Hepatic necrosis; Myocarditis; Pericarditis; Pulmonary oedema; Renal tubular necrosis.
- Autopsy: Abdominal distension; Generalised oedema.
- Comment: The subject experienced the events in the course of a complicated septic arthritis for which multiple antibiotic regimens were administered, and subject showed persistent abnormalities indicating a microbial infection. The clinical course was complicated by a lung injury consolidation and ground glass opacities and occurrence of gastrointestinal bleeding that hindered the necessary respiratory support. On autopsy, external examination showed diffuse intravascular coagulation and systemic multi-organ injury. Unfortunately, the patient died. On autopsy, external examination showed anasarca and increased abdominal volume. The internal organs showed diffuse oedema, including the brain, with pleural, pericardial, and peritoneal cavitory effusion. The heart exhibited a granular, opaque, whitish external surface, akin to fibrin deposits on the pericardium. The myocardium had a soft consistency, alternating between pale and haemorrhagic areas, while the valves remained preserved. Microscopy revealed disseminated vascular thromboembolism. The condition was diagnosed as acute pericarditis and myocarditis, without valve involvement, with heart failure leading to pulmonary oedema, complicated by acute tubular necrosis and ischemic hepatic necrosis. Based on available information, the causal association between the myocarditis and pericarditis and suspect drug BNT162b2 cannot be excluded completely.

Subjects aged 12 – 15 years

Clinical Trial Data

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

⁶³ Sousa PM, Silva EA, Campos MA, et al. Fatal Myocarditis following COVID-19 mRNA Immunization: A Case Report and Differential Diagnosis Review. *Vaccines*. 2024;12(2):194.

Post-Authorisation Data

- Number of cases: 7 (monovalent original [7]; 0.02% of 34,843 cases, the total PM dataset, 2.1% of the 328 subjects aged 12-15 years), compared to 36 cases (0.03%) retrieved in the PSUR #6.
- Country/region of incidence: Germany (2), Canada, Greece, Japan, Poland, US (1 each).
- Subjects' age in years: n = 7, range: 12 – 15, mean: 14.4, median: 15.0.
- Medical history (n = 2): Claustrophobia, Exercise adequate (athlete of Taekwondo), Tobacco user (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥ 2): Brain oedema, Interstitial lung disease, Myocardial necrosis, Pneumonia bacterial, Subclavian vein thrombosis (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 29.

Table 29. Myocarditis in Subjects Aged 12 – 15 years (N = 7)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	4	0
	No	1	0	0
Relevant PT ^a	Carditis	1	0	0
	Myocarditis	2	4	0
Hospitalisation required/prolonged	Yes	0	2	0
	No	3	2	0
Relevant suspect dose	Dose 1	1	2	0
	Dose 2	2	1	0
	Dose 3	0	1	0
Vaccine Presentation	Original	3	4	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 3	≤ 24 hours	0	1	0
	1-5 days	0	1	0
	14-21 days	0	1	0
Event Outcome	Fatal	1	0	0
	Not resolved	0	1	0
	Resolved	0	3	0
	Unknown	2	0	0
Duration of event ^b n = 1, median: NA	11-26 days	0	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1):

A 14-year-old female subject, dose 2 (monovalent original), NMC, US:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PT with fatal outcome: Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Myocarditis. It was not reported if an autopsy was performed.
- Comment: This is a legal case that only reports that subject received 2 doses of vaccine and died of myocarditis and flu-like symptoms. Although the case describes that the subject received medical attention for flu-like symptoms, there is no information about myocarditis diagnosis. Limited information on the clinical course details, subject's medical history, concomitant medication precluded a meaningful causality assessment in this case.

Subjects aged 16 – 17 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 20 (monovalent original [18], bivalent Omicron BA.4/BA.5, monovalent Omicron XBB.1.5 [1 each]; 0.06% of 34,843 cases, the total PM dataset, 8.2% of the 245 subjects aged 16-17 years), compared to 37 cases (0.03%) retrieved in the PSUR #6.
- Country/region of incidence: Germany (6), Japan, US (3 each), Canada (2), Austria, Costa Rica, South Korea, Poland, Sweden, UK (1 each).
- Subjects' age in years: n = 12, range: 16 – 17, mean: 16.3, median: 16.0.
- Medical history (n = 2): Chest pain, Chills, Crush injury, Drug hypersensitivity, Emergency care, Pyrexia (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Co-reported PTs: Atrial tachycardia, Cardiogenic shock, Cardiomyopathy, Dizziness, Fatigue, Heart valve incompetence, Hyperhidrosis, Incorrect dose administered, Leukocytosis, Multisystem inflammatory syndrome in children, Muscular weakness, Myocardial fibrosis, Palpitations, Pancreatitis, Performance status decreased, Pericardial

effusion, Pericarditis, Pleuritic pain, Supraventricular tachycardia, Tachycardia, Vomiting (1 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 30.

Table 30. Myocarditis in Subjects Aged 16 – 17 years (N = 20)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	1	12	1
	No	0	6	0
Relevant PT ^a	Myocarditis	1	17	1
	Myopericarditis	0	1	0
Hospitalisation required/prolonged	Yes	1	9	1
	No	0	9	0
Relevant suspect dose	Dose 1	0	1	0
	Dose 2	0	6	0
	Dose 3	1	4	0
	Dose unknown	0	7	1
Vaccine Presentation	Original	1	16	1
	Bivalent BA.4/BA.5	0	1	0
	Omicron XBB.1.5	0	1	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 7	1-5 days	0	4	0
	6-13 days	0	1	0
	32-60 days	0	1	0
	61-180 days	0	1	0
Event Outcome	Fatal	0	0	0
	Not resolved	0	1	0
	Resolved	0	8	0
	Resolving	1	3	0
	Resolved with sequelae	0	2	0
Duration of event ^b n = 1, median: N/A	Unknown	0	4	1
	181-365 days	0	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case: none.

Subjects aged 18 – 24 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 42 (monovalent original [39], monovalent Omicron XBB.1.5 [2], bivalent Omicron BA.4/BA.5 [1]; 0.1% of 34,843 cases, the total PM dataset, 3.7% of the 1146 subjects aged 18-24 years), compared to 62 cases (0.06%) retrieved in the PSUR #6.
- Country/region of incidence: Germany (15), Japan (5), France (4), UK (3), Austria, Poland, Spain, Turkey, US (2 each), Brazil, Norway, Portugal, Sweden, Taiwan (1 each).
- Subjects' age in years: n = 42, range: 18 – 24, mean: 21.2, median: 21.0.
- Medical history (n = 15): the most frequently (≥ 2) reported medical conditions included Abstains from alcohol, Non-tobacco user, Seasonal allergy, and Syncope (2 each).
- COVID-19 Medical history (n = 6): COVID-19 (5), Suspected COVID-19 (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥ 3): Chest pain (5), Fatigue, Pericarditis, Pyrexia (4 each), Headache, and Pericardial effusion (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 31.

Table 31. Myocarditis in Subjects Aged 18 – 24 years (N = 42)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	6	19	1
	No	5	11	0
Relevant PT ^a	Myocarditis	6	26	1
	Myopericarditis	5	5	0
Hospitalisation required/prolonged	Yes	10	22	1
	No	1	8	0
Relevant suspect dose	Dose 1	1	7	0
	Dose 2	3	15	1
	Dose 3	3	6	0
	Dose 5	1	0	0
	Dose Unknown	3	2	0
Vaccine Presentation	Original	10	28	1
	Bivalent BA.4/BA.5	1	0	0
	Omicron XBB.1.5	0	2	0

Table 31. Myocarditis in Subjects Aged 18 – 24 years (N = 42)

Characteristics		Gender		
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 29	≤ 24 hours	1	1	0
	1-5 days	0	13	0
	6-13 days	0	2	0
	14-21 days	3	0	0
	22-31 days	0	1	0
	61-180 days	0	2	0
	> 365 days	2	4	0
Event Outcome	Fatal	2	0	0
	Not resolved	0	6	0
	Resolved	5	14	0
	Resolving	0	3	0
	Resolved with sequelae	2	3	0
	Unknown	2	5	1
Duration of event ^b n = 8, median: 31.5 days	Upto 3 days	0	2	0
	4 to 6 days	0	1	0
	11 to 26 days	0	1	0
	27 to 57 days	0	1	0
	181 to 365 days	0	1	0
	>365 days	1	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal cases (2):

An 18-year-old female subject, dose 2 (original), NMC, US

- Medical history: Appendicectomy, Appendicitis, COVID-19, ‘unknown congenital heart issue’ (as reported, verbatim).
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Acute pulmonary oedema, Blood glucose increased, Blood loss anaemia, Brain injury, Brain oedema, Cardiomegaly, Circulatory collapse, Diabetes mellitus, Dilated cardiomyopathy, Dyspnoea, Ear haemorrhage, Embolism venous, Encephalopathy, Epistaxis, Eye haemorrhage, Gastrointestinal haemorrhage, Hyperglycaemia, Hyponatraemia, Hypoproteinaemia, Injury, Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome in children, Myocardial infarction, Myocardial ischaemia, Myocarditis, Pulmonary artery thrombosis, Pulmonary embolism, Right ventricular failure, Shock, Skin discolouration, Thrombosis with thrombocytopenia syndrome, Toxicity to various agents.
- Time to onset (myocarditis): unknown.
- Causes of death: All the above events reported a fatal outcome.
- Comment: In this case, the subject had COVID-19 twice and later received 2 doses of COVID-19 (BNT162b2) vaccination with a time gap of approximately 100 days between the 2 doses of the vaccination. Approximately after 12 days, the subject died due to the

above events. The lack of information regarding the clinical course details precluded a meaningful causality assessment in this case.

A 19-year-old female subject, dose: unknown (original), MC, Germany:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PT with fatal outcome: Myopericarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Myopericarditis.
- Autopsy: Myopericarditis
- Comment: There is no information regarding the latency, date of death, subject's medical, vaccination history and concomitant medications thus precluding a meaningful causality assessment in this case.

Subjects aged 25 – 29 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 38 (monovalent original [37], monovalent Omicron JN.1 [1]; 0.1% of 34,843 cases, the total PM dataset, 3.0% of the 1275 subjects aged 25-29 years), compared to 32 cases (0.03%) retrieved in the PSUR #6.
- Country/region of incidence: Germany (14), Japan (5), Sweden (4), US (3), Australia, Chile (2 each), Austria, Brazil, France, Lithuania, Peru, Poland, Switzerland, UK (1 each).
- Subjects' age in years: n = 38, range: 25 – 29, mean: 27.1, median: 27.0.
- Medical history (n = 19); the most frequently (≥ 2) reported medical condition included Asthma, Hypothyroidism, Tobacco user (3 each), Abortion spontaneous, Drug hypersensitivity, Ovarian operation, Pregnancy, and Seasonal allergy (2 each).
- COVID-19 Medical history (n = 3): COVID-19 (2), Coronavirus infection (1).
- Co-suspect medications: Influenza vaccine inact split 4V, Varicella zoster vaccine RGE (CHO) (1 each).
- Most frequently co-reported PTs (≥ 3): Chest pain (10), Fatigue (8), Tachycardia (7), Dyspnoea, Pericarditis (6 each), Asthenia, Dizziness, Palpitations (5 each), Angina pectoris, Chest discomfort, Malaise, Myocardial fibrosis, Pyrexia (4 each), Bradycardia,

Cardiac disorder, Disturbance in attention, Dyspnoea exertional, Headache, Memory impairment, Mental disorder, Postural orthostatic tachycardia syndrome, Sleep disorder, and Vertigo (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 32.

Table 32. Myocarditis in Subjects Aged 25 – 29 years (N = 38)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	4	11	0
	No	8	15	0
Relevant PT ^a	Carditis	1	0	0
	Myocarditis	11	25	0
	Myopericarditis	0	2	0
Hospitalisation required/prolonged	Yes	6	17	0
	No	6	9	0
Relevant suspect dose	Dose 1	3	5	0
	Dose 2	5	11	0
	Dose 3	2	4	0
	Dose unknown	2	6	0
Vaccine Presentation	Original	12	25	0
	Omicron JN.1	0	1	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 16	≤ 24 hours	1	1	0
	1-5 days	1	5	0
	6-13 days	0	1	0
	14-21 days	0	1	0
	22-31 days	1	1	0
	32-60 days	0	1	0
	> 365 days	0	3	0
Event Outcome	Fatal	1	0	0
	Not resolved	2	3	0
	Resolved	0	10	0
	Resolving	2	4	0
	Resolved with sequelae	2	3	0
	Unknown	5	7	0
Duration of event ^b n = 3; median: 6 days	Upto 3 days	0	1	0
	4 to 6 days	0	1	0
	>365 days	1	0	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1):

A 28-year-old female subject, dose 2 (monovalent original), MC, Japan

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Cardiac dysfunction, Circulatory collapse, General physical health deterioration, Myocarditis, Seizure.
- Time to onset (myocarditis): unknown.
- Causes of death: All the above events reporting a fatal outcome. It was not reported if an autopsy was performed.
- Comment: The subject experienced convulsive status after 21 days of receiving the 2nd dose of monovalent original vaccine that due to emergence of cardiac insufficiency, required cardiac support. The case reports that a definitive diagnosis of myocarditis could not be made; the removal of cardiac support is reported, but it is unclear whether the subject's circulatory function recovered, and the case reports that subject expired due to cerebral failure approximately 42 days of vaccination. The reporting physician assessed the causality between the events and the vaccine as unassessable. Considering the convulsive event at the origin of the cardiac deterioration and death due to loss of brain function, and in the absence of information regarding subject's history and clinical course during hospitalisation, an individual contributory role of the original vaccine towards the fatal events cannot be established.

Subjects aged 30 – 39 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 60 (monovalent original [56], monovalent Omicron XBB.1.5 [4]; 0.2% of 34,843 cases, the total PM dataset, 1.6% of the 3745 subjects aged 30-39), compared to 75 cases (0.07%) retrieved in the PSUR #6.
- Country/region of incidence: Germany (17), UK (10), Austria, Sweden (4 each), France, Japan, Norway, US (3 each), Australia, Italy, Poland, Spain (2 each), Argentina, Finland, South Korea, Malaysia, Netherlands (1 each).
- Subjects' age in years: n = 60 range: 30 – 39, mean: 34.7, median: 35.0.
- Medical history (n = 19); the most frequently (≥ 2) reported medical conditions included Hypertension, Hypothyroidism, Palpitations (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (3), Suspected COVID-19 (1).

- Co-suspect medications: Andusomeran, COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19), Influenza vaccine inact sag 4V(1 each).
- Most frequently co-reported PTs (≥ 5): Fatigue (16), Palpitations (15), Chest pain (14), Tachycardia (11), Dyspnoea (10), Dizziness (9), Arrhythmia, Headache (6 each), Pericardial effusion, Pyrexia (5 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 33.

Table 33. Myocarditis in Subjects Aged 30 – 39 years (N = 60)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	9	18	0
	No	16	17	0
Relevant PT ^a	Carditis	1	1	0
	Eosinophilic myocarditis	0	2	0
	Giant cell myocarditis	0	1	0
	Myocarditis	19	28	0
	Myopericarditis	6	3	0
Hospitalisation required/prolonged	Yes	13	25	0
	No	12	10	0
Relevant suspect dose	Dose 1	5	10	0
	Dose 2	8	10	0
	Dose 3	5	5	0
	Dose 4	0	1	0
	Dose unknown	7	9	0
Vaccine Presentation	Original	25	31	0
	Omicron XBB.1.5	0	4	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 33	≤ 24 hours	1	5	0
	1-5 days	4	3	0
	6-13 days	3	3	0
	22-31 days	1	1	0
	32-60 days	1	2	0
	61-180 days	0	3	0
	181-365 days	1	3	0
	> 365 days	1	1	0
Event Outcome	Fatal	1	1	0
	Not resolved	8	7	0
	Resolved	3	7	0
	Resolving	3	5	0
	Resolved with sequelae	4	4	0
	Unknown	7	11	0
Duration of event ^b n = 7, median: 8 days	upto 3 days	0	1	0
	7 to 10 days	1	2	0
	27 to 57 days	1	0	0
	>365 days	1	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal cases (2):

A 35-year-old male subject, dose 2 (monovalent original), MC, Germany

- Medical history: Hypertrophic cardiomyopathy.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Brain oedema, Cardiac arrest, Coma, Myocarditis, Sepsis, Subarachnoid haemorrhage.
- Time to onset (myocarditis): 3 days.
- Causes of death: All the above events that reported a fatal outcome.
- Autopsy: An autopsy was performed, but details were unavailable.
- Comment: The subject with a history of hypertrophic cardiomyopathy experienced sepsis 3 days after the second dose of the vaccine. The case lacks details about the infectious event (sepsis) but reports subject could not be resuscitated, and thus it is more likely the cardiac injury is a secondary reactive event to the systemic infection reported, and thus a role of the vaccine is unlikely.

A 32-year old female subject, dose: unknown (monovalent original), NMC, UK

- Medical history: Cardiac disorder, COVID-19, Dyspnoea, Palpitations, Stress.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Cardiac arrest, Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Cardiac arrest.
- Autopsy: Myocarditis.
- Comment: The subject had a history of an unspecified heart condition with dyspnoea and palpitations prior to vaccination with no treatment or cardiologic supervision reported. The case reports subject started to experience palpitations again 2 years after vaccination and died. Given the reported history and long latency since vaccination, it is more likely the subject's condition and outcome were a reflection of a pre-existing yet untreated arrhythmic disorder.

Subjects aged ≥40 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 184 (monovalent original [137], monovalent Omicron XBB.1.5 [28]; monovalent Omicron JN.1 [9]; bivalent Omicron BA.4/BA.5 [5]; bivalent Omicron BA.1

[3], monovalent Omicron KP.2 [2]; 0.5% of 34,843 cases, the total PM dataset, 0.9% of the 20,458 subjects ≥ 40 years), compared to 192 cases (0.2%) retrieved in the PSUR #6.

- Country/region of incidence: Germany (46), France (25), UK (23), Japan, Sweden (15 each), Austria (8), Australia, US (7 each), Italy (5), Canada, Taiwan, province of China (4 each), Denmark, Ireland, South Korea, Norway (3 each), Finland, Portugal (2 each), Argentina, Estonia, Greece, Hong Kong, Netherlands, Romania, South Africa, Spain, and Thailand (1 each).
- Subjects' age in years: $n = 183$, range: 40 – 95, mean: 58.6, median: 57.0.
- Medical history ($n = 100$); the most frequently (≥ 3) reported medical conditions included Hypertension (32), Hypercholesterolaemia (10), Atrial fibrillation, Drug hypersensitivity (8 each), Sinus node dysfunction, Tobacco user (7 each), Type 2 diabetes mellitus (6), Cardiac pacemaker insertion, Cerebrovascular accident, Gastrooesophageal reflux disease, Hypothyroidism, Obesity, Seasonal allergy (5 each), Benign prostatic hyperplasia, Colitis ulcerative, Depression, Overweight, Tonsillectomy (4 each), Appendectomy, Asthma, Chronic obstructive pulmonary disease, Dyslipidaemia, Ex-tobacco user, Gastrointestinal disorder, Hypersensitivity, Migraine, and Surgery (3 each).
- COVID-19 Medical history ($n = 10$): COVID-19 (6), Suspected COVID-19 (3), COVID-19 immunisation (1).
- Co-suspect medications: Elasomeran, Influenza vaccine inact sag 4V, Pembrolizumab (3 each), Influenza vaccine inact split 4V (2), Diazepam, Fluoxetine, Influenza vaccine, Ocrelizumab (1 each).
- Most frequently co-reported PTs (≥ 10): Fatigue (35), Dyspnoea (27), Chest pain, Palpitations (21 each), Dizziness, Pericarditis, Tachycardia (17 each), Pyrexia (14), Cardiac failure, Headache (13 each), Arrhythmia, Asthenia, Visual impairment (12 each), Ventricular extrasystoles (11), Arthralgia, Atrial fibrillation, and Pericardial effusion (10 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 34.

Table 34. Myocarditis in Subjects Aged ≥40 years (N = 184)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	49	57	3
	No	40	35	0
Relevant PT ^a	Carditis	3	0	0
	Chronic myocarditis	1	0	0
	Eosinophilic myocarditis	0	1	0
	Giant cell myocarditis	1	1	0
	Hypersensitivity myocarditis	1	0	0
	Myocarditis	74	81	3
	Myopericarditis	10	11	0
Hospitalisation required/prolonged	Yes	38	54	3
	No	51	38	0
Relevant suspect dose	Dose 1	28	31	0
	Dose 2	26	26	0
	Dose 3	16	15	0
	Dose 4	5	2	0
	Dose 5	0	2	0
	Dose 6	1	1	0
	Dose unknown	13	15	3
Vaccine Presentation	Original	63	71	3
	Bivalent BA.1	2	1	0
	Bivalent BA.4/BA.5	3	2	0
	Omicron XBB.1.5	19	9	0
	Omicron JN.1	1	8	0
	Omicron KP.2	1	1	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 74	≤ 24 hours	6	11	0
	1-5 days	2	8	0
	6-13 days	2	12	0
	14-21 days	3	2	0
	22-31 days	3	2	0
	32-60 days	4	2	0
	61-180 days	6	2	0
	181-365 days	2	2	0
	> 365 days	2	3	0
Event Outcome	Fatal	6	5	1
	Not resolved	26	22	0
	Resolved	12	15	0
	Resolving	7	16	2
	Resolved with sequelae	8	12	0
	Unknown	31	24	0
Duration of event ^b n = 9, median: 18 days	upto 3 days	0	1	0
	4 to 6 days	1	1	0
	7 to 10 days	0	1	0
	11 to 26 days	0	1	0
	27 to 57 days	0	1	0
	58 to 180 days	0	1	0
	>365 days	1	1	0

a. All serious occurrences.

Table 34. Myocarditis in Subjects Aged ≥40 years (N = 184)

Characteristics	Gender
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b. For those cases where the event resolved or resolved with sequelae.

Fatal cases (12 cases):

Monovalent original (6 cases)

A 67-year-old female subject, dose 3 (monovalent original), MC, UK:

- Medical history: Atrial fibrillation, Chest pain, Depression, Gastroesophageal reflux disease, Hypertension, Hypothyroidism, Oedema, Type 2 diabetes mellitus.
- Co-suspect medications: none.
- Concomitant medications: Apixaban, Atorvastatin, Bisoprolol, Dapagliflozin, Furosemide, Glyceryl trinitrate, Isosorbide mononitrate, Lansoprazole, Levothyroxine, Ramipril, Ranolazine, Sertraline.
- PTs with fatal outcome: Acute left ventricular failure, Atrial fibrillation, Hypertension, Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: All the above events that reported a fatal outcome.
- Comment: The subject died after approximately 884 days of receiving the last dose of COVID-19 (BNT162b2) vaccination and presented multiple co-morbidities including cardiovascular that were more likely as to induce the reported course and outcome.

A 9-decade-old subject⁶⁴ of unknown gender and dose (monovalent original), MC, UK:

- Medical history: Hospitalisation, Malignant melanoma stage IV.
- Co-suspect medications: Pembrolizumab.
- Concomitant medications: not reported.
- PTs with fatal outcome: Myocarditis, Myositis.
- Time to onset (myocarditis): unknown.
- Causes of death: Both the above events that reported a fatal outcome.
- Autopsy: Myocarditis; Myositis.
- Comment: Considering the subject's age, medical history (stage IV malignant melanoma), co-suspect medication (pembrolizumab), and limited information on the therapy dates, an individual contributory role of the monovalent original vaccine is unlikely.

A 42-year-old male subject, dose 2 (monovalent original), NMC, Germany:

- Medical history: not reported.
- Co-suspect medications: none.

⁶⁴ Watson RA, Ye W, Taylor CA, et al. Severe acute myositis and myocarditis on initiation of 6-weekly pembrolizumab post-COVID-19 mRNA vaccination. J Immunother Cancer. 2024 Apr 24;12(4):e008151.

- Concomitant medications: not reported.
- PTs with fatal outcome: Acute myocardial infarction, Myocarditis.
- Time to onset (myocarditis): 1 day.
- Causes of death: Both the above events that reported a fatal outcome.
- Comment: In this case, the subject reported multiple nonserious events including Disturbance in attention, Fatigue, Insomnia, Tachycardia, Anxiety and Chest discomfort after receiving the 2nd dose of COVID-19 vaccine. The subject had fatal events of myocarditis and acute myocardial infarction approximately 452 days after the 2nd dose. However, it was also reported that the subject suddenly fell off the bike during a bike tour and subsequently died the next day, which along with the coronary acute event that represents a criterion of exclusion for myocarditis, are more likely to have resulted in the reported clinical course and outcome.

A 78-year-old male subject, dose: unknown (monovalent original), MC, Japan:

- Medical history: Autoimmune disorder, Dyspnoea, Henoch-Schonlein purpura.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PT with fatal outcome: Myocarditis.
- Time to onset (myocarditis): 1 day.
- Causes of death: Myocarditis.
- Comment: In this case, the subject had a medical history of autoimmune disorder and Henoch-Schonlein purpura and he developed dyspnoea 3 days prior to the vaccination with monovalent original, which 1 day after vaccination aggravated and required advanced life support. A myocarditis was confirmed histologically 1 day after the vaccination, but given the pre-existing symptoms, it is more likely the myocardial injury was already developing in this subject at the time of the vaccination.

A 57-year-old female subject, dose 2 (monovalent original), NMC, US:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Cardiac arrest, Myocarditis.
- Time to onset (myocarditis): 2 days.
- Causes of death: Both the above events that reported a fatal outcome.
- Comment: In this case, the subject received the 1st dose of the monovalent original vaccine which was uneventful. After approximately 21 days, the subject received the 2nd dose of monovalent original vaccine and reported fatigue and chills the next day and subsequently died within 2 days of getting the vaccination. The reporter who is not a medical professional considered the event would have been a myocarditis, but there was no information in the case that presented any objective information that the sudden death was the result of a myocarditis. In absence of any information regarding medical history, clinical course and evaluation, a causality between the event and the outcome is precluded.

A 5-decade-old male subject,⁶⁵ dose 2 (monovalent original), MC, Japan:

- Medical history: Dermatitis atopic.
- Co-suspect medications: none.
- Concomitant medications: none.
- PT with fatal outcome: Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Arrhythmia; Hypoxic-ischaemic encephalopathy; Multiple organ dysfunction syndrome; Myocarditis.
- Comment: After receiving the 2nd dose of monovalent original vaccine, the subsequent day patient developed fever and lost consciousness and on day 9 of admission to emergency department he died. His laboratory results showed elevated troponin, CRP, creatine kinase, creatine-kinase myoglobin binding and brain natriuretic peptide. His autopsy showed hypoxic encephalopathy and multiple organ failure. In the thyroid gland, a minute latent papillary carcinoma and chronic lymphocytic thyroiditis were observed. His heart histology showed several small inflammatory foci that revealed myocardial degeneration, necrosis or granulation changes and the reporter considered the myocarditis secondary to the monovalent original vaccine as confirmed. Based on a temporal relationship, a contributory role of the monovalent original vaccine cannot be completely excluded despite the limited information regarding the subject's medical history and the role of the neoplasm in the reported events and outcome.

Bivalent Omicron BA.1 (1 case)

A 62-year-old male subject, dose 4 (bivalent Omicron BA.1), NMC, Sweden:

- Medical history: Hypertension.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Dizziness, Fatigue, Giant cell myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Giant cell myocarditis.
- Comment: In this case, the subject died approximately after 143 days of receiving the dose 4 (bivalent BA.1) vaccine. Long gap between the latest vaccine date and the subject's death, subject's medical history of hypertension and limited information regarding the clinical course details make an individual contributory role of the COVID-19 vaccine (bivalent BA.1) towards the fatal events unlikely.

Bivalent Omicron BA.4/BA.5 (1 case)

A 72-year-old female subject, dose 4 (bivalent Omicron BA.4/BA.5), NMC, Germany:

- Medical history: Breast cancer female, Mastectomy.

⁶⁵ Minato H, Yoshikawa A, Tsuyama S, et al. Fatal arrhythmia in a young man after COVID-19 vaccination: An autopsy report. *Medicine (Baltimore)*. 2024 Feb 2;103(5):e37196.

- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Fluid retention, Myocarditis, Organising pneumonia, Respiratory distress.
- Time to onset (myocarditis): 76 days.
- Causes of death: Myocarditis.
- Autopsy: Myocarditis; Organising pneumonia.
- Comment: In this case, the subject received dose 1, 2, and 3 from other manufacturer where she reported shortness of breath after receiving the 1st dose of vaccination which got worsened by time. After receiving the 4th dose (bivalent Omicron BA.4/BA.5; booster), the subject also developed fatigue and myalgia. After approximately 76 days of receiving the 4th dose of vaccination, the subject died due to organizing pneumonia and myocarditis. In this case, an individual contributory role of bivalent Omicron BA.4/BA.5 vaccine cannot be established (pneumonia and myocarditis were reported as occurring on the same day).

Monovalent Omicron XBB.1.5 (2 cases)

A 51-year-old female subject, dose 1 (monovalent Omicron XBB.1.5), MC, Estonia:

- Medical history: Blindness, Premature baby, Radial nerve palsy.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Cardiac ventricular thrombosis, Cardiogenic shock, Myocarditis, Pericardial effusion, Pleural effusion.
- Time to onset (myocarditis): 41 days.
- Causes of death: All the above events that reported a fatal outcome.
- Comment: In this case, the acute myocardial infarction, which is a diagnosis of exclusion for myocarditis, was more likely to have triggered the clinical course and reported outcome.

A 59-year-old female subject, dose 1 (monovalent Omicron XBB.1.5), MC, Germany:

- Medical history: Pulmonary fibrosis, Vasculitis.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Haemorrhagic cerebral infarction, Myocarditis, Vasculitis.
- Time to onset (myocarditis): unknown.
- Causes of death: Chronic obstructive pulmonary disease; Haemorrhagic cerebral infarction; Myocarditis; Vasculitis.
- Comment: The subject experienced broncho-pneumonia and massive cerebral haemorrhage which reportedly was considered the cause of death.

Monovalent Omicron KP.2 (1 case)

A 41-year-old female subject, dose 1 (monovalent Omicron KP.2), NMC, US:

- Medical history: Not reported.
- Co-suspect medications: None.
- Concomitant medications: not reported.
- PT with fatal outcome: Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Myocarditis.
- Comment: Limited information regarding the clinical course details, therapy details, vaccination dates and latency in this case precluded a meaningful causality assessment.

Monovalent Omicron JN.1 (1 case)

An 89-year-old male subject, dose 1 (monovalent Omicron JN.1), MC, Japan:

- Medical history: Angina pectoris, Blood cholesterol increased, Cardiac failure, Carotid artery stenosis, Cerebral infarction, Constipation, Diabetes mellitus, Hospitalisation, Hypercholesterolaemia, Hypertension, Intra-cerebral aneurysm operation, Mixed dementia.
- Co-suspect medications: None.
- Concomitant medications: Acetylsalicylic acid, bisoprolol, influenza vaccine, magnesium oxide, pitavastatin, sacubitril/valsartan, spironolactone.
- PTs with fatal outcome: Cardiac failure chronic, Myocarditis.
- Time to onset (myocarditis): 1 day.
- Causes of death: Both the above events that reported a fatal outcome.
- Comment: The 89-year-old subject with end stage heart failure expired during hospitalisation. A confirmation for myocarditis is not provided, nor any information that would help assess the role of the vaccine in inducing a de novo cardiac injury in this elderly individual.

Subjects with Unknown Age

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 41 (monovalent original [30], monovalent Omicron XBB.1.5 [8], bivalent Omicron BA.4/BA.5 [2], bivalent Omicron BA.1 [1]; 0.1% of 34,843 cases, the total PM dataset; 0.6% of the 6432 subjects with unknown age), compared to 43 cases (0.04%) retrieved in the PSUR #6.

- Country/region of incidence: UK (12), Germany (7), Japan, US (6 each), Italy (2), Australia, Brazil, Canada, Ireland, New Zealand, Norway, Portugal, Sweden (1 each).
- Medical history (n = 9): Alcohol use, Arthritis, Autoimmune thyroiditis, Autologous haematopoietic stem cell transplant, B-cell lymphoma, Bipolar disorder, Breast cancer, Gestational diabetes, Immunodeficiency, Infection, Metastatic renal cell carcinoma, Non-tobacco user, Obesity, Thyroidectomy, and Tobacco user (1 each).
- COVID-19 Medical history (n = 3): COVID-19 (2), Suspected COVID-19 (1).
- Co-suspect medications: COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19), Elasmomeran, Pembrolizumab (1 each).
- Most frequently co-reported PTs (≥ 3) included Fatigue (8), Chest pain, Dyspnoea, Palpitations (7 each), Headache, Pericarditis (4 each), Chronic fatigue syndrome, Malaise, Tachycardia (3 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 35.

Table 35. Myocarditis in Subjects Aged Unknown (N = 41)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	5	5	5
	No	11	8	7
Relevant PT ^a	Carditis	1	0	0
	Myocarditis	11	11	12
	Myopericarditis	4	2	0
Hospitalisation required/prolonged	Yes	7	3	4
	No	9	10	8
Relevant suspect dose	Dose 1	6	2	3
	Dose 2	6	4	1
	Dose 3	0	1	1
	Dose 4	0	1	0
	Dose 5	1	0	0
	Dose unknown	3	5	7
Vaccine Presentation	Original	11	11	8
	Bivalent BA.1	0	1	0
	Bivalent BA.4/BA.5	1	0	1
	Omicron XBB.1.5	4	1	3

Table 35. Myocarditis in Subjects Aged Unknown (N = 41)

Characteristics		Gender		
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 9	≤ 24 hours	1	0	0
	1-5 days	0	1	0
	6-13 days	1	0	0
	22-31 days	1	0	0
	32-60 days	1	0	0
	61-180 days	0	1	0
	181-365 days	0	1	1
	> 365 days	0	1	0
Event Outcome	Fatal	1	1	0
	Not resolved	5	1	2
	Resolved	3	1	0
	Resolving	1	3	0
	Unknown	6	7	10
Duration of event ^b n = 0, median: NA	None			

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal cases (2):

A subject of unknown age, male gender, dose 3 (monovalent original), NMC, Germany:

- Medical history: not reported.
- Co-suspect medications: COVID-19 Vaccine NRVV AD (ChAdOx1 nCoV-19).
- Concomitant medications: not reported.
- PTs with fatal outcome: Myocarditis.⁶⁶
- Time to onset (myocarditis): not reported.
- Causes of death: Myocarditis.
- Comment: In view of the long latency (>2 years) from the vaccination and reported event, and the limited clinical information provided, a role of the vaccine in inducing the reported event and outcome is unlikely.

A subject of unknown age, female gender, dose 5 (monovalent original), NMC, US:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PT with fatal outcome: Myocarditis.
- Time to onset (myocarditis): unknown.
- Causes of death: Myocarditis.

⁶⁶ Reportedly also the PT Interchange of vaccine products was reported with a fatal outcome.

- Comment: In this spontaneously reported case, it is reported that the subject experienced feeling unwell after each vaccination and expired after the last dose in a nursing home. Limited information regarding the subject's medical history and the clinical course details precluded a meaningful causality assessment in this case.

16.3.1.1.2. Important Identified Risks – Pericarditis

Search criteria⁶⁷ - SMQ Noninfectious myocarditis/pericarditis (Narrow search).

Overall – All Ages

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 233 (monovalent original [181], monovalent Omicron XBB.1.5 [32], monovalent Omicron JN.1 [9], monovalent Omicron KP.2 [4], bivalent Omicron BA.4/BA.5 [4], bivalent Omicron BA.1 [3]; 0.7% of 34,843 cases of the total PM dataset), compared to 432 cases (0.4%) retrieved in the PSUR #6.
- Country/region of incidence (≥ 10): France (36), UK (25), Australia, Germany (22 each), Italy (16), Sweden (15), US (12), Greece, Japan (11 each), Canada Netherlands, and Norway (10 each). The remaining 33 cases were distributed among 17 countries.
- MC cases (106), NMC cases (127).
- Subjects' gender: female (132), male (99) and unknown (2).
- Subjects' age in years: $n = 211$, range: 7 – 96, mean: 45.7, median: 45.0.
- Medical history ($n = 103$); the most frequently (≥ 5) reported medical history included Hypertension (16), Asthma, Obesity (9 each), Non-tobacco user (8), Pericarditis (7), Drug hypersensitivity, Ex-tobacco user, Hypothyroidism (6 each), and Seasonal allergy (5).
- COVID-19 Medical history ($n = 23$): COVID-19 (18), Suspected COVID-19 (3), Coronavirus infection, and Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (≥ 2 occurrences), ($n = 23$); relevant co-suspect medications included Elasomeran, Influenza vaccine inact split 4V (7 each), Influenza vaccine (3), and COVID-19 vaccine NRVV AD (ChAdOx1 nCoV-19) (2).

⁶⁷ The relevant PTs are: Autoimmune pericarditis; Immune-mediated pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

- Number of relevant events: 233.
- Relevant event seriousness: serious (233).
- Reported relevant PTs: Pericarditis (224), Pericarditis constrictive, Pleuropericarditis (4 each), and Autoimmune pericarditis (1).
- Relevant event outcome: fatal (6), resolved/resolving (81), resolved with sequelae (8), not resolved (78), unknown (60).
- Risk factors:

Of the 233 cases reporting events indicative of pericarditis, 106 cases (45.5%) were medically confirmed. Of the 233 cases, in 66 cases (28.3% 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 233 cases, in 81 cases (34.8%) 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) did not match a suspected vaccine induced event. Of the 233 cases, in 167 cases (71.7%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

Age-stratified data⁶⁸

Subjects aged 6 months through <5 years

Clinical Trial Data

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

Post-Authorisation Data

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

Subjects aged 5 through <12 years

Clinical Trial Data

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

⁶⁸ 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: 1 (monovalent original [1]; 0.003% of 34,843 cases, the total PM dataset; 0.14% of the 716 subjects aged 5-11 years), compared to 1 case (0.001%) retrieved in the PSUR #6.
- Country/region of incidence: Brazil (1).
- Subjects' age in year: 7 years.
- Medical history: not reported.
- COVID-19 Medical history: not reported.
- Co-suspect medications: none.
- Co-reported PTs: Cardiac failure, Myocarditis, and Pulmonary oedema (1 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the Table 36 below.

Table 36. 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	Yes	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	unknown	0	1	0
Event Outcome	Fatal	0	1	0
Duration of event ^b n = 0, median: N/A	None	0	0	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1): This case, involving a 7-year-old male subject is summarised in Section 16.3.1.1.1, in the text below Table 28.

Subjects aged 12 – 15 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 3 (original [3]; 0.009% of 34,843 cases, the total PM dataset; 0.9% of the 328 subjects aged 12-15 years), compared to 11 cases (0.01% of the total PM dataset) retrieved in the PSUR #6.
- Country/region of incidence: Japan (2), Switzerland (1).
- Subjects' age in years: n = 3, range: 12.0 – 15.0, mean: 13.7, median: 14.0.
- Medical history: none.
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Co-reported PTs: Arthralgia, Asthenia, Brain fog, Chronic fatigue syndrome, Diplopia, Dizziness, Dyspnoea exertional, Headache, Hyperacusis, Immune system disorder, Infection, Malaise, Menstrual disorder, Muscle contractions involuntary, Muscle twitching, Myalgia, Nasopharyngitis, Nausea, Pain, Pain in extremity, Palpitations, Poor peripheral circulation, Postural orthostatic tachycardia syndrome, Sleep disorder, Tachycardia, Vaccination site pain, Vision blurred, Visual impairment, and Vomiting (1 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 37.

Table 37. Pericarditis in Subjects Aged 12-15 (N = 3)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	0	2	0
	No	1	0	0
Relevant PT ^a	Pericarditis	1	2	0
Hospitalisation required/prolonged	No	1	2	0
Relevant suspect dose	Dose 1	1	1	0
	Dose 3	0	1	0
Vaccine Presentation	Original	1	2	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 3	1-5 days	0	1	0
	6-13 days	0	1	0
	unknown	1	0	0
Event Outcome	Resolved	0	2	0
	Unknown	1	0	0
Duration of event ^b n = 2, median: 40	11-26 days	0	1	0
	58-180 days	0	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 16 – 17 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 2 (monovalent original [1], bivalent Omicron BA.4/BA.5 [1]; 0.006% of 34,843 cases, the total PM dataset; 0.8% of the 245 subjects aged 16-17 years), compared to 16 cases (0.01% of the total PM dataset) retrieved in the PSUR #6.
- Country/region of incidence: Austria, Japan (1 each).
- Subjects' age in years: n = 2, range: 16 – 17, mean: 16.5, median: 16.50.
- Medical history: none.
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Co-reported PTs: Chest pain, Myocardial fibrosis, Myocarditis, Performance status decreased, Pericardial effusion, and Pyrexia (1 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 38.

Table 38. Pericarditis in Subjects Aged 16-17 (N = 2)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	0	2	0
	No	0	0	0
Relevant PT ^a	Pericarditis	0	2	0
Hospitalisation required/prolonged	Yes	0	2	0
Relevant suspect dose	Dose 2	0	1	0
	Dose 4	0	1	0
Vaccine Presentation	Original	0	1	0
	Bivalent BA.4/BA.5	0	1	0

Table 38. Pericarditis in Subjects Aged 16-17 (N = 2)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 2	1-5 days	0	2	0
Event Outcome	Resolved	0	1	0
	Resolving	0	1	0
Duration of event ^b n = 1, median: N/A	Unknown	0	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 18 – 24 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 20 (monovalent original [19]; monovalent Omicron XBB.1.5 [1]; 0.06% of 34,843 cases, the total PM dataset; 1.7% of the 1146 subjects aged 18-24 years), compared to 40 cases (0.04% of the total dataset) retrieved in the PSUR #6.
- Country/region of incidence: Italy (4), Germany, Sweden (3 each), France, Japan (2 each), Australia, Austria, Netherlands, Spain, Turkey, UK (1 each).
- Subjects' age in years: n = 20, range: 19 – 24, mean: 22.2, median: 22.0.
- Medical history: Non-tobacco user, Seasonal allergy (2 each), Abstains from alcohol, Allergy to animal, Migraine, Mite allergy, Myocarditis, Pericarditis, Rhinitis allergic, Syncope (1 each).
- COVID-19 Medical history (n = 3): COVID-19 (3).
- Co-suspect medications: Elasomoran (2).
- Most frequently co-reported PTs (≥3): Dyspnoea (6), Chest pain, Myocarditis, Pericardial effusion (4 each), Extrasystoles, Interchange of vaccine products, Nausea, and Palpitations (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 39.

Table 39. Pericarditis in Subjects Aged 18-24 (N = 20)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	5	0
	No	8	4	0
Relevant PT ^a	Pericarditis	11	8	0
	Autoimmune Pericarditis	0	1	0
Hospitalisation required/prolonged	Yes	5	6	0
	No	6	3	0
Relevant suspect dose	Dose 1	4	3	0
	Dose 2	3	0	0
	Dose 3	1	4	0
	Unknown	3	2	0
Vaccine Presentation	Original	10	9	0
	Omicron XBB.1.5	1	0	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 20	<24 hours	1	0	0
	>365 days	2	0	0
	1-5 days	0	3	0
	6-13 days	1	1	0
	32-60 days	1	0	0
	61-180 days	1	1	0
	Unknown	5	4	0
Event Outcome	Not resolved	5	1	0
	Resolved	3	3	0
	Resolving	2	2	0
	Unknown	1	3	0
Duration of event ^b n = 6, median: 261.5	4-6 days	0	1	0
	>365 days	0	1	0
	Unknown	3	1	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 25 – 29 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 25 (monovalent original [23], monovalent Omicron XBB.1.5 [1], monovalent Omicron JN.1 [1]) 0.07% of 34,843 cases, the total PM dataset; 2.0% of the 1275 subjects aged 25-29 years), compared to 56 cases (0.05% of the total PM dataset) retrieved in the PSUR #6.

- Country/region of incidence: Germany (6), France, UK (3 each), Australia, Canada, Italy, Sweden (2 each), Belgium, Peru, Spain, Turkey, and US (1 each).
- Subjects' age in years: n = 25, range: 25 – 29, mean: 27, median: 27.0.
- Medical history (n = 9): the medical conditions reported more than once included Hypothyroidism (3).
- COVID-19 Medical history (n = 2): Coronavirus infection, and COVID-19 (1 each).
- Co-suspect medications (n = 3): COVID-19 vaccine NRVV AD, Influenza vaccine inact sag 4V, Influenza vaccine inact split 4V, Varicella zoster vaccine RGE (1 each)
- Most frequently co-reported PTs (≥ 2): Chest pain, Dyspnoea, Myocarditis (6 each), Fatigue, Palpitations (5 each), Pyrexia (4), Angina pectoris, Tachycardia (3 each), Headache, Myalgia, and Pericardial effusion (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 40.

Table 40. Pericarditis in Subjects Aged 25-29 (N = 25)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	8	4	0
	No	5	8	0
Relevant PT ^a	Pericarditis	13	11	0
	Pericarditis constrictive	0	1	0
Hospitalisation required/prolonged	Yes	4	7	0
	No	9	5	0
Relevant suspect dose	Dose 1	3	0	0
	Dose 2	3	9	0
	Dose 3	3	0	0
	Unknown	4	3	0
Vaccine Presentation	Original	12	11	0
	Omicron XBB.1.5	1	0	0
	Omicron JN.1	0	1	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 25	1-5 days	3	2	0
	6-13 days	2	0	0
	22-31 days	1	1	0
	32-60 days	1	1	0
	61-180 days	0	1	0
	>365 days	0	2	0
	Unknown	6	5	0
Event Outcome	Not resolved	4	6	0
	Resolved	3	1	0
	Resolving	2	3	0
	Resolved with sequelae	0	1	0
	Unknown	4	1	0

Table 40. Pericarditis in Subjects Aged 25-29 (N = 25)

Characteristics		Gender		
		Female No. of Events	Male No. of Events	Unknown No. of Events
Duration of event ^b n = 5, median: 78	11-26 days	1	0	0
	58-180 days	1	0	0
	Unknown	1	2	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Subjects aged 30 – 39 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 34 (monovalent original [30]; monovalent Omicron JN.1 [2]; monovalent Omicron XBB.1.5 [1]; bivalent Omicron BA.4/BA.5 [1]) 0.10% of 34,843 cases, the total PM dataset; 0.9% of the 3745 subjects aged 30-39 years), compared to 77 cases (0.07% of the total PM dataset) retrieved in the PSUR #6.
- Country/region of incidence: France (9), Australia (5), Germany, UK (4 each), Austria, Canada, Netherlands (2 each), Belgium, Greece, Norway, Romania, Turkey, and US (1 each).
- Subjects' age in years: n = 34, range: 30 – 39, mean: 35.0, median: 35.50.
- Medical history (n = 14): the medical conditions reported more than once included Asthma (3), Non-tobacco user, Pneumonia, Road traffic accident, and Sinus tachycardia (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect medications (n = 3); Elasomeran, Influenza vaccine, Influenza vaccine inact split 4V (1 each)
- Most frequently co-reported PTs (≥3): Fatigue, Pericardial effusion (6 each), Chest pain, Dyspnoea (5 each), Exercise tolerance decreased, Pain, Palpitations, Tachycardia (4 each), Headache, Hypertension, Hypoaesthesia, Myocarditis, Pain in extremity, and Vertigo (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 41.

Table 41. Pericarditis in Subjects Aged 30-39 (N = 34)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	11	7	0
	No	8	8	0
Relevant PT ^a	Pericarditis	18	14	0
	Pericarditis constrictive	1	1	0
Hospitalisation required/prolonged	Yes	3	7	0
	No	16	8	0
Relevant suspect dose	Dose 1	6	7	0
	Dose 2	5	2	0
	Dose 3	5	2	0
	Unknown	3	4	0
Vaccine Presentation	Original	19	11	0
	Bivalent BA.4/BA.5	0	1	0
	Omicron XBB.1.5	0	1	0
	Omicron JN.1	0	2	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 34	<24 hours	2	1	0
	1-5 days	0	1	0
	6-13 days	2	3	0
	14-21 days	2	0	0
	22-31 days	0	1	0
	32-60 days	1	1	0
	61-180 days	3	0	0
	181-365 days	1	0	0
	Unknown	8	8	0
Event Outcome	Fatal	1	0	0
	Not resolved	11	6	0
	Resolved	2	3	0
	Resolving	2	1	0
	Resolved with sequelae	1	0	0
	Unknown	2	5	0
Duration of event ^b n = 6, median: N/A	Up to 3 days	1	0	0
	None	2	3	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1):

A 33-year-old female subject, dose 3 (original), MC, UK:

- Medical history: Alcohol use, Anaemia, Arthralgia, Asthma, Autism spectrum disorder, Back pain, Cardiac disorder, Cardiomegaly, Conjunctivitis, Contusion, Decreased appetite, Depression, Drug hypersensitivity, Head injury, Hepatomegaly, Joint dislocation, Kidney infection, Ligament sprain, Limb injury, Lower respiratory tract infection, Mental disorder, Migraine, Non-tobacco user, Patellofemoral pain syndrome,

Pectus excavatum, Physiotherapy, Radius fracture, Self-injurious ideation, Soft tissue injury, Surgery, Vomiting, Weight decreased, and Wrist fracture⁶⁹.

- Co-suspect medications: Influenza vaccine.
- Concomitant medications: Amoxicillin, Beclometasone dipropionate, Colchicine, Flucloxacillin, Lansoprazole, Prednisolone, Salbutamol.
- PTs with fatal outcome: Ascites, Cardiac valve disease, Congestive hepatopathy, Oedema peripheral, Pericarditis constrictive, Pericardial fibrosis, Pleural effusion, Pneumothorax, Pulmonary oedema, Reexpansion pulmonary oedema, Vasculitis.
- Time to onset (pericarditis): 354 days.
- Causes of death: Pericardial fibrosis, Pleural effusion, Pericarditis constrictive, and Reexpansion pulmonary oedema.
- Comment: The subject with multiple medical history, the first symptoms started approximately 4-5 months after the second dose of mRNA-1273. The subject also received third dose of Comirnaty vaccine 8 months after second dose. The symptoms persisted in the next 2 years with occasional worsening which led to the death. Based on autopsy examinations, re-expansion pulmonary oedema after drainage, and constrictive pericarditis are considered as the cause of death. However, an individual role of BNT162b2 vaccine cannot be established in isolation.

Subjects aged ≥40 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 128 (monovalent original [87], monovalent Omicron XBB.1.5 [27], monovalent Omicron JN.1 [6], monovalent Omicron KP.2 [4], bivalent Omicron BA.1 [3], bivalent Omicron BA.4/BA.5 [1]; 0.4 % of 34,843 cases, the total PM dataset; 0.6% of the 20,458 subjects ≥ 40 years), compared to 205 cases (0.2%) retrieved in the PSUR #6.
- Country/region of incidence (>5): France (22), UK (15), Greece, Sweden (10 each), Italy, US (9 each), Australia (8), Netherland, Norway (7 each), Germany, and Japan (6 each).
- Subjects' age in years: n = 126, range: 40 – 96, mean: 57.5, median: 56.0.
- Medical history (n = 67): the medical conditions reported more than 3 times included PTs Hypertension (16), Obesity (9), Asthma, Ex-tobacco user (5 each), Drug hypersensitivity, Dyslipidaemia, and Pericarditis (4 each).

⁶⁹ Reportedly “Completed suicide” was a MH for this subject; a follow-up has been requested from the HA.

- COVID-19 Medical history (n = 13): COVID-19 (9), Suspected COVID-19 (3), Post-acute COVID-19 syndrome (1).
- Co-suspect medications (n= 14) (≥ 2): Influenza vaccine inact split 4V (5), Elasomeron (3), and Influenza vaccine (2).
- Most frequently co-reported PTs (≥ 10): Fatigue (26), Chest pain, Dyspnoea (24 each), Tachycardia (17), Myocarditis, Palpitations (16 each), Pyrexia (15), and Pericardial effusion (14).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 42.

Table 42. Pericarditis in Subjects Aged ≥ 40 years (N = 128)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	29	27	0
	No	45	27	0
Relevant PT ^a	Pericarditis	74	49	0
	Pericarditis constrictive	0	1	0
	Pleuropericarditis	0	4	0
Hospitalisation required/prolonged	Yes	24	31	0
	No	50	23	0
Relevant suspect dose	Dose 1	26	31	0
	Dose 2	20	11	0
	Dose 3	13	4	0
	Dose 4	1	0	0
	Dose 6	1	1	0
	Unknown	13	7	0
Vaccine Presentation	Original	53	34	0
	Bivalent BA.1	2	1	0
	Bivalent BA.4/BA.5	0	1	0
	Omicron XBB.1.5	13	14	0
	Omicron JN.1	5	1	0
	Omicron KP.2	1	3	0

Table 42. Pericarditis in Subjects Aged ≥ 40 years (N = 128)

Characteristics		Gender		
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 128	< 24 hours	3	1	0
	1-5 days	10	5	0
	6-13 days	5	5	0
	14-21 days	1	3	0
	22-31 days	4	1	0
	32-60 days	4	1	0
	61-180 days	3	1	0
	181-365 days	4	3	0
	>365 days	2	2	0
	Unknown	38	32	0
Event Outcome	Fatal	0	3	0
	Not resolved	27	10	0
	Resolved	16	11	0
	Resolving	11	10	0
	Resolved with sequelae	4	2	0
	Unknown	16	18	0
Duration of event ^b n = 33, median: 39.5	Up to 3 days	1	1	0
	4 to 6 days	1	0	0
	11 to 26 days	1	1	0
	27 to 57 days	1	1	0
	58 to 180 days	1	0	0
	None	15	10	0

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal cases (3):

Elderly:

A 70-year-old male subject, dose 2 (monovalent original), NMC, Greece:

- Medical history: not reported.
- Co-suspect medications: none.
- Concomitant medications: not reported.
- PTs with fatal outcome: Pericarditis, Thrombosis.
- Time to onset (pericarditis): unknown.
- Causes of death: All the above PTs were reported with fatal outcome.
- Comment: Limited information regarding the subject's medical history and the clinical course details precluded a meaningful causality assessment in this case.

A 76-year-old male subject, dose 1 (monovalent original), NMC, Netherlands:

- Medical history: COVID-19, Hypertension, Obesity.
- Co-suspect medications: none.

- Concomitant medications: none.
- PT with fatal outcome: Hepatic cancer, Inflammation, Immune system disorder, Pericarditis, Neoplasm malignant.
- Time to onset (pericarditis): unknown.
- Causes of death: All the above PTs were reported with fatal outcome.
- Comment: The subject with the history of COVID-19, obesity, and hypertension received the first dose of BNT162b2 for COVID-19 immunisation and experienced events with fatal outcome. It was not reported if an autopsy was performed. The individual role of BNT162b2 vaccine cannot be assessed.

An elderly male subject, dose 1 (monovalent original), NMC, Netherlands:

- Medical history: none.
- Co-suspect medications: none.
- Concomitant medications: none.
- PT with fatal outcome: Pericarditis, Neoplasm malignant, Immunodeficiency.
- Time to onset (pericarditis): unknown.
- Causes of death: All the above PTs were reported with fatal outcome.
- Comment: The subject received the first dose of BNT162b2 for COVID-19 immunisation and experienced the events with fatal outcome. It was not reported if an autopsy was performed. Limited information on the clinical course details and latency precluded a meaningful causality assessment in this case.

Subjects with Unknown Age

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 20 (monovalent original [17], bivalent Omicron BA.4/BA.5 [1], monovalent Omicron XBB.1.5 [2]; 0.06% of 34,843 cases, the total PM dataset; 0.3% of the 6432 subjects with unknown age), compared to 26 (0.02% of the total PM dataset) cases retrieved in the PSUR #6.
- Country/region of incidence: Australia (6), Germany (3), Canada, Norway, UK (2 each), Iceland, Italy, Romania, Ukraine, and US (1 each).
- Medical history (n = 7): the medical conditions reported more than once included PTs Alcohol use, and Non-tobacco user (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medication: Elasomeran (1).

- Most frequently co-reported PTs (≥ 3): Malaise (4), Chest pain, Dizziness, Dyspnoea, and Myocarditis (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 43.

Table 43. Pericarditis in Subjects with unknown age (N = 20)

Characteristics		Gender		
		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	3	1
	No	11	1	1
Relevant PT ^a	Pericarditis	14	4	2
Hospitalisation required/prolonged	Yes	5	2	0
	No	9	2	2
Relevant suspect dose	Dose 1	3	1	1
	Dose 2	4	2	1
	Dose 3	3	0	0
	Unknown	4	1	0
Vaccine Presentation	Original	11	4	2
	Omicron BA.4/BA.5	1	0	0
	Omicron XBB.1.5	2	0	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n = 20	1-5 days	1	0	0
	22-31 days	1	1	0
	181-365 days	0	0	1
	Unknown	12	3	1
Event Outcome	Fatal	0	1	0
	Not resolved	6	1	1
	Resolved	0	0	1
	Resolving	1	0	0
	Unknown	7	2	0
Duration of event ^b n = 1, median: N/A	None	0	0	1

a. All serious occurrences.

b. For those cases where the event resolved or resolved with sequelae.

Fatal case (1):

A male subject, dose unknown (monovalent original), MC, Germany:

- Medical history: none.
- Co-suspect medications: none.
- Concomitant medications: none.
- PT with fatal outcome: Myocardial infarction, Pericarditis.
- Time to onset (pericarditis): unknown.
- Causes of death: All the above PTs were reported with fatal outcome.
- Comment: The subject received the BNT162b2 for COVID-19 immunisation and experienced events with fatal outcome. It was not reported if an autopsy was performed.

Limited information on the clinical course details and latency precluded a meaningful causality assessment in this case.

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.

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

In the PRAC AR of the PSUR #5 (EMA/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.

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 (EMA/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 (EMA/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.

In the PRAC AR of the PSUR #3 (EMA/H/C/PSUSA/00010898/202206), the following request was made: *for future PSURs, local adverse reactions, and/or severe reactogenicity should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Upon review of the incremental data of cases evaluated for all the above-mentioned topics, no new safety issues/signals or reporting pattern changes were detected. These topics have been removed from this Section of the PSUR.

16.3.4. Evaluation of Special Situations

In the PRAC AR of the PSUR #3 (EMA/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 (EMA/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 (EMA/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 (EMA/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 in 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 (EMA/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 Subjects

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: 47 (bivalent Omicron BA.4/BA.5 [12] and monovalent Omicron XBB.1.5 [35] originated from clinical studies C4591048-SSA [46] and C4591048-SSB [1]; 83.9% of 56 cases, the total CT dataset), compared to 5 cases (26.3%) retrieved in the PSUR #6.
- Country/region of incidence: South Africa (30), Brazil (9), US (7), and Puerto Rico (1).
- Participant' gender: female (21) and male (26).
- Participant' age in years: n = 47, range: 6 months – 4 years, mean: 1.5, median: 1.0.

- Medical history (n = 16): the most frequently (≥ 2) reported medical conditions included Neurodevelopmental delay, Tonsillar hypertrophy (3 each), Gastroenteritis, Hydronephrosis, and Wheezing (2 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Reported PTs in participants with ages of 6 months - 4 years (n = 47)⁷⁰:
 - o Following dose 1
 - Formulation 3 mcg (Maroon cap): none.
 - Formulation other/unknown (n = 27): PTs Gastroenteritis, Pneumonia, Bronchiolitis (3 each), Upper respiratory tract infection, Drowning (2 each), Gastroenteritis viral, Anaemia, Foreign body aspiration, Diabetic ketoacidosis, Lower respiratory tract infection, Encephalitis viral, Exanthema subitum, Accident, Nephroblastoma, Humerus fracture, Abscess limb, Helminthic infection, Viral tonsillitis, Near drowning, Sinusitis, Gastrointestinal viral infection, and Pneumonia viral (1 each).
 - o Following dose 2
 - Formulation 3 mcg (Maroon cap) (n = 1): PTs Escherichia urinary tract infection and Gastroenteritis (1 each).
 - Formulation other/unknown (n = 15): PTs Thermal burn (3), Gastroenteritis, Bronchiolitis (2 each), Pneumonia necrotizing, Urinary tract infection, Croup infectious, Pyrexia, Urosepsis, Pneumonia, Tracheobronchitis, Thermal burn, Dehydration, Respiratory tract infection, and Upper respiratory tract infection (1 each).
 - o Following dose 3
 - Formulation 3 mcg (Maroon cap): none.
 - Formulation other/unknown (n = 3): PTs Lower respiratory tract infection, Road traffic accident, Febrile convulsion, Gastroenteritis, Metabolic acidosis, Tonsillitis (1 each).
 - o Following dose other/unknown
 - Formulation 3 mcg (Maroon cap): none.
 - Formulation other/unknown (n = 1): PT COVID-19
- Among all 47 cases reporting 56 AEs, 55 AEs were assessed as unrelated to bivalent BA.4/BA.5 or monovalent Omicron XBB.1.5; while 1 AE (PT coded to Pyrexia) was assessed as related to monovalent Omicron XBB.1.5. Pyrexia is a listed event according to the current RSI of COVID-19 mRNA vaccine.
- Time to event onset: n = 56, range: from 1 day to 225 days, median: 49.
 - 1 day: 1 event;

⁷⁰ One case may record more than 1 PT.

- 2-7 days: 7 events;
 - 8-14 days: 4 events;
 - 15-60 days: 22 events;
 - 61-100 days: 12 events;
 - 101-225 days: 10 events.
- Duration of relevant events: n = 56, range: 19 hours to 40 days, median: 7.5 days.
 - < 24 hours: 1 event;
 - 1 day: 1 event;
 - 2-5 days: 20 events;
 - 6-10 days: 8 events;
 - 11-20 days: 10 events;
 - 21-40 days: 7 events.
 - Event outcome: fatal (5), resolved/resolving (49), and resolved with sequelae (2).

Fatal cases (5)

- Age: 1 year and 3 years (2 each), and 2 years (1).
- Gender: females (2) and males (3).
- Country/region of incidence: South Africa (4) and US (1).
- Fatal PTs (5): reported AEs included Drowning (2), Accident, Nephroblastoma, and Road traffic accident (1 each).
- Medical history (n = 3): Premature baby, Jaundice neonatal, and Neonatal respiratory distress syndrome (1 each).

Among these 5 fatal cases, 4 participants died due to accidents (drowning in 2 cases, accidental falling of bricks on the participant in 1 case, and road traffic accident in 1 case). Both the Investigator and the Sponsor considered the reported events were not related to the vaccination. In the remaining case, a 1-year-old female participant experienced Wilms tumour (PT coded to Nephroblastoma) more than 1 month after receiving monovalent Omicron XBB.1.5, solution for injection as dose 1, single for COVID-19 immunization. The participant's relevant medical history and concomitant medications were not reported. Both the Investigator and the Sponsor considered the reported event was likely coincidental and not related to COVID-19 mRNA vaccine.

Post-Authorisation Data

- Number of cases: 404⁷¹ (monovalent original [25], bivalent Omicron BA.4/BA.5 [4], monovalent Omicron XBB.1.5 [229], monovalent Omicron JN.1 [6] and monovalent

⁷¹ One case may contain more than 1 suspect presentation of COVID-19 mRNA vaccine.

Omicron KP.2 [142]; 1.2% of 34,843 cases, the total PM dataset), compared to 395 cases (0.4%) retrieved in the PSUR #6.

- MC cases (336), NMC cases (68).
- Country/region of incidence: US (373), Japan (7), Canada (6), Brazil (4), UK (3), Australia (2), China, France, India, Italy, Netherlands, Poland, Portugal, Spain, Taiwan, Province of China (1 each).
- Subjects' gender: females (132), males (144), and unknown (128).
- Subjects' age in years: n = 322, range: 2 months – 4 years, mean: 2.2, median: 2.0.
- Medical history (n = 32); the most frequently (≥ 2) reported medical conditions included Drug hypersensitivity, Pyrexia (4 each), Asthma, Cardiac disorder, Febrile convulsion, Food allergy, Seizure (2 each).
- COVID-19 Medical history (n = 3): COVID-19 (2) and COVID-19 immunisation (1).
- Co-suspect medications (n = 44); the most frequently (≥ 2) reported included Sodium chloride (20), Sodium chloride (device constituent) (19), Influenza vaccine (6), and Elasomeran (2).
- Number of events: 852.
- Most frequently reported PTs (≥ 2) in subjects with ages of 2 months through 4 years (n = 852):
 - o Following dose 1
 - Formulation 3 mcg (Maroon cap): Product preparation issue, Underdose (40 each), Overdose, Product preparation error (5 each), Poor quality product administered, and Product administration error (2 each).
 - Formulation other/unknown: Overdose (51), Product preparation error (39), Poor quality product administered (33), Product administration error (18), Product administered to patient of inappropriate age (16), Product temperature excursion issue (8), Pyrexia (6), Incorrect dose administered (5), Expired product administered, Product preparation issue (4 each), Accidental overdose, Decreased appetite, Fatigue, Off label use, Product use issue, and Underdose (2 each).
 - o Following dose 2
 - Formulation 3 mcg (Maroon cap): Inappropriate schedule of product administration (2).
 - Formulation other/unknown: Poor quality product administered (11), Overdose, Product administration error (7 each), Inappropriate schedule of product administration (6), Product administered to patient of inappropriate age, Product

preparation error, Underdose (5 each), Product temperature excursion issue (4), and Product preparation issue (3).

- o Following dose 3
 - Formulation 3 mcg (Maroon cap): Inappropriate schedule of product administration and Pyrexia (2 each).
 - Formulation other/unknown: Poor quality product administered (3), Overdose, Product administered to patient of inappropriate age, and Product administration error (2 each).
- o Following dose other/unknown
 - Formulation 3 mcg (Maroon cap): Poor quality product administered and Product administration error (2 each).
 - Formulation other/unknown: Poor quality product administered (107), Overdose (79), Product preparation error (77), Product administration error (74), Expired product administered (20), Product administered to patient of inappropriate age (19), Product preparation issue (12), Underdose (11), Product temperature excursion issue (7), Diarrhoea, Incorrect route of product administration, Interchange of vaccine products, Pyrexia, and Wrong product administered (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 (31), non-serious (821).
- Time to event onset: n = 475, range: from <24 hours to 45 days, median: 1.5 days.
 - <24 hours: 458 events;
 - 1 day: 15 events;
 - 2 days: 1 event;
 - 45 days: 1 event.
- Duration of relevant events: n = 7, range: from 1 day to 2 months, median: 30.5 days.
 - 1 day: 6 events;
 - 2 months: 1 event.
- Event outcome: fatal (2), resolved/resolving (67), not resolved (8), unknown (775).

Fatal case (1)

- Age: 6 months (1).
- NMC case (1).
- Gender: male (1).
- Country/region of incidence: Canada (1).

- Fatal PT: Pulse absent and Shock (1 each).
- Medical history: none.

In this non-medically confirmed case, the subject received multiple co-suspect vaccines [pneumococcal 13-valent conjugate vaccine, diphtheria vaccine toxoid, hib vaccine (Haemophilus influenzae type B vaccine), pertussis vaccine, polio vaccine inactivated, tetanus vaccine toxoid, influenza vaccine, rotavirus vaccine] including COVID-19 mRNA vaccine, which made it difficult to determine the causal relationship between COVID-19 mRNA vaccine and the fatal events. Dose numbers and the dates of immunisation were unknown at the time of this report.

16.3.5.1.2. Paediatric Subjects ≥ 5 Years and ≤ 11 Years of Age

Clinical Trial Data

- Number of cases: 3 (monovalent Omicron XBB.1.5 [3], originated from the clinical study C4591048-SSE [3]; 5.4% of 56 cases, the total CT dataset), compared to 4 cases (21.1%) retrieved in the PSUR #6.
- Country/region of incidence: US (2) and South Africa (1).
- Participants' gender: females (2) and male (1).
- Participants' age in years: n = 3, range: 6-9 years, mean: 7.7, median: 8.0.
- Medical history (n = 1); the reported medical conditions included Asthma (1).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Reported PTs (3): Gastroenteritis (2) and Seizure (1). The 2 Gastroenteritis events were assessed as unrelated to monovalent Omicron XBB.1.5 by both the Investigator and the MAH. In 1 case reporting the event coded to the PT Seizure, the Investigator considered the causality as related, however, the MAH assessed Seizure was not related to the vaccine administration due to limited information provided. The event occurred 12 days post-vaccination with incomplete description of the event, incomplete diagnostic results, and no event history.
- Time to event onset: n = 3, range: 6 days to 94 days, median: 12 days.
 - 6 days, 12 days, and 94 days (1 each).
- Duration of relevant events: n = 3, range: from 1 day to 11 days, median: 4 days.
 - 1 day, 4 days, and 11 days (1 each).
- Event outcome: resolved (3).

Post-Authorisation Data

- Number of cases: 718⁷¹ (monovalent original [122], bivalent Omicron BA.4/BA.5, monovalent Omicron XBB.1.5 [351], monovalent Omicron JN.1 [13 each] and monovalent Omicron KP.2 [223]; 2.1% of 34,843 cases, the total PM dataset), compared to 1697 cases (1.6%) retrieved in the PSUR #6.
- MC cases (629), NMC cases (89).
- Country/region of incidence ($\geq 2\%$): US (527), Canada (51), and Japan (36).
- Subjects' gender: females (194), males (169), and unknown (355).
- Subjects' age in years: n = 417, range: 5-11 years, mean: 8.4, median: 9.0.
- Medical history (n = 55); the most frequently (≥ 2) reported medical conditions included Drug hypersensitivity (9), Attention deficit hyperactivity disorder, Developmental delay (5 each), Asthma, Cardiac operation, Gastrostomy, Hypersensitivity (3 each), Autism spectrum disorder, Coeliac disease, Enteral nutrition, Epilepsy, Food allergy, Gastric fistula, Henoch-Schoenlein purpura, Intellectual disability, Mechanical ventilation, Obesity, Respiratory disorder, Rhinitis allergic, and Tracheostomy (2 each).
- COVID-19 Medical history (n = 2): COVID-19 and Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (n = 122); the most frequently (≥ 2) reported included Sodium chloride, Sodium chloride (device constituent) (20 each), Influenza vaccine (8), Elasmomeran (4), Diphtheria vaccine toxoid, Pertussis vaccine acellular 5-component, Tetanus vaccine toxoid, HPV vaccine, Influenza vaccine inact split 4V, and Pneumococcal vaccine polysacch 23V (2 each).
- Number of events: 1528.
- Event seriousness: serious (136), non-serious (1392).
- Most frequently reported PTs ($\geq 2\%$ of cases): Poor quality product administered (327), Product administration error (241), Product administered to patient of inappropriate age (207), Overdose (183), Product temperature excursion issue (66), Expired product administered (59), Underdose (31), Pyrexia (18), Accidental overdose (15), and Headache (14).
- Time to event onset: n = 652, range: from <24 hours to 533 days, median: 18.5 days.
 - <24 hours: 528 events;
 - 1 day: 36 events;
 - 2-7 days: 31 events;
 - 8-14 days: 26 events;
 - 15-40 days: 14 events;

- 41-100 days: 4 events;
- 101-533 days: 13 events;
- Duration of relevant events: n = 25, range: from <24 hours to 913 days, median: 5 days.
 - <24 hours: 4 events;
 - 1 day: 2 events;
 - 2-7 days: 14 events;
 - 8-913 days: 5 events.
- Relevant event outcome: fatal (22), resolved/resolving (104), resolved with sequelae (8), not resolved (37), unknown (1357).

Fatal cases (4)

- Age: 9 years and 7 years (2 each).
- MC cases and NMC cases (2 each).
- Gender: female (1) and males (3).
- Country/region of incidence: Germany, Japan, Brazil, and Canada (1 each).
- Fatal PTs (22): reported AEs included Death, Myocarditis, Pericarditis, Cardiac failure, Pulmonary oedema, Encephalitis, Encephalopathy, Pyrexia, Respiratory distress, Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood creatine phosphokinase increased, Coagulation test abnormal, Renal impairment, Hypoglycaemia, Cyanosis, Multiple organ dysfunction syndrome, Brain stem syndrome, Viral infection, Cardiac arrest, Tonic convulsion, and Haemorrhage (1 each).
- Medical history (n = 15): Asthma, Developmental delay, Enteral nutrition, Epilepsy, Gastric fistula, Gastrostomy, Intellectual disability, Mechanical ventilation, Oxygen therapy, Pneumonia, Pyrexia, Respiratory disorder, Sputum increased, Tracheostomy, Wheezing (1 each).

Among these 4 fatal cases, 2 NMC cases provided limited information for a meaningful assessment, including cause of death, medication therapy dates, medical history, event onset, and concomitant medications, etc. One (1) MC case described a 9-year-old subject with co-suspect vaccine products (influenza vaccine, influenza vaccine inact SAG 4V) and underlying diseases/conditions (asthma, developmental delay, enteral nutrition, epilepsy, gastric fistula, gastrostomy, intellectual disability, mechanical ventilation, oxygen therapy, pneumonia, pyrexia, respiratory disorder, sputum increased, tracheostomy, and wheezing), making it difficult to determine the causality.

The remaining MC literature case⁶³ is summarised in Section 16.3.1.1.1 *Important Identified Risks – Myocarditis* in the Subjects aged 5 through <12 years subsection.

16.3.5.1.3. Paediatric Subjects ≥ 12 to ≤ 17 Years of Age

Clinical Trial Data

- Number of cases: 1 (monovalent Omicron XBB.1.5 [1], originated from the clinical study C4591054-SSA [1]; 1.8% of 56 cases, the total CT dataset). No cases were retrieved in the PSUR #6.
- Country/region of incidence: US (1).
- Participant's gender: male (1).
- Participant's age in years: 15 years.
- Medical history: none.
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Reported PT (1): Cellulitis. The event was assessed as unrelated to monovalent Omicron XBB.1.5.
- Time to event onset: 129 days (1).
- Duration of relevant events: unknown (1).
- Event outcome: resolving (1).

Post-Authorisation Data

- Number of cases: 573 (monovalent original [455], bivalent Omicron BA.4/BA.5 [14], multivalent NOS [1], monovalent Omicron XBB.1.5 [82], monovalent Omicron JN.1 [5] and monovalent Omicron KP.2 [19]; 1.6% of 34,843 cases, the total PM dataset), compared to 4690 cases (4.4%) retrieved in the PSUR #6.
- MC cases (311), NMC cases (262).
- Country/region of incidence ($>2\%$): US (93), Germany (73), France (62), Portugal (59), and Japan (57).
- Subjects' gender: females (309), males (235), and unknown (29).
- Subjects' age in years: $n = 531$, range: 12 – 17 years, mean: 14.7, median: 15.0.
- Medical history ($n = 168$); the most frequently (≥ 5) reported medical conditions included Asthma (14), Drug hypersensitivity (11), Migraine (9), Food allergy, Obesity, Seasonal allergy (8 each), Hypersensitivity, Menarche, and Mite allergy (5 each).

- COVID-19 Medical history (n = 42): COVID-19 (42).
- Co-suspect medications (n = 34); the most frequently (>1) reported included COVID-19 vaccine, Hepatitis B vaccine RHBSAG (YEAST), and Influenza vaccine (3 each).
- Number of events: 1974.
- Relevant event seriousness: serious (985), non-serious (989).
- Most frequently reported PTs ($\geq 3\%$): Headache (69), COVID-19 (58), Fatigue (53), Pyrexia (45), Dizziness (40), Underdose (35), Product administered to patient of inappropriate age (34), Drug ineffective (32), Malaise, Poor quality product administered (29 each), Myalgia (28), Myocarditis, Vaccination failure (25 each), Dyspnoea, Pain in extremity (23 each), Arthralgia, Nausea (22 each), Asthenia, Chest pain, Heavy menstrual bleeding (21 each), Product administration error (20), Pain (19), Vomiting (18), and Abdominal pain (17).
- Time to event onset (n = 1052): range from <24 hours to 1043 days, median: 140 days.
 - <24 hours: 326 events;
 - 1 day: 172 events;
 - 2-7 days: 98 events;
 - 8-14 days: 42 events;
 - 15-40 days: 84 events;
 - 41-100 days: 154 events;
 - 101-180 days: 35 events;
 - 181-240 days: 12 events;
 - 241-360 days: 38 events;
 - 361-720 days: 53 events;
 - 721-1043 days: 38 events.
- Duration of relevant events: n = 155, range: <24 hours to 1166 days, median: 13 days.
 - <24 hours: 12 events;
 - 1 day: 30 events;
 - 2-7 days: 35 events;
 - 8-14 days: 32 events;
 - 15-40 days: 12 events;
 - 41-180 days: 9 events;
 - 181-1166 days: 25 events.
- Relevant event outcome: fatal (16), resolved/resolving (408), not resolved (652), resolved with sequelae (82), unknown (816).

Fatal cases (10)

- Age: 17 years, 15 years, 12 years (2 each), 16 years, 14 years, 13 years, and unknown (1 each).
- MC cases and NMC cases (5 each).
- Gender: females (3) and males (7).
- Country/region of incidence: Malaysia, US (2 each), Australia, Belgium, Brazil, Canada, Germany, and Philippines (1 each).
- Fatal PTs (16): reported AEs included Death (5), Myocardial infarction (2), Brain injury, Circulatory collapse, Coma, Multiple organ dysfunction syndrome, Pneumonia bacterial, Subclavian vein thrombosis, Lymphoma, Cardiac arrest, and Myocarditis (1 each).
- Medical history (n = 2): Abstains from alcohol, Abstains from recreational drugs (1 each).

Among these 10 fatal cases, 6 cases (MC and NMC [3 each]) provided limited information for a meaningful assessment, including cause of death, medication therapy dates, medical history, event onset, and concomitant medications, etc. Of these 6 cases, 5 cases recorded the subjects' death as the only event (PT coded to Death). In 1 NMC case, a 17-year-old male subject had the history of alcohol and recreational drugs, making it difficult to determine the causal relationship between COVID-19 mRNA vaccine and the reported fatal event (PT coded to Cardiac arrest). In 1 MC case, the MAH considered the fatal event (PT coded to Lymphoma) represented an intercurrent malignancy and was not related to the vaccine use.

In the remaining 2 cases, potential explanations other than vaccination for death are not evident in the reports. One MC case involved a 15-year-old female subject who received monovalent original vaccine dose 1, single on 15 September 2021 and dose 2, single on 25 October 2021. In November 2021, the subject experienced events coded to the PTs Pneumonia bacterial, Brain injury, Circulatory collapse, Subclavian vein thrombosis, Cardiac arrest, and Loss of consciousness; while the onset dates of the other reported events (PTs coded to Multiple organ dysfunction syndrome, Coma, Myocardial infarction, Brain oedema, Interstitial lung disease, Myocardial necrosis, Carditis, and Vasculitis) were not reported. The subject died on [REDACTED] and her medical history, concomitant medications, and detailed information on autopsy were not provided. Another NMC case involved a 14-year-old female subject who died of myocarditis. Please refer to the description of the fatal case after Table 29.

Analysis of confounders and risk factors

Among the 1746 cases involving paediatric subjects, 451 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (251 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 ($\geq 2\%$) 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.

16.3.5.2. Use in Pregnant/Lactating Women

Clinical Trial Data

There were no pregnancy or lactation cases in the clinical trial dataset for this reporting period as in the previous PSUR #6.

Post-Authorisation Data

- Number of pregnancy cases^{72,73}: 371 (monovalent original [298], bivalent Omicron BA.1 [7], bivalent Omicron BA.4/BA.5 [11], monovalent Omicron XBB.1.5 [41], monovalent

⁷² Exposure *in utero* cases are included.

⁷³ 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.

Omicron JN.1 [11], monovalent Omicron KP.2 [3]; 1.1% of 34,843 cases, the total PM dataset), compared to 232 cases (0.2%) retrieved in the PSUR #6. These 371 cases represent 314 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 57 pregnancies).

- Country/region of incidence (>10 occurrences): Germany (138), France (41), US (33), UK (26), Norway (17), Australia (15), Italy (14), Sweden (13).
- Of the 262 mother cases, 93 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 (72), Maternal exposure timing unspecified (12), Maternal exposure before pregnancy (8), Exposure during pregnancy (1).
- There were 169 mother cases of which 102 were serious and 67 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (77), Maternal exposure timing unspecified (15), Maternal exposure before pregnancy (9), Exposure during pregnancy (2). Additional pregnancy related events reported in these cases (>10 occurrences) were coded to the PTs Abortion spontaneous (30). Other frequently reported clinical events (≥10 occurrences) were coded to PTs COVID-19 (17), Headache (13), Fatigue (10).
- Eighty-two (82) baby/foetal cases, 79 serious and 3 non-serious. Cases are classified according to pregnancy outcome.
 - Pregnancy outcome “Live birth with congenital anomaly”: 45 of these cases reported 80 congenital anomalies. The frequently reported congenital events (>1 occurrence) were coded to PTs Atrial septal defect (9), Ventricular septal defect (8), Congenital hydronephrosis, Hypospadias (4 each), Patent ductus arteriosus, Heart disease congenital (3 each), Congenital tricuspid valve incompetence, Macrocephaly, Cardiac aneurysm, Congenital vesicoureteric reflux, Congenital anomaly, Kidney duplex, Congenital central nervous system anomaly, Congenital megaureter (2 each). Of these 45 cases, information regarding trimester of exposure was available in 35 cases. Of these 35 cases, in 29 cases foetus was exposed during 1st trimester, in 5 cases, foetus was exposed during 2nd trimester and remaining 1 case, foetus was exposed during 3rd trimester. Of these 45 cases, in 2 cases, mother of the baby was on multiple co-suspect/concomitant medications which might have contributed to the development of the reported events. In the remaining 43 cases, there was limited information regarding mother’s medical/ obstetric history and/or trimester of exposure which precluded meaningful causality assessment.
 - Pregnancy outcome “Spontaneous abortion”: 4 cases reported spontaneous abortion. Of these 4 cases, the information regarding trimester of exposure was unknown in 3 cases and in the remaining 1 case the foetus was exposed during the 3rd trimester. The clinical events reported in these 4 cases other than exposure related events were coded to PTs Foetal growth restriction (3), Foetal disorder, Antiphospholipid syndrome, Abortion spontaneous (1 each). In these 4 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome “Elective termination”: 3 case reported elective termination of pregnancy due to foetal defects. Of these 3 cases, information regarding trimester of exposure was unknown in 2 cases and in the remaining 1 case the foetus was exposed during the 1st trimester. The events reported in these cases other than exposure related events were coded to PTs Thanatophoric dysplasia, Foetal malformation, Polyhydramnios, Oesophageal atresia, Coarctation of the aorta (1 each). In these 3 cases, there was limited information regarding mothers medical or obstetric history and/or co-suspect medications which precluded meaningful causality assessment.
- Pregnancy outcome “Stillbirth”: 6 cases reported foetal death/ neonatal death. Of these 6 cases, 1 case reported stillbirth with foetal defect and 5 cases reported stillbirth without foetal defect. The information regarding trimester of exposure was available in 4 cases. Of these 4 cases, in 2 cases foetus was exposed during 1st trimester and in the remaining 2 cases, foetus was exposed during 2nd and 3rd trimester (1 each). The events reported in these cases other than exposure related events were coded to PTs Foetal death (2), Foetal hypokinesia, Trisomy 18, Foetal malformation, Hydrops foetalis, Hypercoagulation, Infarction, Thrombosis (1 each). Of these 6 cases, in 1 case mother of the baby had underlying history of hypertension and Rhesus antigen negative, which might have contributed to the reported event (i.e., infarction and thrombosis). In the remaining 5 cases, there was limited information regarding mother’s medical/ obstetric history and/or trimester of exposure which precluded meaningful causality assessment.
- Pregnancy outcome “Live birth without congenital anomaly”: 24 cases reported live birth babies without congenital anomaly. Of these 24 cases, information regarding trimester of exposure was available in 9 cases. Of these 9 cases, in 6 cases foetus was exposed during the 1st trimester, in 1 case foetus was exposed during 2nd trimester and in 2 cases foetus was exposed during 3rd trimester. The frequently reported events (>1 occurrence) reported in these 24 cases other than exposure related events were coded to PTs Premature baby (7), Neonatal seizure, Neonatal hypoacusis, Neonatal respiratory distress syndrome (2 each). Of these 24 cases, in 1 case reporting neonatal seizure and cerebral venous sinus thrombosis, the mother of the baby was on multiple co-suspect/concomitant medications which might have contributed to the development of the reported events. In the remaining 23 cases, there was limited information regarding mother’s obstetric history which precluded meaningful causality assessment.

Of the 344 cases, 332 cases provided pregnancy outcomes which are provided in Table 44 below. Pregnancy outcome was pending or not provided in the remaining 12 cases.

Table 44. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval^a

Pregnancy outcome	Prospective cases 93 (27.0% of pregnancy cases)				Retrospective cases 239 (69.5% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1 st trimester	After 1 st trimester	During all pregnancy	Unknown	1 st trimester	After 1 st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	0	0	0	1
Spontaneous abortion	0	0	0	1	3	3	0	25
Elective termination (foetal defects)	0	0	0	0	1	0	0	4
Elective termination (no foetal defects or unknown)	0	0	0	0	1	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	0	0	1
Stillbirth without foetal defects	0	1	0	1	4	4	0	10
Live birth with congenital anomaly	4	0	0	3	55	12	0	15
Live birth without congenital anomaly	9	14	0	60	20	19	0	61
Total	13	15	0	65	84	38	0	117

a. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception.

Lactation cases

- Number of lactation cases: 27 (monovalent original [23], monovalent Omicron XBB.1.5, monovalent Omicron JN.1 [2 each]; 0.1% of 34,843 cases, the total PM dataset), compared to 94 cases (0.1%) retrieved in the PSUR #6.
 - Breast feeding baby cases: 24, of which:
 - Sixteen (16) cases reported exposure to vaccine during breastfeeding (Exposure via breast milk) without the occurrence of any clinical events.
 - Eight (8) cases, 4 serious and 4 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk). The reported clinical events other than exposure related events were coded to PTs Pyrexia, Infantile diarrhoea (2 each), Abdominal discomfort, Ataxia, Crying, Death, Dermatitis, Diarrhoea, Fatigue, Growth retardation, Immune system disorder, Iron

deficiency anaemia, Pemphigoid, Periorbital dermatitis, Restlessness, Rheumatoid arthritis, Somnolence, (1 each).

- Breast feeding mother cases: 3 (serious [1], non-serious [2]), of which
- The reported clinical events in mothers who were breast feeding; other than exposure related events were coded to PTs Chills, Dizziness postural, Fall, Gait disturbance, Headache, Lactation insufficiency, Lactation disorder, Pain in extremity, Sweating fever (1 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

As reported in Section 16.1 *Summary of Safety Concerns*, the MAH submitted the EU-RMP version 12.0 (approved with procedure EMEA/H/C/005735/II/0201 and EC decision on 03 July 2024) to remove the missing information “Interaction with other vaccines” from the list of safety concerns in the EU-RMP, based on the C4591030 final study report and the non-interventional effectiveness data from a large retrospective cohort study of commercially insured US adults conducted by the MAH supported by the results from 15 prospective study publications describing the effect of coadministration of COVID-19 vaccine dose(s) with an influenza vaccine on immune responses and safety.

In line with this update to the EU-RMP, the MAH proposes to remove this missing information from the list of safety concerns for the next PSURs.

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 risks⁷⁴ of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 11.0 adopted 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 2024 is provided in Section 16.4.1.1 and Section 16.4.1.2.

⁷⁴ None.

16.4.1.1. Cumulative Characterisation of Important Identified Risks

Table 45. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
Myocarditis and Pericarditis	Cumulatively, there were 6 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). <u>Myocarditis</u> - Number of cases: 4 (original [3], BNT162b2 B.1.617.2 [1]). - Number of SAEs: 4. - Subjects' gender: male (4). - Subjects' age: 16, 17, 42 and 43 years, mean and median: 29.5. - Relevant PTs: Myocarditis, Myopericarditis (2 each). - Related SAEs: Myopericarditis (2), Myocarditis (1). - Relevant event outcome: Resolved (3), Resolved with sequelae (1) <u>Pericarditis</u> - Number of cases: 2 [original]. - Number 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 24,725 cases of Myocarditis and Pericarditis: 15,265 cases reported myocarditis, and 11,820 cases reported pericarditis (in 2360 of these 27,085 cases, the subjects developed both myocarditis and pericarditis). <u>Myocarditis</u> - Number of cases^a: 15,265 (monovalent original [15,015], bivalent Omicron BA.1 [80], bivalent Omicron BA.4/BA.5 [92], multivalent NOS [8], monovalent Omicron XBB.1.5 [69], monovalent Omicron JN.1 [10], monovalent Omicron KP.2 [2]). - Subjects' gender: female (5277), male (9441) and unknown (547). - Subjects' age in years (n = 13,756), range: 1.25 – 102 years, mean: 35.9 years, median: 32.0 years. - Age group: Paediatric (2195), Adults (10796), Elderly (1218), and Unknown (1056). - Case source: Spontaneous (14,667), Literature (528), Clinical study (34), Other Solicited (36). - Relevant PTs: Myocarditis (12,839), Myopericarditis (2337), Carditis (205), Eosinophilic myocarditis (22), Giant cell myocarditis (10), Hypersensitivity myocarditis (9), Autoimmune myocarditis, Chronic myocarditis (7 each), Immune-mediated myocarditis (6). - Relevant event seriousness^b: serious (15,442) - Relevant event outcome^c: fatal (316), resolved/resolving (5871), resolved with sequelae (498), not resolved (4319), unknown (4452). - Frequently co-reported PTs (≥200): Chest pain (4948), Dyspnoea (3298), Fatigue (2696), Palpitations (2441), Pericarditis (2353), Pyrexia (2215), Tachycardia (1674), Chest discomfort (1624), Headache (1338), Dizziness (1010), Off label use (924), Troponin increased (900), Immunisation (899), Interchange of vaccine products (853), Malaise (764), Asthenia (730), Inappropriate schedule of product administration (715), Arrhythmia (710), Nausea (637), Myalgia (617), Pain (594), Pain in extremity (573), Pericardial effusion (520), Chills (505), Angina pectoris (489), Arthralgia (473), Syncope (466), Vomiting (394), Heart rate increased (390), Cough (362), Cardiac failure (361), Paraesthesia (345), Dyspnoea exertional (341), Hyperhidrosis (322), Diarrhoea (309), Hypertension (284),

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Table 45. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Influenza like illness (282), C-reactive protein increased (266), Hypoaesthesia (264), Vaccination site pain (262), COVID-19, Lymphadenopathy (255 each), Back pain (245), Myocardial infarction (234), Atrial fibrillation (232), Lethargy (206), Electrocardiogram ST segment elevation (204), and Drug ineffective (203). <u>Pericarditis</u> - Number of cases: 11,820 (original [11,631], bivalent Omicron BA.1, bivalent Omicron BA.4/BA.5 [61 each], monovalent Omicron XBB.1.5 [59], monovalent Omicron JN.1 [9] multivalent NOS [5], monovalent Omicron KP.2 [4]). - Subjects' gender: female (5591), male (5968) and unknown (261). - Subjects' age in years (n = 10917), range: 2-98 years, mean: 40.2 years, median: 37.0 years. - Age group: Paediatric (773), Adults (9247), Elderly (1173), and Unknown (627). - Case source: Spontaneous (11630), Literature (127), Clinical study (46), Other solicited sources (17). - Relevant PTs: Pericarditis (11,717), Pleuropericarditis (90), Pericarditis constrictive (34), Autoimmune pericarditis (2), Pericarditis adhesive (1). - Event seriousness: serious (11,844). - Event outcome: fatal (57), resolved/resolving (4364), resolved with sequelae (224), not resolved (4011), unknown (3200). - Frequently co-reported PTs (≥2%): Chest pain (4793), Dyspnoea (3013), Myocarditis (2192), Fatigue (2115), Palpitations (1931), Pyrexia (1355), Tachycardia (1294), Chest discomfort (1270), Pericardial effusion (1006), Headache (941), Dizziness (722), Immunisation (687), Off label use (649), Interchange of vaccine products (604), Malaise (544), Nausea (501), Myalgia (483), Pain (481), Asthenia (460), Arthralgia (459), Pain in extremity (448), Inappropriate schedule of product administration (407), Paraesthesia (339), Syncope (323), Cough (293), Angina pectoris (285), Chills (277), Heart rate increased (276), Electrocardiogram abnormal (255), Lethargy (249), Arrhythmia (231), Pleural effusion (228), Back pain (226), Dyspnoea exertional (222), Lymphadenopathy (217), Hyperhidrosis (215), Vomiting (213), Influenza like illness, Vaccination site pain (211 each),

Table 45. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Hypoaesthesia (205), Myopericarditis (202), Hypertension (198), Diarrhoea (194), and C-reactive protein increased (192). Based on the cumulative PM data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.

- Subjects have received more than one vaccine (i.e., at different timepoints), hence the sum of the vaccines are more than the case count.
- 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.
- 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.

16.4.2. Description of Missing Information

Table 46 describes missing information associated with the use of BNT162b2.

Table 46. 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 <i>Use in Pregnant/Lactating Women</i>.

Table 46. Description of Missing Information

Topic	Description	
Use in immunocompromised patients ⁷⁵	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
	- Number of cases: 2 (monovalent Omicron JN.1 and monovalent Omicron KP.2; 3.6% of 56 cases, the total CT dataset) compared to 2 cases (10.5%) retrieved in the PSUR #6. - Subjects' gender: female (2). - Subjects' age: 59 years and 66 years, mean: 62.5 year. - Reported clinical PTs: Cerebrovascular accident and Dehydration (1 each). - Related SAEs: none. - Reported event outcome: resolved and not resolved (1 each). - Relevant medical history: Breast cancer, Hysterectomy (1 each).	- Number of cases: 1482 (original [868], bivalent Omicron BA.1 [32], bivalent Omicron BA.4/BA.5 [107], monovalent Omicron XBB.1.5 [347], monovalent Omicron JN.1 [99], monovalent Omicron KP.2 [29]; 4.3% of 34,843 cases, the total PM dataset) compared to 1653 cases (1.5%) retrieved in the PSUR #6. - Subjects' gender: female (922), male (524) and unknown (36). - Subjects' age in years: n = 1374, range: 7 years – 95 years, mean: 62.4 year, median: 65.0 year. - Most frequently reported clinical PTs (≥4%): COVID-19 (327), Fatigue (178), Vaccination failure (128), Pyrexia (124), Headache (121), Arthralgia (99), Dyspnoea (88), Myalgia (83), Dizziness, Pain in extremity (74 each), Asthenia (72), Malaise (61), Vaccination site pain (60). - Event seriousness: serious (3333), non-serious (2850). - Event outcome: fatal (132), resolved/resolving (1500), resolved with sequelae (159), not resolved (1572), unknown (2820). - Relevant medical history (>50): Breast cancer (172), Immunodeficiency (157), Hysterectomy (100), Thyroidectomy (90), Neoplasm malignant (77), Prostate cancer (73), Chemotherapy (65), Radiotherapy (55).

⁷⁵ 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 46. 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) ⁷⁶	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: 8 (monovalent Omicron XBB.1.5 [4], monovalent Omicron JN.1 [3], bivalent Omicron BA.4/BA.5 [1]; 14.3% of 56 cases), compared to 2 cases (10.5%) retrieved in the PSUR #6. - Subjects' gender: female and male (4 each). - Subjects' age in years: n = 8, range: 0.75 – 66.0 years, mean: 22.7, median: 4.0. - Reported PTs: Bronchiolitis (3), Dehydration, Diverticulitis, Gastroenteritis, Upper respiratory tract infection, Viral infection (1 each). - Related SAEs: none. - Event outcomes: resolved (7), resolved with sequelae (1).	Post-Marketing Data - Number of cases^a: 2860 (Monovalent original [1628], monovalent Omicron XBB.1.5 [704], monovalent Omicron JN.1 [260], bivalent Omicron BA.4/BA.5 [197], monovalent Omicron KP.2 [70], bivalent BA.1 [27], and multivalent NOS [13]; 8.2% of 34,843 cases), compared to 3170 cases (3.0%) retrieved in the PSUR #6. - Subjects' gender: female (1672), male (1134), and unknown (54). - Subjects' age in years: n = 2704, range: 0.5 – 102.0 years, mean: 60.6, median: 63.0. - Most frequently reported PTs (≥2%): COVID-19 (618), Drug ineffective (380), Fatigue (343), Headache (267), Vaccination failure (257), Pyrexia (219), Dyspnoea (192), Malaise (182), Arthralgia (180), Myalgia (177), Dizziness (166), Pain in extremity (165), Nausea (150), Asthenia (143), Vaccination site pain (129), Inappropriate schedule of product administration (112), Interchange of vaccine products (110), Pain (108), Chills (105), Chest pain (90), Palpitations (89), Gait disturbance (86), Paraesthesia (82), Vomiting (76), Condition aggravated (75), Diarrhoea (71), Muscular weakness (68), Asthma, Cough (67 each), Hypoaesthesia (66), Pruritus (61), and Disturbance in attention (57).

⁷⁶ 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 46. 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) <i>Cont'd</i>	Relevant medical history (>1 occurrences): Asthma (3), Hydronephrosis, Osteoarthritis, Wheezing (2 each).	- Event seriousness^b: serious (6498), non-serious (6022). - Event outcome^c: fatal (250), resolved/resolving (2983), resolved with sequelae (500), not resolved (3654), unknown (5140). - Relevant medical history (>100): Asthma (1052), Hypertension (817), Diabetes mellitus (493), Type 2 diabetes mellitus (463), Chronic obstructive pulmonary disease (253), Drug hypersensitivity (231), Obesity (189), Hypothyroidism (165), Seasonal allergy (164), Depression (162), Hypersensitivity (142), Food allergy (139), Chronic kidney disease (117), Atrial fibrillation (116), and Hypercholesterolaemia (103).
Use in patients with autoimmune or inflammatory disorders ⁷⁷	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.	
	Clinical Study Data - Number of cases: 1 (monovalent Omicron JN.1, 1.8% of 56 cases, the total CT dataset), compared to 2 cases (10.5%) retrieved in the PSUR #6. - Subjects' gender: female (1). - Subjects' age in years: 66 (n = 1). - Reported PTs: Dehydration (1). This event was assessed as not related to monovalent Omicron JN.1 by both the investigator and the Sponsor. - Event outcome: resolved (1).	Post-Marketing Data - Number of cases: 3172⁷¹ (monovalent original [1902], bivalent Omicron BA.1 [34], bivalent Omicron BA.4/BA.5 [220], multivalent NOS [11], monovalent Omicron XBB.1.5 [730], monovalent Omicron JN.1 [248], monovalent Omicron KP.2 [78]; 9.1% of 34,843 cases in the total PM dataset), compared to 3392 cases (3.2%) retrieved in the PSUR #6. - Subjects' gender: female (2225), male (907), unknown (40). - Subjects' age in years: n = 3015, range: 4 – 98, mean: 57.5, median: 59.0. - Most frequently reported PTs (≥100): COVID-19 (689), Drug ineffective (420), Fatigue (394), Headache (357), Vaccination failure (285), Pyrexia (249), Arthralgia (243), Malaise (212), Myalgia (208), Pain in extremity (193), Nausea (168), Dizziness (167), Asthenia (162), Vaccination site pain (159), Dyspnoea (148), Chills (134), Pain (131), Inappropriate schedule of product administration (129), Interchange of vaccine products (126), Condition aggravated (118), Paraesthesia (116), Palpitations (102). - Event seriousness: serious (6278), non-serious (7161).

⁷⁷ 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 46. Description of Missing Information

Topic	Description	
Use in patients with autoimmune or inflammatory disorders <i>Cont'd</i>		Event outcome: fatal (132), resolved/resolving (3341), resolved with sequelae (446), not resolved (4131), unknown (5396).
	Of the 188 PM cases that reported PTs indicative of exacerbation or flare, 101 cases were determined to be non-contributory and were not included in the analysis because the events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (e.g., COVID-19/long COVID). Therefore, 87 PM cases were included in the analysis below.	
	Clinical Study Data (Exacerbation or flare-up)	Post-Marketing Data (Exacerbation or flare-up)
	No cases were retrieved in the reporting period, compared to 1 case retrieved in the PSUR #6.	- Number of cases: 87 cases (monovalent original [70], bivalent Omicron BA.4/BA.5 [4], multivalent NOS [1], monovalent Omicron XBB.1.5 [9], monovalent Omicron JN.1 [3]; 0.2% of the total PM dataset), compared to 77 cases (0.1%) retrieved in the PSUR #6. - Subjects' gender: female (63), male (23), unknown (1). - Subjects' age in years: n = 82, range: 14 – 84, mean: 52.9, median: 57.0. - Relevant medical history: the most frequently (≥ 3) reported medical conditions included: Hypothyroidism (9), Graves' disease (8), Autoimmune thyroiditis (7), Crohn's disease (6), Uveitis (4), Alopecia areata, Ankylosing spondylitis, Asthma, Autoimmune arthritis, Hidradenitis, Rheumatoid arthritis, Vitiligo (3 each). - Number of events: 424 (of which 88 were events of interest ie, exacerbation/flare AEs). - Relevant event seriousness: serious (69), non-serious (19). - Most frequently reported relevant PTs: Condition aggravated (61), Disease recurrence (22), Concomitant disease aggravated (3), Disease progression (2). - Relevant event outcome: fatal (1), resolved/resolving (31), resolved with sequelae (7), not resolved (24), unknown (25).

Table 46. Description of Missing Information

Topic	Description	
Interaction with other vaccines ^{d,78}	Clinical Study Data	Post-Marketing Data
	No relevant cases were retrieved in the reporting period; no cases were retrieved in the PSUR #6.	- Number of relevant cases: 6 (original [1], monovalent Omicron XBB.1.5 [2], monovalent Omicron JN.1 [3]); 0.2% of 34,843 cases, the total PM dataset) compared to 2 cases retrieved in the PSUR #6. The interacting vaccines included Influenza vaccine inact sag 4V (4), Influenza vaccine, Influenza vaccine inact sag 3V and Pneumococcal polysaccharide 23V vaccine (1 each). There were 2 interacting vaccines in 1 case. There was 1 serious case with a fatal outcome; after the vaccination with monovalent Omicron JN.1 and influenza vaccine inact sag 4V. The subject, an 80-year-old female, became bradycardic with frequency dropping from 40 towards 20 and then her radial pulse was no longer palpable. Cardiopulmonary resuscitation was attempted but the subject died. The cause of death was uncertain, but there was suspicion of a connection to a known abdominal aortic aneurysm, or possibly an intracerebral event. It was reported that an autopsy was requested. - In 1 non-serious case, the vaccine interaction led to more pronounced reactions to influenza vaccination (not reported). The co-reported events in the remaining 4 non-serious cases, included Pain in extremity (2), Arthralgia, Headache, Insomnia, Musculoskeletal stiffness, Myalgia, Vaccination site reaction (1 each). The information provided in all these cases was 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.	

- a. Subjects have received more than one vaccine (i.e., at different timepoints), hence the sum of the vaccines are more than the case count.
- b. Multiple episodes of the same event were reported with different event seriousness within some cases hence the sum of the event seriousness exceed 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.
- d. The MAH had removed the missing information “Interaction with other vaccines” from the list of safety concerns in the EU-RMP version 12.0. This version was approved with procedure EMEA/H/C/005735/II/0201 and EC decision on 03 July 2024. The MAH proposes to remove the missing information from the list of safety concerns in the future PSURs.

⁷⁸ Search criteria: HLT Interactions (All Paths).

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.⁷⁹

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.⁸⁰ The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.^{79,80} 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,⁸¹ were included as were participants with known stable infection with HIV, HCV, or HBV.^{79,80}

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.

⁷⁹ As per information reported in the CDS version 29.0 dated 27 November 2024, in effect at the end of the reporting period.

⁸⁰ Ref #12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2.

⁸¹ Ref #21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

Table 47. 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^{*,82}			
Subgroup	TRADENAME (Original) 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 infection⁸³			
Subgroup	TRADENAME (Original) 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)

⁸² 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.

⁸³ 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 47. 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

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

*Participants who had no evidence of past SARS-CoV-2 infection (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 48) 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 48. 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^{84,85}			
	TRADENAME (Original) Cases n1^a Surveillance Time (n2^b)	Placebo Cases n1^a Surveillance Time (n2^b)	Vaccine Efficacy % (95% CI^c)
After Dose 1 ^d	1 8.439 ^e (22,505)	30 8.288 ^e (22,435)	96.7 (80.3, 99.9)
7 Days after Dose 2 ^f	1 6.522 ^g (21,649)	21 6.404 ^g (21,730)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition^{86,87}			
	TRADENAME (Original) 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 ^c (22,473)	45 8.269 ^c (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:⁸⁸

⁸⁴ 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.

⁸⁵ 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.

⁸⁶ 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.

⁸⁷ 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.

⁸⁸ 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.

Table 48. 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

• Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ 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:⁸⁸ • 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.⁸⁹ 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.^{89,89} 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 49.

⁸⁹ Ref #62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 49. 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 Infection⁹⁰			
	TRADENAME N^a=1005 (Original) 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 Infection⁹¹			
	TRADENAME (Original) 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- 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

⁹⁰ 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.

⁹¹ 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.

adolescents 12 to 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 through 25 years of age (n = 170), based on results for 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.⁹²

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 μ g 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 was a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose

⁹² 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.

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 consisted of 3 cohorts:

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).

A robust immune response against Omicron BA.1 was elicited by 1 (third dose), or 2 doses (third and fourth doses) of BNT162b2 Omi 30 μg in participants ≥ 18 years of age through ≤ 55 years of age who received 2 prior doses of BNT162b2 30 μg compared with those who received 1 dose (Dose 3) of BNT162b2.

- GMR of Omicron BA.1-neutralizing titers at 1-month post-Dose 1 (third dose) in participants who received BNT162b2 Omi to those at 1-month post-Dose 1 (third dose) in participants who received BNT162b2 was 2.87 (2-sided 95% CI: 2.18, 3.78).
- GMR of Omicron BA.1-neutralizing titers at 1-month post-Dose 2 (fourth dose) in participants who received 2 doses of BNT162b2 Omi to those at 1-month post-Dose 1 (third dose) in participants who received BNT162b2 was 2.64 (2-sided 95% CI: 2.06, 3.38).
- At 1-month postdose, a higher percentage of participants who received 1 dose (third) or 2 doses (third and fourth doses) with BNT162b2 Omi achieved a seroresponse to Omicron BA.1 compared with those who received 1 dose (third dose) with BNT162b2.
- A fourth dose with BNT162b2 Omi administered 1 month after the third dose did not further elicit higher immune response.

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).

A robust immune response against Omicron BA.1 was elicited by a fourth and fifth dose of BNT162b2 Omi in participants ≥ 18 years of age to ≤ 55 years of age who received 3 prior doses of BNT162b2 30 μg .

- At 1- and 3-month post-Dose 1 (fourth dose), among baseline negative participants, observed GMTs were higher in participants who received BNT162b2 Omi compared with that in participants who received BNT162b2; observed GMTs were similar for both vaccine groups among baseline positive participants.

- Overall, the immune response post-Dose 1 (fourth dose) declined with time, followed by an increase after a fifth dose with BNT162b2 Omi. This post-Dose 2 (fifth dose) immune response also gradually declined by 6-month post-Dose 2.

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), if consent was provided.

A robust immune response against Omicron BA.1 was elicited by 2 doses of BNT162b2 Omi 30 µg in COVID-19 vaccine-naïve participants ≥18 years of age to ≤55 years of age compared with those who received 2 doses of BNT162b2.

- GMR of Omicron BA.1-neutralizing titers at 1-month post-Dose 2 in participants who received BNT162b2 Omi to those at 1-month post-Dose 2 in participants who received BNT162b2 was 9.95 (2-sided 95% CI: 7.90, 12.53). Superiority and “super” superiority of BNT162b2 Omi to BNT162b2, based on GMR, were met.
- A similar percentage of participants who received 2 doses of BNT162b2 Omi achieved a seroresponse at 1-month post-Dose 2 to Omicron BA.1 compared with those who received 2 doses of BNT162b2. Noninferiority based on seroresponse for the BNT162b2 Omi compared with BNT162b2 was met.

Substudy E of C4591031 was 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 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.

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titer for participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 μg group to C4591031 Substudy E participants >55 years of age in the BNT162b2 30 μg group was 2.91 (2-sided 95% CI: 2.45, 3.44). As the model-based lower bound of the 2-sided 95% CI for GMR was >1 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. This was also met in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination.

In the evaluable immunogenicity participants with or without prior evidence of infection up to 1 month after study vaccination, 66.7% of participants >55 years of age and 46.5% of participants >55 years of age in the BNT162b2 30 μg group achieved a seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 μg group compared with participants given BNT162b2 30 μg as a second booster dose in C4591031 Substudy E was 26.77 % (95% CI: 19.59, 33.95). Noninferiority based on seroresponse for participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 μg group compared to participants >55 years of age in the BNT162b2 30 μg was met, as the adjusted lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was $>-5\%$.

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titers for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg group to >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg group was 0.98 (2-sided 95% CI: 0.83, 1.16). Noninferiority of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg in 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 group was met, as the model-based lower bound of the 2-sided 95% CI for GMR was >0.67. This was also met in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination.

In the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination, 61.2% of participants 18 through 55 years and 66.7% of participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg groups achieved a seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants with a seroresponse to Omicron BA.4/BA.5 between 18 through 55 years of age and >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg groups was - 3.03 % (95% CI: -9.68, - 3.63). Noninferiority based on seroresponse for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg group to participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg group was met, as the adjusted lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-10% for the comparison. This was also met in the evaluable immunogenicity population without prior evidence of infection up to 1 month after study vaccination.

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.

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 was 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 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 2021⁹³ 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 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).⁹⁴

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

⁹³ 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.

⁹⁴ 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.

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%).⁹³

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 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 was a 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 $\geq 72.5\%$, 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 December 2023 through 18 December 2024

During the reporting period, a systematic review and meta-analysis by Song et al⁹⁵ published in Vaccine in April 2024 reported on the real-world effectiveness of BA.1 and BA.4/BA.5 bivalent mRNA (BNT162b2 or mRNA-1273) booster vaccines against Omicron-related endpoints.⁹⁵ The systematic review included a total of 28 studies published through 8 November 2023, including a combined 55,393,303 patients. The authors found that bivalent mRNA booster vaccination was effective against symptomatic or any infection and against

⁹⁵ Song S, Madewell ZJ, Liu M, et al. A systematic review and meta-analysis on the effectiveness of bivalent mRNA booster vaccines against Omicron variants. Vaccine 2024; 42(15):3389-96.

severe events when compared to unvaccinated persons and to those who received ≥ 2 or ≥ 3 original monovalent doses.

Against symptomatic or any infection in all ages, bivalent mRNA VE was 53.5% (95% CI: -22.2 to 82.3) when compared to unvaccinated, 30.8% (95% CI: 22.5 to 38.2) compared to ≥ 2 original monovalent doses, and 28.4% (95% CI: 10.2 to 42.9) compared to ≥ 3 original monovalent doses. Among adults ≥ 60 years, VE against symptomatic or any infection was 22.5% (95% CI: 16.8 to 39.8) compared to unvaccinated, 31.4% (95% CI: 27.7 to 35.0) compared to ≥ 2 original monovalent doses, and 30.6% (95% CI: -13.2 to 57.5) compared to ≥ 3 original monovalent doses.

Against severe events, including hospitalisation and/or death, meta-analysis effectiveness estimates tended to be higher. Among all ages, bivalent mRNA VE was 72.9% (95% CI: 60.5 to 82.4) compared to unvaccinated, 57.6% (95% CI: 42.4 to 68.8) compared to ≥ 2 original monovalent doses, and 62.1 (95% CI: 54.6 to 68.3) compared to ≥ 3 original monovalent doses. Among adults ≥ 60 years, VE against severe events was 72.0% (95% CI 51.4 to 83.9) compared to unvaccinated, 63.4% (95% CI: 41.0 to 77.3) compared to ≥ 2 original monovalent doses, and 60.7% (95% CI: 52.4 to 67.6) compared to ≥ 3 original monovalent doses. These findings were generally similar to an earlier meta-analysis of bivalent relative vaccine effectiveness that included 22 studies.⁹⁶

Through 18 December 2024, the MAH not aware of any systematic review of vaccine effectiveness for XBB.1.5-adapted mRNA vaccines. Individual XBB.1.5-adapted VE studies are described in Section 17.2.4.

17.2. Newly Identified Information on Efficacy and Effectiveness

17.2.1. Clinical Study Data in Individuals ≥ 12 Years of Age

Clinical Study Data for BNT162b2 in pregnant participants ≥ 18 years of age

The Phase 2/3 Study C4591015 was designed to assess the safety of a 30 μ g BNT162b2 in pregnant women and their infants, and the immunogenicity of BNT162b2 in pregnant women, the transfer of antibody to their infants, and the kinetics of antibody transfer in the infant. This was a randomized, placebo-controlled, observer-blind study in approximately 350 healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks' gestation. This study will evaluate the safety, tolerability, and immunogenicity of 2 doses of BNT162b2 or placebo administered 21 days apart. The Phase 2 portion of the study included approximately 200 pregnant women randomized 1:1 to receive BNT162b2 or placebo (saline) during their 27 to 34 weeks' gestation. The Phase 3 portion of this study assessed the safety, tolerability, and immunogenicity of BNT162b2 in approximately 150 pregnant women enrolled during their 24 to 34 weeks' gestation who were randomized in a 1:1 ratio to receive BNT162b2 or placebo (saline). Maternal participants who originally received placebo received BNT162b2 at defined time points as part of the study. The primary immunogenicity

⁹⁶ Cheng M-Q, Li R, Weng Z-Y, et al. Relative effectiveness of bivalent COVID-19 vaccine: a systematic review and meta-analysis. *Front. Med.* 10:1322396. doi: 10.3389/fmed.2023.1322396

objective of the study was to describe the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation and reference to the immune response in nonpregnant women 18 years of age or older from the C4591001 study without evidence of past SARS-CoV-2 infection.

BNT162b2 elicited robust immunogenicity responses in healthy pregnant women 18 years of age and older, with SARS-CoV-2 neutralizing titers that were notably higher compared to placebo. However, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 (evaluable immunogenicity population), numerically lower GMTs were observed in the maternal participants compared to the selected nonpregnant female participants from Study C4591001. The ratio of the neutralizing GMT (GMR) in Study C4591015 maternal participants in the BNT162b2 (30 µg) group to that of Study C4591001 nonpregnant females who received BNT162b2 30 µg was 0.67 (95% CI: 0.50, 0.90).

A similar pattern was shown in those with or without SARS-CoV-2 infection after adjusting the baseline neutralizing titers, and numerically lower GMTs were observed in the maternal participants compared to the selected nonpregnant female participants. For these participants with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 (evaluable immunogenicity population), the model-adjusted ratio of the neutralizing GMT (adjusted GMR) in Study C4591015 maternal participants in the BNT162b2 (30 µg) group to that of Study C4591001 nonpregnant females who received BNT162b2 30 µg was 0.95 (95% CI: 0.69, 1.30).

Infants born to vaccinated maternal participants had higher S-binding IgG concentrations at birth and at 6 months after delivery when compared to infants born to maternal participants from the placebo group. Breastfed infants had marginally higher antibody levels at 6 months after delivery than non-breastfed infants. No safety issues attributable to BNT162b2 exposure were identified in infants born to maternal participants who were vaccinated during pregnancy.

Secondary efficacy objectives included vaccine efficacy against the confirmed COVID-19 cases and against asymptomatic SARS-CoV-2 infection through 1 month after delivery. Due to the very small sample size resulting from early termination of enrollment, and hence number of COVID-19 cases, VE results are uninterpretable.

Clinical Study Data for BNT162b2 in immunocompromised participants ≥ 2 years of age

Study C4591024 was a Phase 2b study which evaluated the safety, tolerability, and immunogenicity of BNT162b2 in participants ≥2 years of age based on representative medical conditions and utilized a primary vaccination series of 3 doses followed by a fourth booster dose. For the participants who were >12 years of age, a 30-µg dose level was used. For participants who were 5 to <12 years of age, a 10-µg dose level was used. For participants who were 2 to <5 years of age, a 3-µg dose level was used. These are the same dose levels that were selected for participants <5 years of age and 5 to <12 years of age, respectively, in the Phase 2/3 C4591007 study. This was an open-label study with BNT162b2 in immunocompromised participants ≥18 years of age treated for NSCLC or CLL, who received hemodialysis treatment secondary to end-stage renal disease, or who received immunomodulator therapy for an autoimmune inflammatory disorder, and in

immunocompromised participants 2 to <18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrollment. The study consisted of 4 doses, with the primary series consisting of 2 doses separated by 21 days and a third dose occurring at 28 days after Dose 2. There was a fourth dose (booster) which occurred 3-6 months after Dose 3, the timing of this fourth dose was determined by the investigator's discretion. Approximately 7 immunocompromised participants ≥ 18 years of age and 117 immunocompromised participants <18 years of age were vaccinated in this study.

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to <5 years of age, 56 participants 5 to <12 years of age, 11 participants 12 to <18 years of age, and 4 participants ≥ 18 years of age) and 1 month after Dose 4 (16 participants 2 to <5 years of age, 31 participants 5 to <12 years of age, 6 participants 12 to <18 years of age, and 4 participants ≥ 18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response. GMTs were observed to be higher at 1 month after Dose 3 and 1 month after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets. Similar to the pattern observed in GMTs, the GMFRs were observed to be higher 1 month after Dose 3 and 1 month after Dose 4 across age groups and disease subsets. The proportion of participants achieving seroresponse to the reference strain at was observed to be highest at 1 month after Dose 4 across age groups and disease subsets.

Clinical Study Data for Omicron XBB.1.5-Adapted Vaccines in Individuals ≥ 12 Years of Age

C4591054 Substudy A was an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants 12 through 55 and >55 years of age who had received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5-adapted bivalent vaccine received at least 150 days prior to study vaccination, received a single open-label 30- μ g dose of BNT162b2 (Omi XBB.1.5). Participants ≥ 12 years of age from Study C4591044 Cohort 2/Cohort 3 who received bivalent BNT162b2 (WT/Omi BA.4/BA.5) 30 μ g as a fourth dose after receiving 3 prior doses of 30 μ g BNT162b2 were used as a historic control group.

Among participants in the evaluable immunogenicity population, GMTs and GMFRs against Omicron XBB.1.5 in both vaccine groups increased from baseline to 1 month after vaccination across all age groups. GMTs/GMFRs against Omicron XBB.1.5 were higher in the BNT162b2 (Omi XBB.1.5) group compared with that in the bivalent BNT162b2 (WT/Omi BA.4/BA.5) group both at baseline and at 1 month after vaccination across all age groups. The GMTs against Omicron XBB.1.5 were higher in participants who were baseline positive compared with those who were baseline negative at baseline and at 1 month after study vaccination within all age groups in both vaccine groups. Overall, the GMFRs against Omicron XBB.1.5 were generally similar in participants who were baseline positive and those who were baseline negative within both vaccine groups. This is different from what has been observed in previous studies where baseline positive groups usually had lower GMFRs than baseline negative groups due to higher prevaccination titers.

Study C4591054 SSB was an open-label Phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of an updated vaccine against COVID-19. Participants ≥ 12 years of age who were previously exposed to SARS-CoV-2 and were COVID-19 vaccine-naïve received a single 30- μ g dose of BNT162b2 (Omi XBB.1.5). Participants from C4591054 Substudy A who received BNT162b2 (Omi XBB.1.5) 30 μ g were used as a control group to assess the immunogenicity objectives.

The noninferiority criterion for SARS-CoV-2 XBB.1.5 neutralizing titers in Substudy B compared to the subset of Substudy A was met. In the evaluable immunogenicity population,

GMTs against Omicron XBB.1.5 were higher in the Substudy B group compared with the subset of Substudy A at the 1-month postdose visit. The model-based GMR (95% CI) of Omi XBB.1.5-neutralizing antibodies for the vaccine-naïve Substudy B group to the vaccine experienced Substudy A group was 1.93 (1.52, 2.44). The lower limit of the 2-sided 95% CI for GMR was >0.67 , indicating the prespecified noninferiority criterion based on GMR was met.

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

A higher immunogenic response was observed at 1-month post dose following a fourth dose with bivalent BNT162b2 at 6 or 10 μ g than at the 3 μ g dose in participants ≥ 6 months to <2 years and ≥ 2 to <5 years of age in C4591048 Substudy C, particularly amongst baseline positive participants. A meaningful comparison between the 6- and 10- μ g dose levels could not be made due to the small number of participants.

At 1-month after study vaccination, a third or fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 μ g in participants ≥ 6 months to <5 years of age in C4591048 Substudy B Group 1 who received 3 doses of original BNT162b2 at 3 μ g elicited a robust immune response against Omicron BA.4/BA.5 and Omicron XBB.1.5. The immune response against Omicron BA.4/BA.5 and Omicron XBB.1.5 elicited by bivalent BNT162b2 (original/Omi BA.4/BA.5) was generally higher compared with C4591007 Phase 2/3 participants of the same age who received 3 doses of original BNT162b2. Immune responses against reference strain were generally similar in the C4591048 bivalent BNT162b2 (original/Omi BA.4/BA.5) and C4591007 BNT162b2 groups. In the C4591048 bivalent BNT162b2 (original/Omi BA.4/BA.5) group, immune responses were generally higher or similar at 1 month after Dose 4 compared to 1 month after Dose 3.

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 μ g 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 μ g.

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 paediatric age group that is closely matched to current circulating strains.

17.2.4. Real World Data for Omicron-Adapted Vaccines

At least fifteen studies reporting the VE of the XBB.1.5-adapted BNT162b2 vaccine were published during the reporting period. VE estimates from these studies are summarized in the table below.

**Table 50. Studies Reporting VE of the XBB1.5-Adapted BNT162b2 Vaccine*
Published Between 19 December 2023 and 18 December 2024**

Author, study design	Country	Age group	Adjusted VE [^]				
			Medically attended	ED/UC visit	Hospitalisation	ICU admission	Death
Hansen et al, ⁹⁷ retrospective cohort	Denmark	>65y			76% (62 to 85)		
Monge et al, ⁹⁸ retrospective cohort	EU/EEA	≥65y			65–79y: 67% (58 to 74) ≥80y: 66% (57 to 73)		65–79y: 67% (42 to 81) ≥80y: 72% (51 to 85)
van Werkhoven	Netherlands	≥60y			71% (67 to 74)	73% (42 to 88)	

⁹⁷ Hansen CH, Moustsen-Helms IR, Rasmussen M et al. Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. The Lancet Infectious Diseases, Vol. 24, Issue 2, 2024, Pages e73–e74. ISSN 1473-3099, [https://doi.org/10.1016/S1473-3099\(23\)00746-6](https://doi.org/10.1016/S1473-3099(23)00746-6).

⁹⁸ Monge S, Humphreys J, Nicolay N et al. Effectiveness of XBB.1.5 Monovalent COVID-19 Vaccines During a Period of XBB.1.5 Dominance in EU/EEA Countries, October to November 2023: A VEBIS-EHR Network Study.

**Table 50. Studies Reporting VE of the XBB1.5-Adapted BNT162b2 Vaccine*
Published Between 19 December 2023 and 18 December 2024**

Author, study design	Country	Age group	Adjusted VE [^]				
			Medically attended	ED/UC visit	Hospitalisation	ICU admission	Death
et al, ⁹⁹ screening method							
Tartof et al, ¹⁰⁰ test-negative case-control	US	≥18y		58% (48 to 67)	62% (32 to 79)		
Laniece Delaunay et al, ¹⁰¹ test-negative case-control	10 countries in Europe	≥5y	40% (26 to 53)				
Huiberts et al, ¹⁰² prospective cohort	Netherlands	≥18y	18–59y: 41% (23 to 55) 60–85y: 50% (44 to 56)				
UKHSA, ¹⁰³ NR	England	≥65y			55% (47 to 62)		
Caffrey et al, ¹⁰⁴ test-negative case-control	US	≥18y	XBB: 51% (27 to 67) JN.1: 24% (5 to 39)	XBB: 50% (35 to 61) JN.1: 33% (22 to 43)	XBB: 61% (44 to 73) JN.1: 35% (20 to 48)		

⁹⁹ 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. *Euro Surveill.* 2024;29(1):2300703.

¹⁰⁰ Tartof SY, Slezak JM, Frankland TB, et al. Estimated Effectiveness of the BNT162b2 XBB Vaccine Against COVID-19. *JAMA Intern Med.* 2024;184(8):932–40.

¹⁰¹ Laniece Delaunay C, Melo A, Maurel M, et al. Effectiveness of COVID-19 vaccines administered in the 2023 autumnal campaigns in Europe: Results from the VEBIS primary care test-negative design study, September 2023–January 2024. *Vaccine* 2024;42(19):3931-37.

¹⁰² Huiberts AJ, Hoeve CE, de Gier B, et al. Effectiveness of Omicron XBB.1.5 vaccine against infection with SARS-CoV-2 Omicron XBB and JN.1 variants, prospective cohort study, the Netherlands, October 2023 to January 2024. *Euro Surveill.* 2024;29(10): 2400109.

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https://assets.publishing.service.gov.uk/media/662a43ed55e1582b6ca7e5ec/Vaccine_surveillance_report_2024_week_17.pdf

¹⁰⁴ Caffrey AR, Appaneal HJ, Lopes VV et al. Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System. *Nat Commun* 2024;15, 9490.

**Table 50. Studies Reporting VE of the XBB1.5-Adapted BNT162b2 Vaccine*
Published Between 19 December 2023 and 18 December 2024**

Author, study design	Country	Age group	Adjusted VE [^]				
			Medically attended	ED/UC visit	Hospitalisation	ICU admission	Death
Shrestha et al, ¹⁰⁵ prospective cohort	US	Working age	Before JN.1: 42% (32 to 51) During JN.1: 19% (-1 to 35)				
Nunes et al, ¹⁰⁶ retrospective cohort	EU/EEA	≥65y			65–79y: 50% (45 to 55) ≥80y: 41% (35 to 46)		65–79y: 58% (42 to 69) ≥80y: 48% (38 to 57)
Tartof et al, ¹⁰⁷ test-negative case-control	US	≥18y		XBB: 59% (48 to 68) JN.1: 52% (39 to 61)	XBB: 74% (49 to 87) JN.1: 50% (15 to 71)		
Nguyen et al, ¹⁰⁸ test-negative case-control	Belgium, Germany, Italy, Spain	≥18y			JN.1: 54% (38 to 65)		
Shrestha et al, ¹⁰⁹ prospective cohort	US	Working age	JN.1: 23% (6 to 38)				
Merdrignac et al, ¹¹⁰ test-negative case-control	Europe	≥50y	26% (3 to 44)				

¹⁰⁵ Shrestha NK, Burke PC, Nowacki AS, et al. Effectiveness of the 2023–2024 formulation of the COVID-19 messenger RNA Vaccine. *Clinical Infectious Diseases* 2024;79(2):405–11.

¹⁰⁶ Nunes B, Humphreys J, Nicolay N, et al. Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR network study. *Expert Review of Vaccines* 2024; 23(1):1085–90.

¹⁰⁷ Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness of BNT162b2 XBB Vaccine Against XBB and JN.1 Sublineages. *Open Forum Infectious Diseases* 2024; 11(7): <https://doi.org/10.1093/ofid/ofae370>

¹⁰⁸ Nguyen JL, Mitratza M, Volkman HR, et al. Effectiveness of the BNT162b2 XBB.1.5-adapted vaccine against COVID-19 hospitalization related to the JN.1 variant in Europe: a test-negative case-control study using the id.DRIVE platform. *eClinicalMedicine* 2025;79:102995.

¹⁰⁹ Shrestha NK, Burke PC, Nowacki AS, et al. Effectiveness of the 2023–2024 formulation of the Coronavirus Disease 2029 mRNA vaccine against the JN.1 variant. *medRxiv* 2024.04.27.24306378.

¹¹⁰ Merdrignac L, Laniece Delaunay C, VerdascaN, et al. Effectiveness of XBB.1.5 vaccines against symptomatic SARS-CoV-2 infection in older adults during the JN.1 lineage-predominant period, European VEBIS Primary Care Multicentre Study, 20 November 2023–1 March 2024.

**Table 50. Studies Reporting VE of the XBB1.5-Adapted BNT162b2 Vaccine*
Published Between 19 December 2023 and 18 December 2024**

Author, study design	Country	Age group	Adjusted VE^				
			Medically attended	ED/UC visit	Hospitali- sation	ICU admission	Death
Tartof et al, ¹¹¹ test- negative case-control	US	5–17y		65% (36 to 81)			

*Studies are listed if ≥85% of the vaccinated population received BNT162b2 XBB.1.5-adapted vaccine
^VE reported as estimate (95% CI); each endpoint is COVID-19 associated
Abbreviations and acronyms: ED/UC: emergency department/urgent care; EU/EEA: European Union/European Economic Area; ICU: intensive care unit; NR: not reported; VE: vaccine effectiveness; y: years.

These fifteen studies found the XBB.1.5-adapted BNT162b2 vaccine was effective against COVID-19-associated medically-attended and ED/UC visits. VE tended to be higher against more severe endpoints such as COVID-19-associated hospitalisation, ICU admission, and death. VE tended to be higher during XBB predominance and lower during JN.1 predominance, though confidence intervals within studies overlapped. There were mixed findings about potential differences in VE by age group across the studies. Only one study reported VE for the XBB.1.5-adapted vaccine among children in which VE was reported for a composite endpoint of ED/UC visit or hospitalisation.¹¹¹

Through 18 December 2024, to our knowledge, no real-world vaccine effectiveness evidence was yet published for JN.1 or KP.2-adapted COVID-19 vaccines.

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. 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.

¹¹¹ Tartof SY, Frankland TB, Puzniak L. BNT162b2 XBB vaccine for COVID-19 among children 5-17 years of age. JAMA Netw Open. 2024;7(12): e2449944.

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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.¹¹² 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.¹¹³

In May 2023, the World Health Organization determined the COVID-19 pandemic no longer constituted a public health emergency of international concern (PHEIC).¹¹⁴ Following this determination, many countries ended reporting of SARS-CoV-2 incidence, positive tests, cases, hospitalisations, deaths, and other public health indicators such as hospital bed capacity and wastewater surveillance. Therefore, recent data on incidence and similar indicators for the reporting period are sparse. The following estimates of SARS-CoV-2 incidence and similar indicators use data from Worldometer, a trusted independent organization that collects COVID-19 data from official reports and publishes global and country-specific statistics online through its final reporting date, 13 April 2024.¹¹⁵

As of 13 April 2024, the overall number of SARS-CoV-2 cases was over 704 million worldwide. In the EU and UK, by 13 April 2024, the total number of confirmed COVID-19 cases was more than 211 million, or 412,940 per one million population. Across countries in the EU, the cumulative number of confirmed cases ranged from 176,524 to 670,727 cases per one million population. Poland, Romania, and Bulgaria reported the lowest cumulative cases rates while Austria, Slovenia, and France reported the highest.

In the US, the number of confirmed cases had reached over 111 million (333,985 per one million population) by 13 April 2024.

¹¹² 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.

¹¹³ World Health Organization. (2020). Novel Coronavirus (2019-nCoV): situation report, 11. World Health Organization: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4.

¹¹⁴ [https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-coronavirus-disease-\(covid-19\)-pandemic](https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic)

¹¹⁵ Worldometer. Reported Cases and Deaths by Country or Territory. <https://www.worldometers.info/coronavirus/> Accessed on 23 January 2025

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 present are likely to reflect the Omicron variant, which is currently the predominant strain in many countries, including in the US,¹¹⁶ where XEC and KP.3.1.1 - sub-lineages of KP.3 - were responsible for 65% of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 21 December 2024.

Other Authorised Vaccines:

Through 18 December 2023, other COVID-19 vaccines are currently authorised¹¹⁷ 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 mRNA vaccine - Spikevax (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^{118,119,120,121} to critical illness and death. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are

¹¹⁶ CDC. Variant Proportions. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions> Accessed on 23 January 2025

¹¹⁷ Union Register of Medicinal Products. <https://ec.europa.eu/health/documents/community-register/html> Accessed on 24 January 2025.

¹¹⁸ Pollock AM, Lancaster J. Asymptomatic transmission of covid-19. BMJ. 2020;371:m4851.

¹¹⁹ Toba N, Gupta S, Ali AY, et al. COVID-19 under 19: A meta-analysis. *Pediatr Pulmonol*. 2021;56(6):1332-41.

¹²⁰ 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.

¹²¹ 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).

associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities.¹²¹ A meta-analysis has estimated that 46.7% of infections in children are asymptomatic.¹²¹ The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults.^{122,123} 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%.¹²⁴

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.^{125,126} 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.¹²⁶ 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.^{126,127}

Progression and Timeline of Severe Disease Requiring Hospitalisation

Those with severe disease will require hospitalisation to manage their illness. Based on data from CDC COVID-NET, from 1 October 2023 to 28 September 2024, the cumulative rate of COVID-19 hospitalisations was 198.8 per 100,000 population.¹²⁸

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

¹²² 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.

¹²³ 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.

¹²⁴ Kumar B, Scheffler P. Ear, Nose, and Throat Manifestations of COVID-19 in Children. Pediatr Ann. 2021;50(7):e277-e81.

¹²⁵ 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.

¹²⁶ Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020;383(18):1757-66.

¹²⁷ 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.

¹²⁸ <https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network>.

diarrhoea (33%).^{129,130,131,132} COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).¹³³ Among non-hospitalised children < 18 years of age, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three.¹³¹ Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care^{130,134,135} 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.¹³⁶ More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.¹³⁷

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.¹³⁸ 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.¹¹⁹ 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.¹³⁹

¹²⁹ 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.

¹³⁰ 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.

¹³¹ 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.

¹³² 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.

¹³³ 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.

¹³⁴ 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.

¹³⁵ 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.

¹³⁶ 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.

¹³⁷ 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.

¹³⁸ 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.

¹³⁹ 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

Mortality data are also presented from Worldometer, 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 13 April 2024, the overall SARS-CoV-2 mortality for the EU and UK was 1,494,184 deaths, or 2,916 per one million population. Reported mortality among EU countries and the UK ranged from 1,336 to 5,661 deaths per one million population. The Netherlands, Denmark, and Ireland reported the lowest mortality; Bulgaria, Hungary, and Croatia reported the highest.¹¹⁵

As of 21 December 2024, there were 1,214,736 deaths reported in the US by the CDC for all age groups (3,660 per one million).¹⁴⁰ Mortality in the US was higher than that of the UK (3,389 per one million).¹¹⁵

Complications of COVID-19 and Post-acute COVID

Evidence has shown that a range of persistent symptoms can remain long after the acute SARS-CoV-2 infection. This condition has been called long COVID or post-acute COVID by some recognised research institutes; a universally accepted definition of long COVID has yet to be established.

Studies have shown that long COVID can affect individuals with COVID-19 across a wide spectrum of severity, from those with very mild acute disease to the most severe forms.

Studies around the world have reported various incidence rates for long COVID with different follow-up examination times after the acute infection, including 76% of people at 6 months, one study reporting 32.6% at 60 days while another reporting 87% at 60 days, and 96% at 90 days. Findings are not fully consistent nor comparable across studies, but they do show that a substantial proportion of people who have had COVID-19 may develop long COVID.¹⁴¹

Assuming at least 10% of COVID-19 survivors develop long COVID, it is estimated that 5 million people are facing long COVID globally.¹⁴²

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,

¹⁴⁰ https://covid.cdc.gov/covid-data-tracker/#trends_totaldeaths_select_00.

¹⁴¹ Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *Bmj*. 2021;374:n1648.

¹⁴² Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)*. 2021;53(10):737-54.

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. 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.¹⁴²

Studies that have evaluated a potential impact of SARS-CoV-2 vaccination on long COVID include:

Ayoubkhani et al,¹⁴³ described that a first dose of COVID-19 vaccine was associated with a reduction in long COVID symptoms of 12.8% (95% confidence interval –18.6% to –6.6%, $P<0.001$), and evidence suggested a sustained improvement after a second dose, with an initial 8.8% decrease (95% confidence interval –14.1% to –3.1%, $P=0.003$) in the odds of long COVID, with a subsequent decrease by 0.8% per week (–1.2% to –0.4% per week, $P<0.001$), at least over the median follow-up of 67 days in this study.

No evidence was found of differences in this relationship by sociodemographic characteristics, health related factors, vaccine type, or duration from infection to vaccination.

Although causality cannot be inferred from this observational evidence, vaccination may contribute to a reduction in the population health burden of long COVID.¹⁴³

Furthermore, Kuodi et al,¹⁴⁴ 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 performed 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.¹⁴⁵

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,

¹⁴³ 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.

¹⁴⁴ 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.

¹⁴⁵ 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.

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.^{146,147}

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.^{146,147}

Further research is needed, but vaccination may contribute to a reduction in the population health burden of long COVID.

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

- a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.
- b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

¹⁴⁶ 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.

¹⁴⁷ 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.

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 51.

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,
- Small fiber neuropathy.

These topics will be monitored using routine pharmacovigilance and presented in future PSURs only if any significant new information is identified.

Table 51. 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.	Refer to Section 11 <i>Literature</i> for the 4 clinical studies that presented relevant safety findings for myocarditis cases after vaccination with any BNT162b2 vaccine presentation.	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				

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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 52. 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 all the BNT162b2 vaccine presentations monovalent (original, Omicron XBB.1.5, Omicron JN.1 and Omicron KP.2) and bivalent (Omicron BA.1 and Omicron BA.4/BA.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.

Based on the clinical trial data of study C4591030, the MAH had removed the missing information “Interaction with other vaccines” from the list of safety concerns in the EU-RMP version 12.0. This version was approved with procedure EMEA/H/C/005735/II/0201 and EC decision on 03 July 2024. The MAH proposes to remove this missing information from the list of the safety concerns in the future PSURs.

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.