Comirnaty : Periodic safety update report assessment

19 December 2022 to 18 June 2023

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period 19 December 2022 to 18 June 2023 and;

2. The Comirnaty PSUR itself.

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

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

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

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

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

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

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

EMA/PRAC/585967/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202306

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

Period covered by the PSUR: 19/12/2022 To: 18/06/2023

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	14 September 2023	14 September 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 November 2023	09 November 2023
☐	MS/PRAC members and MAH comments	13 December 2023	13 December 2023
☐	PRAC Rapporteur's updated assessment report following comments	28 December 2023	21 December 2023
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	11 January 2024	11 January 2024

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

2. Assessment conclusions and actions

The MAH submitted the 5th EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 17 Aug 2023) covering the interval period 19 Dec 2022 to 18 Jun 2023.

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

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

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

During the interval period, 257,566,530 doses of Comirnaty original and bivalent vaccines were shipped worldwide. Cumulatively, 4,615,732,025 doses of Comirnaty original and bivalent vaccines were shipped worldwide.

Raxtozinameran (COMIRNATY Omicron XBB.1.5) was approved in the EU on 31st August 2023, after the data lock point (DLP).

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

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

- Myositis (EPITT 19883); Pemphigus and Pemphigoid (EPITT 19859).

The following were ongoing signals during the interval period:

- Menstrual irregularities (closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);
- Sensorineural hearing loss (closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);
- Retinal vascular occlusion (ongoing, MAH's evaluation is awaited).

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

- Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Haemophagocytic lymphohistiocytosis (HLH); Pemphigus and Pemphigoid (new cases/data through 18 Jun 2023).

During the interval period, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of

safety concerns in the Comirnaty RMP and PSUR, and will continue to monitor through routine pharmacovigilance.

Concerning the adverse event of special interest (AESI) the acute disseminated encephalomyelitis (ADEM), the age stratified O/E ratios of more age groups were >1 compared to the previous 4th PSUR and for the age group 25-49 years considered statistically significant. Therefore, the MAH was requested to further discuss in detail the results of the O/E analyses concerning ADEM with focus on the age group 25-49 years within this PSUSA procedure. The MAH provided additional O/E analyses (including O/E analyses with only BC level 1, 2 and 3 ADEM cases) and a cumulative review of cases reporting ADEM through 18 Jun 2023, including causality assessment of the selected ADEM cases. Overall, based on the data provided there is no evidence for a causal relationship between Comirnaty exposure and ADEM. Cases reporting ADEM should continue to be monitored with routine pharmacovigilance.

The PSUR cycle is aligned with the EURD, one additional 6-monthly PSUR will be submitted, followed by the yearly PSUR.

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

4. Issues to be addressed in the next PSUR

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

1. The MAH should continue to closely monitor hemophagocytic lymphohistiocytosis (HLH) and report all new (literature) cases of HLH including a WHO-UMC causality assessment per case and age-stratified observed/expected analyses using 21-day and 42-day risk intervals.
2. 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.
3. 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.

5. PSUR frequency

☒ No changes of PSUR frequency proposed.

Of note, in the previous 4th PSUSA (procedure EMEA/H/C/PSUSA/00010898/202212) changes of the PSUR frequency was proposed: The PSUR cycle is aligned with the list of Union reference dates

(EURD), one additional 6-monthly PSUR (DLP December 2023) will be submitted, then a first yearly PSUR (DLP December 2024).

Annex: Updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the 5th PSUR for Comirnaty (tozinameran) (also referred to as BNT162b2 Original), Comirnaty Original/Omicron BA.1 (tozinameran/riltozinameran) and Comirnaty Original/Omicron BA.4-5 (tozinameran/famtozinameran), covering the period 19 December 2022 to 18 June 2023, which is assessed in this report.

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

Comirnaty was approved in the EU through a centralised procedure on 21 December 2020 and is currently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 6 months of age and older. It is administered intramuscularly. Please refer to the table below for formulations, presentations and posology in the approved populations:

Age group	12 years and older					5 through 11 years				6 months through 4 years	
Presentation	PBS sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose
Name	Comirnaty	Comirnaty	Comirnaty Original/ Omicron BA.1	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5[10]
Dose	30 mcg (with dilution)	30 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	10 mcg (with dilution)	5/5 mcg (with dilution)	5/5 mcg (no dilution)	5/5 mcg (no dilution)	3 mcg (with dilution)	1.5/1.5 mcg (with dilution)
Vial cap colour	Purple	Grey	Grey	Grey	Light Gray[7]	Orange	Orange	Dark blue[8]	Light blue[9]	Maroon	Maroon
Dose Volume	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL
Dose per vial	6 doses per vial (after dilution)	6 doses per vial	6 doses per vial	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)
Route of Administration	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM

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

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

1.2. Worldwide marketing authorisation status

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

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020. In the European Union, conditional marketing authorisation was granted on 21 December 2020; this was switched to a standard marketing authorisation on 10 October 2022. Overall, BNT162b2 original received marketing authorisation approval in 104 countries/regions.

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

Different dosages are available for use in different age groups:

BNT162b2 original formulations:

- PBS/Sucrose 30 µg formulation for individuals 12 years and older [Purple cap];
- Tris/Sucrose formulation:
  - at the dosage of 30 µg for individuals aged 12 years and older [Grey cap];
  - at the dosage of 10 µg for individuals aged 5 years to <12 years [Orange cap];
  - at the dosage of 3 µg for individuals aged 6 months to <5 years [Maroon cap].

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

- original/Omicron BA.1 at the dosage of 15/15 µg for individuals aged 12 years and older [Grey cap].

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

- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Grey cap];**Error! Bookmark not defined.**
- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Light grey cap];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Orange cap];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Dark blue cap];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Light blue cap];**Error! Bookmark not defined.**
- original/Omicron BA.4/BA.5 at the dosage of 1.5/1.5 µg for individuals aged 6 months to <5 years [Maroon cap];**Error! Bookmark not defined.**

[6] Multi-dose cap vials; [7] Single-dose cap vials first approved in European Union (EU) after data lock point (DLP) on 22 June; [8] Multi-dose cap vials, first approved in EU after DLP on 22 June 2023; [9] Single-dose cap vials, first approved in European Union (EU) after data lock point (DLP) on 22 June 2023; [10] First approved in EU after DLP on 22 June 2023.

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, the following action was taken with respect to BNT162b2 for safety reasons. In Switzerland the approval for bivalent Omi BA.1 was not obtained for individuals 12 to less than 18 years because there was no clinical data available for that population. Because country-specific packaging was not available, Switzerland received EU packaging that displayed age on the carton as 12+ (as per EU MA). Therefore, an information Letter (in English) explaining the

discrepancy between age on the carton and age approved by Swissmedic was provided with each shipment. In addition, the MAH provided electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

Rapporteur assessment comment: The provided information is noted.

1.3.2. Changes to reference safety information

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 121.0 dated 25 May 2023, in effect at the end of the reporting period and included in Appendix 1 of the PSUR (not reproduced here).

Three previous CDS versions (version 20.0 dated 22 February 2023, version 19.0 dated 22 December 2022 and version 18.0 dated 05 December 2022) were also in effect during the reporting interval.

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

After the DLP, an updated CDS (version 22.0) was made effective on 24 July 2023. This updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5); several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.

Rapporteur assessment comment: The EU SmPC of Comirnaty (version 10 Aug 2023 which is after the PSUR DLP) is in line with the CDS.

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively, 69,372 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates:

- BNT162b2: 63,843participants of which 35,274 had received BNT162b2; 26,489 had received BNT162b2 post-unblinding and had received placebo before; 959 had received BNT162b2/placebo; 2 had received BNT162b2/ Seasonal inactivated influenza vaccine (SIIV); 1119 had received BNT162b2/ SIIV/ placebo.
- Variant and variant-adapted vaccines based on BNT162b2: 8,851 participants.
- Early development candidates: 633 participants.
- Blinded therapy: 2 participants.

Rapporteur assessment comment: In the previous fourth PSUR, the MAH reported that 8,958 participants received blinded therapy, and that in the current fifth PSUR only 2 participants received blinded therapy. The MAH should explain this discrepancy concerning the cumulative number of clinical trial participants receiving blinded therapy. **Request for supplementary information**

- Placebo: 6,352 participants.
- SIIV/placebo: 7 participants.

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

- B747: 372 participants received BNT162b2 as a study vaccine or as a comparator in the clinical study B7471026;
- C526: 796 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine or as a comparator in the clinical study C5261001.
- C548: 757 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine in the clinical study C5481001.

Post-marketing exposure

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

Worldwide exposure:

- Cumulative exposure:
    - Approximately a total of **4,615,732,025 doses of BNT162b2 (original and bivalent) were shipped** worldwide from the receipt of the first temporary authorisation for emergency supply on **01 Dec 2020 through 18 Jun 2023**, of which 4,154,348,225 were original and bivalent adult presentations (including PBS and Tris/Sucrose); 461,383,800 were original and bivalent paediatric presentations; 686,454,460 were bivalent vaccines of which 21,075,900 were for paediatric presentations; 2,446,319,885 doses of BNT162b2 (original and bivalent) were shipped to rest of world.
    - Table 7 below displays the cumulative EU/EEA published data with number of doses administered for each age group and by vaccine type:

Table 7. EU/EEA – Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[g]	TOTAL
< 18 years	27055225	25854	65085[c]	25068[c]	27171232
0 – 4 years	15576[d]	NA[e]	NA[e]	NA[e]	15576
5 – 9 years	4143991[h]	NA[e]	2510[f]	0	4146501
10 – 14 years	4336133	830	9472[f]	7864	4354299
15 – 17 years	8230880	4099	9601	19266	8263846
18 – 24 years	30506062	136044	113494	97169	30852769
25 – 49 years	138812452	1016068	1374517	859745	142062782
50 – 59 years	67561353	1064487	1805745	961536	71393121
60 – 69 years	55528600	1592713	1352473	2687844	61161630
70 – 79 years	54055930	1992782	1155012	2733674	59937398
⩾ 80 years	40376375	1283438	1313886	2130269	45103968
Age Unknown	263332	43	160	0	263535
All	**497783992**	**7085524**	**15136438**	**9470237**	**529476191**

- Table 8 through table 11 of the PSUR (not reproduced here) provide the cumulative total number of administered Comirnaty doses for both BNT162b2 original and bivalent Omi in EU/EEA, by age group for each dose (up to dose 7).

- Interval exposure:
  - Approximately **257,566,530 doses of BNT162b2 original and bivalent vaccines were shipped** worldwide during the current reporting interval from **19 Jun 2022 through 18 Jun 2023**, of which 29,554,970 were original adult presentations (including PBS and Tris/Sucrose); 57,416,700 were original paediatric presentations; 170,594,860 were bivalent vaccines of which 10,112,000 were for paediatric presentations; 183,755,610 doses of BNT162b2 (original and bivalent) were shipped to rest of world.
  - Table 18 below displays the interval EU/EEA published data with number of doses administered for each age group and by vaccine type:

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

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi[a]	TOTAL
< 18 years	33417	1689	19974	17872	72952
0 – 4 years	12557	NA	NA	0	12557
5 – 9 years	24332	NA	1442	0	25774
10 – 14 years	13488	160	5166	5437	24251
15 – 17 years	8459	228	4987	12368	26042
18 – 24 years	34167	4323	56288	49221	143999
25 – 49 years	193716	28470	375046	360812	958044
50 – 59 years	97515	21557	276502	450303	845877
60 – 69 years	73753	44960	338320	508671	965704
70 – 79 years	50345	51616	436450	314054	852465
≥ 80 years	32411	51794	338984	130268	553457
Age Unknown	52019	2	56	0	52077
All	530237	202720	4260084	1813329	6806370

Interval period: 2022 week 51 through 2023 week 24.
a. Not specified if BA.1 or BA.4/BA.5.
Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 18 June 2023.

  - Table 19 through table 22 (not reproduced here) provide for the interval reporting period the total number of administered Comirnaty doses for both BNT162b2 original and bivalent Omi in EU/EEA, by age group for each dose (up to dose 7).

Rapporteur assessment comment:

Cumulatively, worldwide a total of 4,615,732,025 doses of Comirnaty were shipped.

During the reporting period, in the EU-EEA countries a total of 6,806,370 doses of Comirnaty were administered and cumulatively 529,476,191 doses.

1.3.4. Data in summary tabulations

During the reporting period, 43,064 cases were downloaded from EudraVigilance and 42,941 cases (99.7% of the total downloaded cases) were included in the data tabulations presented in the PSUR. There were 123 cases (0.3%, 48 serious and 75 non-serious) not included in the PSUR.

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 of the PSUR (not reproduced here) provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in Pfizer clinical trial cases received by the MAH. This

appendix is organised according to MedDRA SOC. This appendix includes SAEs originated from the following studies: BNT162-17 , C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, C4591024, C4591030, C4591031, C4591044 and C4591048.

Appendix 2.1.1 of the PSUR (not reproduced here) provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in BioNTech and Fosun clinical trial cases. This appendix includes SAEs originated from the following studies: BNT162-01, BNT162-03, BNT162-04, BNT162-06, BNT162-14, and BNT162-21.

Rapporteur assessment comment: Cumulatively in clinical trials, a total of 2,804 cases with 3,682 SAEs were reported in MAH's safety database.

Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 of the PSUR (not reproduced here) provides the overall (including original and bivalent vaccines) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. Appendix 2.2.1 through Appendix 2.2.4 of the PSUR (not reproduced here) provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [BNT162b2 original and BNT162b2 bivalent (Omi BA.1, Omi BA.4/BA.5, Omi)]. These tabulations include serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources.

Rapporteur assessment comment: During the interval period, post-marketing there were 74,102 cases reporting 242,787 AEs. Cumulatively, a total of 1,839,454 cases with 6,059,820 AEs were reported in MAH's safety database.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Clinical trials

Completed clinical trials

- Safety trials: During the reporting period, no interventional safety studies were completed with a final CSR.
- Other trials: During the reporting period, no trials that reported new significant efficacy information were completed with a final CSR.
- Remaining trials: During the reporting interval, there was a single completed clinical trial (BNT162-01) with a final CSR (available upon request). No clinically important new information has emerged from this clinical trial.

Ongoing clinical trials

During the reporting period, there were 12 ongoing sponsor-initiated clinical trials.

1. Safety trials:

- Original vaccine

- PASS C4591015 [A phase 2/3, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.
- PASS C4591024 [A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.

- Original and Bivalent
  - PASS C4591036 [Low-interventional cohort study of myocarditis/pericarditis associated with COMIRNATY in persons less than 21 years of age].

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

- None.

2. Other trials that reported new significant efficacy information:

- There were 7 ongoing clinical trials, of which 3 were with the BNT162b2 original vaccine (BNT162-14, C4591001 and C4591007) and 3 were with the bivalent vaccine (BNT162-21, C4591044 and C4591048); in the 7th clinical trial (C4591031) both original and bivalent vaccine were administered.:

  Original vaccine

  - BNT162-14: A Phase II, open-label rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.
  - C4591001, A phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.
  - C4591007, A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults.

  Original and bivalent vaccines

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

    Study C4591031 consists of 6 substudies. Substudies A and B (both with original) were completed and provided clinically important emerging efficacy and safety findings, while for the remaining 4 ongoing substudies (C [original] and D through F [bivalent vaccine]) no clinically significant safety and/or efficacy information has emerged.

    Study C4591031 Substudy A was a Phase 3 randomized, placebo-controlled, observer-blind substudy aimed at evaluating the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who had completed a 2-dose primary

series of BNT162b2 in Study C4591001 at least 6 months prior to randomization, were enrolled and randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization was stratified by age, such that approximately 60% of participants enrolled were ≥16 through 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 randomized to placebo were offered a dose of BNT162b2 30 µg.

Conclusions from the final study report for Substudy A:

- The cumulative incidence of confirmed COVID-19 cases showed that BNT162b2 30 µg provided strong protection against the Delta variant of SARS CoV 2, with waning efficacy following the rise of the Omicron variant. Severe COVID-19 cases remained rare in the study population, despite increasing cases overall.
- The tolerability and safety profile of BNT162b2 30 µg in participants ≥16 years of age at up to 12 months after booster vaccination was acceptable and consistent with results previously reported from the clinical trial experience with BNT162b2 2-dose primary vaccination.

Substudy B of C4591031 was a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age that received 2 or 3 prior doses of BNT162b2 (30-µg doses), with their last dose at least 4 months (120 days) prior to randomization, were enrolled. Participants were randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at their first vaccination visit and then crossed over to the alternative, four weeks later and were stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Serum samples were tested for troponin before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration. The percentages of participants with elevated serum troponin I levels in participants aged 12 to 30 years who had received 2 or 3 prior doses of BNT162b2 (30-µg doses) showed no significant difference between BNT162b2 30 µg and placebo.

- A total of 9 and 7 participants (0.7% and 0.5%) had elevated troponin I results at the 1-month visit (28-35 days) after BNT162b2 and placebo vaccination, respectively.
- The percentages of elevated troponin I results were similar between the two vaccine groups (after BNT162b2 or after placebo) across age group, sex, race, and ethnicity subgroups. In both vaccine groups, the percentages of elevated troponin I results were generally higher in younger age groups (12-17 years) and males.
- At the 4-day visit (2-5 days) after BNT162b2 or placebo, the difference in percentage of elevated troponin I results between the 2 groups was -0.5% (95% CI: -1.1%, 0.2%), which was not statistically significant. Similarly, 1 month (28-35 days) after BNT162b2 or placebo, the difference of 0.2% (95% CI: -0.3%, 0.7%) in the elevated troponin I results between the 2 groups was also not statistically significant.

Bivalent vaccine

- BNT162-21: An exploratory Phase I, randomized, observer-blind, active controlled dose escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults. This trial uses BNT162b4 as IMP in combination with BNT162b2 Bivalent and BNT162b2 Bivalent as investigational and active comparator.
- C4591044: An interventional, randomized, active-controlled, phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b RNA-based vaccine candidates as a booster dose in COVID-19 vaccine-experienced healthy individuals.
- C4591048: A master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA-based vaccine candidate(s) in healthy children.

No clinically important new safety information has emerged from ongoing clinical trials. During the reporting period, there were no cases reporting serious adverse reactions or fatal outcomes considered possibly related to study vaccine from ongoing studies.

3. Remaining trials

- There were 2 ongoing clinical trials:

  Original vaccine

  - BNT162-17, A Phase II trial to evaluate the safety and immunogenicity of a SARS-CoV-2 monovalent and multivalent RNA vaccine in healthy subjects.
  - C4591030, A phase 3, randomized, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.

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

Long-term follow-up

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

Other therapeutic use of medicinal product

BNT162b2 was also administered as study vaccine in other Pfizer-sponsored clinical development programs (C526 and C548). There was no new clinically important safety information identified for this reporting period.

New safety data related to fixed combination therapies

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

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

1.3.5.2. Findings from non-interventional studies

During the reporting period, there were there were 15 ongoing sponsor-initiated non-interventional studies and one non-interventional study (C4591006) was completed.

Completed non-interventional study

Safety studies

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

Other study

- During the reporting period, the study C4591006 was completed. No new safety information emerged from this non-interventional study, the summary of results from this study is provided below.

Table 25. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591006	General Investigation of COMIRNATY Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post-Approval Stage).	Through the follow-up period after the primary series vaccination, no new safety concerns or risks were identified.

Ongoing non-interventional studies

Safety Studies:

- PASS: Non-interventional studies C4591008,C4591009, C4591010, C4591012, C4591021, C4591022, C4591038 and C4591055 are PASS. No clinically important information has emerged from PASS.

Other Studies, 7 ongoing non-interventional studies:

- C4591014, Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.
- C4591025, A prospective, single-arm, open-label, non-interventional, multi-center to assess the safety of BNT162b2 in domestic post-marketing surveillance.
- C4591034, Patient-reported health-related quality of life associated with COVID-19: A prospective survey study on symptomatic adults confirmed with RT-PCR from outpatient settings in the US.
- C4591042, Patient characteristics, healthcare resource utilization and costs among patients with COVID-19 in England.
- C4591050 , Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance.
- C4591053, The impact of Pfizer-BioNTech (BNT162b2) vaccination on the long-term effects of COVID among adults in England diagnosed with COVID prior to Omicron dominance.

- C4591061, Investigating uptake and subsequent health outcomes associated with Pfizer-BioNTech bivalent COVID-19/Influenza vaccine concomitant administration using a claims-based real-world data source in the US.

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

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

1.3.5.3. Information from other clinical trials and sources

Other clinical trials

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

Medication errors

Clinical trial data

- Number of cases: none; no cases were retrieved in the PSUR#4.

Post-authorisation data

From the global safety database, 11,362 cases reporting 32,838 events (15.3% of 74,102 cases, the total PM dataset for the reporting period) indicative of potential medication errors were retrieved compared to 56,865 relevant cases (20.1%) analysed in the PSUR#4.

Among the medication error cases (11,362 cases), compared to 56,865 medication errors in the PSUR#4, 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)]: 360 cases (3.2%) compared to 1670 cases (2.9%) in the PSUR#4.
- Medication errors without harm [i.e. not resulting in adverse reaction(s)]: 10,995 cases (96.8%) compared to 55,167 (97.0%) in the PSUR#4.
- Potential medication errors: 6 cases (0.1%) compared to 39 cases (0.1%) in the PSUR#4.
- Intercepted medication errors: 1 case (0.001%) compared to 3 cases (0.01%) in the PSUR#4.

MAH's conclusion:

Overall, among the 11,362 relevant medication error PM cases, 360 cases (0.5% of the total interval cases, 3.2% of total relevant medication error cases) were considered harmful because they were accompanied by clinically relevant co-reported events.

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

Some medication errors are expected to occur despite written instructions for handling the vaccine and educational activities for the HCPs or due to national or regional recommendations regarding dosing schedules that may differ from recommendations in the product labelling. The number and seriousness

of the reported medication errors events do not indicate there is the need for any additional mitigation activity to prevent harm.

Rapporteur assessment comment:

Clinical trial data

No cases indicative of a medication error were reported.

Post-marketing data

During the reporting period, a slight increase of the number of medication errors resulting in adverse reaction(s) has been reported, i.e. 360 cases (3.2%) as compared to 1,670 cases (2.9%) in the previous reporting period. However, no specific trend or pattern was observed.

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

1.3.5.4. Non-clinical data

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

1.3.5.5. Literature

Nonclinical (Published)

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

Clinical (Published)

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

However, during the current reporting period, the literature article "Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023" (*Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023*) reported important safety information about the use of bivalent vaccines and young children.

Hause et al state that no reports of myocarditis were recorded in VAERS by 01 January 2023 for the 861,251 children aged 5-11 years, who received a bivalent Pfizer-BioNTech booster in the US in the same period.

Rapporteur assessment comment:

The MAH identified no clinical trials that presented important new safety findings after Comirnaty exposure.

For myocarditis, one article was retrieved reporting that no cases of myocarditis were recorded in VAERS by 01 January 2023 for the 861,251 children aged 5-11 years, who received a bivalent Pfizer-BioNTech booster in the US.

During the interval period, the study of *Yonker LM, Swank Z, Bartsch YC, et al. (Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis. Circulation. 2023;147:867–876. DOI: 10.1161/CIRCULATIONAHA.122.061025)* was published in March 2023. This study of Yonker et al.

sheds light on mechanisms of myocarditis with COVID-19 mRNA vaccines, and implicates elevated circulating spike protein as a potential cause or marker of myocarditis. However, further studies are needed to elucidate the reasons for and effects of elevated spike protein levels and whether levels can be monitored to adjust dose and frequency and mitigate individualised risk. In addition, studies are needed for the identification of risk factors (including genetic predisposition) and potential mechanisms and reasons for sex- and age-related differences, as well as the long-term impact of myocarditis after SARS-CoV-2 vaccination. The MAH is requested to discuss the study of Yonker et al. with a focus on the possibilities to mitigate individualized risk on myocarditis after Comirnaty exposure. (**Request for supplementary information**)

All Other Published Sources

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

Unpublished manuscripts

During the reporting period, no new information that presented important new safety findings were identified.

1.3.5.6. Other periodic reports

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

1.3.5.7. Lack of efficacy in controlled clinical trials

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

1.3.5.8. Late-breaking information

After the DLP,

- An updated CDS (version 22.0) was made effective on 24 July 2023; this updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5), several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.
- Signals:
    - A new signal (Mastitis/Breast swelling) was opened based upon an enquiry from the Australian regulatory authority (TGA). The signal is ongoing.
    - The ongoing signals (Menstrual irregularities and Sensorineural Hearing Loss) were closed as no risk on 26 July 2023 and on 19 July 2023, respectively.
- The CHMP approved on 22 June 2023, the EU-RMP versions 9.1 through 9.5, up-versioned to version 10.0 of the EU-RMP in the context of the procedures EMEA/H/C/005735/X/0176 (Original/Omicron BA.4/BA.5 in 6 month-4 year primary series and booster including revised vaccination posology), EMEA/H/C/005735/II/0177(Original/Omicron BA.4/BA.5 in 5-11 years and 12+ years primary series including revised vaccination posology) and EMEA/H/C/005735/X/0180 (Original/Omicron BA.4/BA.5 in 5-11 years (Ready To Use – blue caps).

Rapporteur assessment comment:

MAH's evaluation of the new signal Mastitis/Breast swelling issued after DLP of the current PSUR is awaited.

Please refer regarding the reported ongoing signals Menstrual irregularities and Sensorineural hearing loss to section 2.2 - Signal evaluation of this AR below.

2. Signal and risk evaluation

2.1. Summary of safety concerns

The important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU RMP version 9.0 adopted 10 Nov 2022 (procedure number EMEA/H/C/005735/II/0147):

Ongoing Safety Concerns

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

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

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

1. Version 9.1 submitted on 03 March 2023:
    - To support the extension of the indication to paediatric individuals aged 6 months to 4 years to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty original/Omicron BA.4-5 (3 micrograms) for primary series and as a 4th dose booster.
    - To support the variation of the indication to paediatric individuals aged 5 to 11 years to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty Original/Omicron BA.4/BA.5 (10 micrograms) for primary series.
    - To support the variation of the indication to individuals 12 years of age and older to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty Original/Omicron BA.4-5 (30 micrograms) for primary series.

2. Version 9.2 submitted on 14 April 2023:
    - To support the extension of the 10 mcg dose presentations for ages 5-11 years: the BA.4-5 (5/5 mcg) Dark Blue (multi-dose) and Light Blue (single dose) cap vials.
3. Version 9.3 submitted on 14 June 2023 to consolidate Version 9.1 and Version 9.2. and to propose:
    - Inclusion of all pre-agreed PAM-MEA milestone changes: implementation of PAM-MEA-011.8 final outcome and PAM-MEA-011.9 preliminary AR outcome (i.e. study C4591010 deletion from the RMP).
    - Removal of the important potential risk VAED/VAERD as result of the preliminary AR PSUR#04 (PSUSA/00010898/202212).

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

4. Version 9.4 submitted on 19 June 2023 to update the milestone for study C4591007 following the EMA approval of Justification milestone extension (EMEA/H/C/005735/X/0176).
5. Version 9.5 submitted on 21 June 2023:
    - To consolidate the EU-RMP version by merging RMP versions 9.3 and 9.4.
    - Updates RMP PART I according to the simplified posology implemented in the SmPC.

All these versions were approved on 22 June 2023 under RMP version 10.0.

Rapporteur assessment comment:

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

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

2.2. Signal evaluation

Tabular overview of signals: new, ongoing or closed during the reporting interval:

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Sensorineural Hearing Loss	15Jun23	Ongoing		Enquiry from a competent authority (TGA, Australia)	Hearing loss has been previously evaluated but was re-opened for signal evaluation due to a request from TGA that Pfizer provide an updated signal analysis on sensorineural hearing loss cases including an observed versus expected analyses in the next periodic safety update report (PSUR)	Post-authorization safety database, medical literature, Clinical Trial database, Observed versus Expected analysis	Under evaluation
Retinal Vascular Occlusion	23May23	Ongoing		Medical literature	Signal evaluation was initiated by MAH based on review of a literature article (Risk assessment of retinal vascular occlusion after COVID-19 vaccine by Li Jing-Xing et al https://doi.org/10.1038/s41541-023-00661-7) population level study	Post-authorization safety database, medical literature, Clinical Trial database	Under evaluation

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Menstrual irregularities	14Feb23	Ongoing		Spontaneous Data: Non statistical Reports; Other (Safety Risk Lead review of PRAC signal of Amenorrhea and Heavy Menstrual Bleeding)	This expanded focus topic (menstrual irregularities) is undergoing internal review following closure of the PRAC signal for Amenorrhea and Heavy Menstrual Bleeding	Post-authorization safety data, clinical study safety data, medical literature	Under evaluation. Following review of data for Heavy Menstrual Bleeding and Amenorrhea (EMA PRAC signals), the MAH determined that the broader concept of menstrual irregularities (not limited to HMB and Amenorrhea) will be evaluated
Myositis	17Jan23	Closed	13Mar 23	Enquiry from a competent authority (EMA PRAC)	Information was shared from Pfizer colleagues about an SAE in a Pfizer-sponsored non-vaccine placebo-controlled clinical trial of an IMP for the treatment of dermatomyositis in which the study participant had attributed the dermatomyositis to BNT162b2 vaccination (see HLH above).	Postauthorization safety data, clinical study safety data, literature review, and O/E analysis.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and dermatomyositis. An update to product labeling is not warranted at this time. Routine monitoring will continue.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Pemphigus and Pemphigoid	25Nov22	Closed	13Feb23	BoH alert/ Enquiry from a competent authority (EMA PRAC)	Signal opened following receipt of EMA PRAC Dec 2022 agenda alert that pemphigus and pemphigoid were to be discussed for Comirnaty at the next PRAC meeting. Subsequently, EMA PRAC request was received for a cumulative review of cases of pemphigus and pemphigoid	Post-authorization safety data, clinical study safety data, medical literature review, and Observed versus Expected analysis	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and pemphigus and pemphigoid. An update to product labeling is not warranted at this time. Routine monitoring will continue

Rapporteur assessment comment:

During the reporting period, the safety signal procedures concerning **Pemphigus and Pemphigoid** (EPITT 19859; confirmed signal, new cases/data [after 15 Nov 2022] in the current 5th PSUR), **Myositis** (EPITT 19883; confirmed signal, closely monitor Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares through routine pharmacovigilance, evaluation as an AESI in ongoing PASS[s]), and the potential signal **myocarditis leading to disabling decompensated heart failure requiring heart transplantation** (EPITT 19712; not confirmed signal, continue closely monitoring through routine pharmacovigilance) were closed.

After DLP of the current PSUR, the potential signal **Rhabdomyolysis** (EPITT 19967; not confirmed signal, continue closely monitoring through routine pharmacovigilance) was closed and the signal **postmenopausal haemorrhage** (EPITT 19989) was started, confirmed and is ongoing.

Other safety topics not considered signals

Multisystem Inflammatory Syndrome (MIS-C/-A)

Introduction (Appendix 5.2 of the PSUR)

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

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

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

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

- MSSR#11 (interval 03 September through 26 October 2021),
- SBSR#1 (interval 27 October through 15 December 2021)
- PSUR#2 (interval 19 June through 18 December 2021)
- SBSR#2 (interval 16 December 2021 through 15 February 2022)
- SBSR#3 (interval 16 February through 15 April 2022)
- PSUR#3 (interval 19 December 2021 through 18 June 2022)
- PSUR#4 (interval 19 June 2022 through 18 December 2022)

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

Methodology

The safety database was searched for all BNT162b2; BNT162b2, BNT162b2 OMI BA.1 and BNT162b2, BNT162b2 OMI BA.4-5 cases reporting MedDRA v26.0 PTs; Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Multiple organ dysfunction syndrome, Systemic inflammatory response syndrome, Cytokine release syndrome, Distributive shock reported 19 December 2022 through 18 June 2023.

Results

Fifty-five cases were retrieved for the current reporting period using the search strategy outlined above.

Two literature cases [redacted][2] and [redacted][3]) were previously analysed and presented in PSUR#4 (interval 19 June through 18 December 2022) as the full published case details were available at the time of PSUR#4 preparation.

In three cases the patient's age was not reported; all were classified as BC level 5.

MIS-C

Nine cases occurred in patients aged <21 years and therefore were classified in consideration for MIS-C. There were no cases retrieved in association with BNT162b2 Bivalent (Original and Omicron BA.1 or Bivalent (Original and Omicron BA.4/BA.5) in patients <21 years old.

Table 1. BC classification of potential MIS-C cases

BC classification	Number of cases
1	3
2	4
3	0
4	2*
5	0

*one literature case from Japan[4]

[redacted] is a literature case report from [redacted][4]. A 15-year-old boy received the first dose of COVID-19 mRNA vaccine 50 days after contracting COVID-19. On the day after vaccination, pyrexia, bulbar conjunctival hyperaemia, lip swelling, and diarrhoea developed, with an increase in c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimer; therefore, the patient was diagnosed with MIS-C. High-dose intravenous immunoglobulins (IVIG) therapy and oral administration of aspirin improved the patient's condition.

MAH comment: In this case, on the currently available data the case would be classified as BC level 4 – the duration of fever is unknown and no measures of disease activity are reported. It is noteworthy that this patient had COVID-19 infection within 12 weeks of the onset of possible MIS-C; given COVID-19 infection is the currently known precipitant it is more likely that this is the cause in this case.

Rapporteur assessment comment:

This MIS-C case reported insufficient evidence to meet BC level 1-3 and therefore it is agreed that this case is considered BC level 4.

BC Level 1 cases: definitive cases of MIS-C

Three cases were assessed as BC level 1 and are presented in Table 2 below:

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary MAH comment
[redacted] 12/male [redacted] Literature source[5]	Multisystem inflammatory syndrome in children	Five weeks after his first (and only) BNT162b2 vaccination, a healthy 12-year-old boy presented to the Emergency Department (ED) with 3 days of low-grade fever and painful left axillary lymphadenopathy and redness (pruritic, nonscarlatinoform contiguous erythema), ipsilateral to vaccination. An ultrasound confirmed nonsuppurative adenitis (multiple enlarged lymph nodes, some 2 cm in diameter, with surrounding soft tissue inflammation). He was prescribed cephalexin for cellulitis. He returned 2 days later with fever (39.4°C) and extension of an erythematous rash to the anterolateral left thorax and a new pruritic macular rash behind both knees and thighs. He had bilateral conjunctivitis, dry cough, and nonbilious vomiting without abdominal pain. He denied recent viral illnesses or previous COVID-19, known contacts with individuals with SARS-CoV-2 infection, skin trauma or foreign travel. Cephalexin was the only recent medication taken. He was admitted and treated with IV vancomycin and cefazolin after obtaining blood and urine cultures. He developed hypotension (systolic blood pressure 70 mmHg, unresponsive to intravenous (IV) fluids) and was transferred to the paediatric intensive care unit (PICU) without requiring inotropic support. Two nasopharyngeal SARS-CoV-2 reverse transcriptase-polymerase chain reaction- nucleic acid amplification test (RT-PCR-NAAT) were negative. Within 24 hours he developed a generalised rash, cracked lips and strawberry tongue. Investigations revealed marked lymphopenia (nadir 0.52 x10^9/l, normal range (NR) 1.30-5.20), elevated CRP (peak 201.5 mg/l, NR <5) and very elevated troponins (peak 11368.2 ng/l normal high range 17.5). Cefazolin was discontinued and ceftriaxone was begun after drawing another blood culture. The electrocardiogram (ECG) suggested pericarditis (generalised T-wave abnormalities) but an echocardiogram (ECHO) was normal. A small pleural effusion was seen on chest x-ray (CXR). He was diagnosed with MIS-C. Other diagnoses considered included Kawasaki disease (KD), toxic shock syndrome (TSS), Mycoplasma pneumonia induced rash and mucositis, Steven-Johnson-Syndrome (SJS), post-viral (non SARS-Cov-2) perimyocarditis, adenoviral

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number	Reported event PTs	Case summary
Age/Sex		MAH comment
	Medical history	
Country of report		
	Concomitant medications	
		infection and MIS-vaccination. Nasal multiplex PCR respiratory panel was negative. He received IVIg, methylprednisolone and acetylsalicylic acid (ASA). Blood cultures were negative. He did not meet criteria for a diagnosis of TSS. Antibiotic therapy was changed to azithromycin and was discontinued after a diagnosis of Mycoplasma pneumoniae induced rash and mucositis and SJS was excluded. Within 24 hours his clinical state and troponin levels rapidly improved. Serial ECGs, ECHOs and CXRs were normal. He went home in a stable condition 2 weeks after admission. Troponins normalised and he remained well 6 weeks post discharge, at which time ASA was stopped. SARS-CoV-2 serological testing showed presence of anti-spike antibodies and absence of anti-nucleocapsid antibodies. *MAH comment* *Although meeting the diagnostic criteria for MIS-C it is noteworthy (and acknowledged by the article authors) that a bacterial infection could not be completely excluded given that the urine culture, blood cultures and throat culture for beta haemolytic streptococci were taken after initiation of antibiotic therapy. The patient's initial presentation with axillary lymphadenopathy with cellulitic features 5 weeks distant from vaccination could suggest an infective source.* *The article authors also acknowledge that the case could be Kawasaki disease unrelated to SARS-CoV-2 vaccination however they report that the older age and lymphopenia are atypical for KD.* *Rapporteur assessment comment:* This MIS-C case is considered BC level 1 and possible related to Comirnaty exposure.
[redacted]	Multisystem inflammatory	A previously healthy 5-year-old male was hospitalised with a fever up to 102°F for 4 days (1st day of fever = day 0 of illness), sore throat,

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary MAH comment
5/male [redacted] Literature source[6]	syndrome in children, Coronary artery aneurysm	myalgias, abdominal pain, conjunctival injection and rash 55 days after onset of a mild COVID-19 illness that did not require hospitalisation and 15 days after receiving the first dose of BNT162b2. The patient had elevated inflammatory markers; white blood cell count (WBC) 15.55 x10^3/µl) (NR 4.3-12.4), CRP 19.3 mg/dl (NR <1) and mildly elevated cardiac biomarkers, brain natriuretic protein (BNP) 103.7 pg/ml (NR <100) and troponin-I 0.036 ng/ml (NR <0.03) with evidence of SARS-CoV-2 infection including positive PCR and anti-nucleocapsid antibody. The authors report that although the patient had features of incomplete Kawasaki disease, given a positive COVID-19 test on both PCR and anti-N antibody, the child met the CDC case definition for MIS-C and was diagnosed as such. He was treated with IVIG, steroids (IV methylprednisolone 1 mg/kg for one day then prednisone 1 mg/kg twice daily for 4 days) and daily aspirin. ECHO during the initial hospitalisation was reassuring with normal cardiac function and no coronary artery dilatation. There was clinical improvement with resolution of symptoms and he discharged home on day 6 of the illness with low-dose aspirin for 6 weeks. A day after completing the prescribed 5-day steroid course the patient was readmitted (day 9) with a slightly elevated temperature (100°F), fatigue, cough, faint blanching macular rash on the chest and abdomen, conjunctivitis and dry cracked lips. Laboratory studies were notable for elevations in WBC (25.6 x10^3/µl), CRP (4.4mg/dl) and D-dimer (405ng/ml, RR 0-220). Troponin and BNP were within normal limits. He was diagnosed with recrudescence of MIS-C with KD features and started on IV methlyprednisolone (1 mg/kg 12 hourly) and low-dose aspirin with resolution of symptoms. ECHO on day 10 was significant for new, moderately dilated coronary arteries with no obvious aneurysms and the patient was promptly given a second dose of IVIg following which he remained afebrile. On day 13 he was discharged with a 2-week taper of prednisolone and low-dose aspirin. Until day 19 of illness he took 1 mg/kg of prednisolone twice daily. On day 20, the patient started a planned taper of prednisolone (1 mg/kg once daily). He then presented with tactile fever, dry cracked lips, conjunctivitis and abdominal pain on day 22. Inflammatory

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number	Reported event PTs	Case summary
Age/Sex		MAH comment
	Medical history	
Country of report		
	Concomitant medications	
		markers had increased since previous discharge. ECHO was significant for severe dilatation to his coronary arteries: right coronary artery (RCA) 4.5 mm and left anterior descending (LAD) artery 6.7 mm. He was admitted for the third time and began treatment for refractory MIS-C with infliximab and IV methlyprednisolone (30mg/kg daily) for 5 days. As the LAD dimensions met criteria for a giant coronary aneurysm he was also given enoxaparin per the American Heart Association Kawasaki guidelines. On day 24 ECHO continued to show severe coronary artery dilatation, most significantly for the LAD (4.4 mm). His inflammatory markers and clinical course improved and he was discharged on day 27 on enoxaparin, daily aspirin and a 30-day steroid taper. Nearly a month after discharge, on day 55, the patient remained asymptomatic but his inflammatory markers began increasing (CRP 11.1 mg/dl) and his steroid taper was further extended. On day 64 a repeat ECHO showed improvement in the diffuse coronary artery dilatation to the mildly dilated range, except for the LAD artery in the moderate range. A cardiac CT on day 94 showed mild RCA dilatation with 3 small- to medium-sized RCA aneurysms in the distal segment not seen on ECHO. The left main coronary artery and LAD were improved to normal except for aneurysmal dilatation at the LAD at the level of the first diagonal branch take off (as seen on ECHO). On day 112 the prednisolone was discontinued and on day 117 his inflammatory markers were notably improved with CRP<1 mg/dl. His last echo on day 139 prior to article submission showed slight improvement. *MAH comment* *It is noteworthy that on the initial admission, although meeting the CDC criteria for MIS-C the patient would have been classified as Brighton Collaboration level 2b – only 1 measure of disease activity reported (elevated cardiac biomarkers, no differential of the white blood cell count is provided). This case is reported in the context of positive PCR for SARS-CoV-2, positive anti-nucleocapsid antibody and*

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary MAH comment
		within 55 days of a symptomatic COVID-19 illness. Given that SARS-CoV-2 is the current known precipitant of MIS-C it is more likely the cause in this case. *The authors acknowledge in the report unusual features of this case; the development of "delayed giant coronary artery aneurysms" and "multiple recrudescent episodes following steroid taper". Although coronary artery changes have been seen in cases of MIS, the prominence in this case is suggestive of an alternative diagnosis of Kawasaki disease. It is noted that approximately 30% of KD patients may have coronary artery dilatation at diagnosis, however frank aneurysms may not be seen until after day 10 of illness.[i] No differential of the white blood cell count is reported and there is a thrombocytosis which is perhaps more in keeping with KD than the thrombocytopenia often seen in MIS.* *Rapporteur assessment comment:* This MIS-C case is considered BC level 1 and unlikely related to Comirnaty exposure due to a positive PCR for SARS-CoV-2 and presence of features suggestive of an alternative diagnosis of Kawasaki disease.
[redacted] 16/male [redacted] Literature source[7]	COVID-19, Drug ineffective, Multi-organ disorder, Multisystem inflammatory syndrome in children Hospitalisation / Loss of consciousness / Mental status changes / Respiration abnormal / Schizophrenia	The patient was referred to the ED on 21 December 2021 because of an altered mental status. The patient, who was raised in an orphanage, had been diagnosed with schizophrenia at the age of 9 and been on medication since. He was frequently admitted to a community hospital for psychosocial rehabilitation and 4 days prior had been admitted to the community hospital at the time an outbreak of COVID-19 occurred in that hospital. One hour prior to admission at around 0800 an orphanage member of staff found the patient unconscious in his bedroom and breathing abnormally. He had received a second dose of BNT162b2 18 days before. On initial examination the patient had hypernea and his blood pressure was unmeasurable. Glasgow coma scale was 5. The patient was not obese (BMI 17.89 kg/m^2). He was immediately intubated and mechanical ventilation initiated. Initial arterial blood gas analysis showed a severe metabolic acidosis, WBC was 9550 /uL and CRP 17.28 mg/dL with prerenal acute kidney injury. There was protein-

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary MAH comment
	Concomitant medications not reported	and haematuria on urinalysis. The troponin I level was normal and the inferior vena cava was collapsed on bedside ECHO. IV bicarbonate and fluid resuscitation were commenced with inotropes and broad-spectrum antibiotics. The patient's mental status fully recovered after 7 hours of emergency management. His abdomen was distended with hypoactive bowel sounds and generalised tenderness. Abdominal radiography and CT revealed severe paralytic ileus with multifocal hypo-enhancing areas in the liver and spleen. A nasogastric tube was inserted and oral intake stopped. Although the patient did not have fever or respiratory symptoms his COVID-19 PCR result was positive; he was commenced on remdesivir and dexamethasone. He was weaned off ventilator support after 11 hours and received respiratory support via nasal cannula. He was admitted to an isolation ward for further management. During the first 4 days of hospitalisation the absolute lymphocyte count and platelet count decreased to 173/ul and 49,000/ul respectively. AST and ALT increased to 447 IU/L and 188 IU/L respectively, total bilirubin increased to 1.8 mg/dl. His serum albumin level was as low as 2.1 g/dl and the CRP peaked at 33.87 mg/dl. On hospital day 4 the patient started passing loose mucoid stool 7 times per day and had persistent diffuse tenderness over the distended abdomen. These abdominal symptoms and laboratory findings gradually improved and the nasogastric tube was removed and oral feeding carefully started on hospital day 7. Remdesivir was administered for 5 days and dexamethasone 10 days (discontinued without tapering). No organisms were isolated in the blood or stool cultures. On hospital day 15 the patient suddenly developed fever up to 39.3°C and started having watery diarrhoea 6 times per day. The following day his blood pressure dropped to 87/50 mmHg and heart rate rose to 103 bpm, hence he was started on a continuous infusion of norepinephrine. The patient did not have a rash or conjunctival injection. On lab exam his absolute lymphocyte count had decreased again to 265/ul, sodium 130.9 mmol/l and albumin 2.8 g/dl. CRP increased to 13.61 mg/dl. PT 1.13 and APTT 28.8 sec. Ddimer 1.44 mg/l and NT-proBNP 286.1 pg/ml troponin I normal. No abnormality

Table 1.Cases classified as BC Level 1; definitive cases of MIS-C

AER number	Reported event PTs	Case summary
Age/Sex		MAH comment
	Medical history	
Country of report		
	Concomitant medications	
		on ECG. No organisms identified in blood/stool/urine cultures. He was diagnosed with MIS-C based on CDC criteria. On hospital day 17, fever and diarrhoea improved without the administration of immunosuppressants and norepinephrine was discontinued as his vital signs stabilised. Lab values gradually normalised. The patient was discharged on hospital day 24 without any complications and remained healthy at 1 week follow-up. *MAH comment* *There are two phases of illness described; the first presumed COVID-19 and the second reported to be MIS. This second episode would be classified as BC level one on the basis of a fever duration 3 days, clinical features of diarrhoea and hypotension, elevated inflammatory markers with lymphopenia and elevated BNP.* *During the initial, presumed COVID-19 episode there is a comment of "multifocal hypo-enhancing areas in the liver and spleen" without further evaluation of the aetiology. In combination with elevated transaminases and a markedly low albumin level there could be an alternative infectious source/pathology involved. Also the initial illness was marked by diarrhoea and abdominal tenderness as was the second "MIS" episode, although stool cultures were negative there is no further evaluation on the aetiology of the diarrhoea.* *Given COVID-19 infection is the current known aetiology of MIS-C it is more likely that this would be the underlying cause in this case than vaccination.* *Rapporteur assessment comment:* This MIS-C case is considered BC level 1 and unlikely related to Comirnaty exposure due to a positive PCR for SARS-CoV-2.

Rapporteur assessment comment:

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

BC Level 2 cases: probable cases of MIS-C

Four cases were classified as BC level 2b; possible cases of MIS-C. Three of the 4 cases are presented in table 3 below; [redacted][2], a case identified from the literature, was analysed in the review of MIS cases included in Appendix 5.6.1 of PSUR#4 and will not be duplicated.

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number **Age/Sex** **Country of report**	**Reported event PTs** **Medical history** **Concomitant medications**	**Case summary** ***MAH comment***
[redacted] 16/female [redacted] Literature case report[8]	Multisystem inflammatory syndrome in children No medical history No concomitant medications	BNT162b2 dose 1 received three months prior, and dose 2 three weeks prior, to the onset of symptoms. In November 2021, a previously healthy 16-year-old female presented with fatigue, fever, body pain, loss of appetite, nausea, vomiting, and diarrhoea two days before admission, and was treated in a primary health care clinic with intravenous fluids and antipyretics. On admission, she was somnolent, pale, and dehydrated, with cyanotic lips and cold extremities. Her blood pressure (79/38 mmHg) was only measured after a rapid fluid infusion. Her heart rate was over 100 beats/min with poorly palpable pulses, and her respiratory rate was greater than 45 breaths/min, with an oxygen blood saturation of 93% on nasal oxygen flow of 3-5 L/min. Her lungs were clear; she had no murmur or cardiac friction rubs. The abdomen was soft and not painful with palpation, and no hepatosplenomegaly was noted. The skin was pale, with cold extremities and no rash or oedema. The lips were dry and there was oropharyngeal hyperaemia without cervical or submandibular lymphadenopathy. No prior history of COVID-19 disease or positive contact with COVID-19-infected individuals or acquaintances who were symptomatic. Nasopharyngeal SARS-CoV-2 PCR test result was negative. Serology revealed low levels of anti-SARS-CoV-2 nucleocapsid IgG antibody (2.6), but high levels of anti-SARS-CoV-2 spike IgG (>2500). Initial laboratory results revealed high levels of inflammatory markers; CRP 234 mg/L (NR 0.0-6.0), ESR of 70 mm/h (NR 5-10), procalcitonin (PCT) of 5.66 ng/mL (NR 0.0-0.5), and Interleukin-6 of 56.68 pg/mL (NR <7.0). There was leukopenia with lymphocytosis. In addition to hypoalbuminaemia and hypoproteinaemia, there was an elevation of ALT, AST, lactic dehydrogenase (LDH), and creatine kinase. Within 24 h, d-dimer increased from 222 ng/mL to 509 ng/mL (ref. range 200), while all other coagulation tests were within normal limits. The capillary blood electrolytes and gases were nearly normal. Urinalysis revealed the presence of proteinuria (30-100 mg/dL), nonsignificant

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number	Reported event PTs	Case summary
	Medical history	*MAH comment*
Age/Sex		
	Concomitant medications	
Country of report		
		leukocyturia, erythrocyturia, and bacteriuria, with two urine cultures being negative, and no other obvious microbial cause of inflammation was found, including a nasopharyngeal culture and two blood cultures for bacterial sepsis. Authors additionally performed tests for toxoplasmosis, rubella, cytomegalovirus, and herpes simplex, which were all negative, but authors did not exclude other viral infections, such as influenza, adenoviruses, or enteroviruses. ECG, ECHO and CXR were all performed. The first ECG showed a slight elevation in the ST segments in leads I and II and ECHO showed ventricular dysfunction with a shortening fraction of 24% and an ejection fraction (EF) of 44%. CXR showed a slightly enlarged cardiac silhouette and congestion of the pulmonary vessels. The patient's clinical condition worsened about 8 hours after admission with chest pain and hypotension. A second ECG revealed pericardial lead ST segment elevation and ECHO showed myocardial hypocontractility with a severe decrease in ventricular EF below 30%. Cardiac enzymes were elevated compared to the first measurement; troponin I from 0.18 to 6.37 (NR 0-0.04ng/ml). A continuous infusion of noradrenalin was initiated which improved the blood pressure and heart rate. After about 16 hours the patient's condition worsened with decreased blood saturation and signs of heart failure with pulmonary vascular congestion. Supportive respiratory care was provided for 24 hours with continuous positive airway pressure (CPAP) and rehydration maintained with fluids, diuretics and inotropes (dopamine and noradrenalin). CXR also showed atelectasis at the left lower lobe "as a result of cut-off of the lower left lobar bronchus (mucus plug)". The authors report that as clinical, laboratory and additional examinations revealed that the patient met the MIS-C criteria they initiated treatment with corticosteroids and immunoglobulin. Anticoagulation therapy with enoxaparin was also administered due to high D-Dimer levels. About 48 hours later, inflammatory parameters began to decrease and condition gradually improved; however inotropic support with continuous reduction was required for 10 days due to low ventricular EF and hypotension. Pulmonary function was improved and blood oxygen saturation was effectively maintained with nasal oxygen.

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary *MAH comment*
		On the 16th day of hospital admission almost all laboratory tests were within the normal range as well as ECG, ECHO, lung and abdominal ultrasound examinations and the patient was discharged home with recommendation of using aspirin 80 mg/day for four weeks. During follow-up outpatient visits the patient's general condition remained stable and blood test including cardiac enzymes as well as ECG and echo were normalised. *MAH comment - This case is categorised as BC level 2b given no body temperature is reported (fever is subjective) and the duration of fever appears to be 2 days.* *The patient is positive for anti-nucleocapsid antibodies and therefore an association of MIS-C with SARS-CoV-2 infection cannot be ruled out. In addition, the authors acknowledge that the possibility of an undetected infection contributing to the case cannot be ruled out as testing for other viral infections such as influenza, adenoviruses, or enteroviruses was not performed.* *Rapporteur assessment comment:* This MIS-C case is considered BC level 2b and unlikely related to Comirnaty exposure due to the possibility of an undetected infection including SARS-CoV-2 as a cause of MIS.
[redacted] 14/male [redacted] Literature case report	Multisystem inflammatory syndrome in children No medical history No concomitant medications	The patient presented with 2 days of abdominal distress (pain and vomiting), and 1 day of fever, truncal rash, and sore throat. Twelve days before the hospital visit, he had nasal congestion and had a negative nasopharyngeal SARS-CoV-2 RT- PCR-NAAT test. He had no history of SARS-CoV-2 infection or known contacts with individuals with SARS-CoV-2 infection. He received his first (and only) dose of BNT162b2 four weeks before his hospital visit. In the ED, he was diagnosed with scarlet fever and discharged on amoxicillin. A bacterial throat swab was not done but nasopharyngeal SARS-CoV-2 RT-PCR-NAAT was negative. He returned the following evening with generalized rash, extremity swelling, and worsening abdominal distress. Investigations revealed

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number Age/Sex Country of report	Reported event PTs Medical history Concomitant medications	Case summary *MAH comment*
		lymphopenia (1.2 x 10^9/L, [NR: 1.30-5.20]), elevated CRP (44 mg/L [NR: 0.00-5.00]), and cholestatic hepatitis (ALT: 190 U/L [NR: 0-18], g glutamyl transferase (GGT): 268 U/L [NR: 0-40], direct bilirubin 13.1 [NR: 1.7-8.6] mmol/L). Initial microbiological investigations were negative and an abdominal US was unremarkable. A diagnosis of "viral illness" was made and amoxicillin was discontinued. Three days later, he returned with non-purulent conjunctivitis, pruritus, and skin desquamation. He was well, but met 5 of 6 diagnostic criteria for KD, had marked lymphopenia (0.27 x 10^9/L), inflammation (CRP: 45 mg/L, ESR: 42 mm/hr [NR: 0-10], Ferritin: 127 mg/L [NR: 6.0-110.0]), and improved hepatic panel tests ALT 78 U/L, GGT 158 U/L, direct bilirubin 3.9 mmol/L). A multiplex RT-PCR respiratory virus assay and a repeat NP SARS-CoV-2 RT-PCR-NAAT were negative. CXR, ECG, and ECHO were normal. The authors report that BC level 1 criteria for MIS-C were met. SARS-CoV-2 serology detected anti-spike but not anti-nucleocapsid antibodies. He was admitted and treated with IVIG and ASA. He quickly became afebrile and was discharged from the hospital 3 days later. On follow-up a week after discharge, mild dilatation of the right distal coronary artery was noted, which normalized 4 weeks later along with the remaining blood work. ASA was stopped after 6 weeks of treatment. The authors concluded that the patient had MIS-vaccination and will receive longitudinal subspecialty follow-up and will be exempted from further SARS-CoV-2 vaccination. *MAH comment - On the basis of the reported information, with a fever duration of 1 day this case has been categorised as BC level 2b. Although meeting the diagnostic criteria for MIS-C it is noteworthy (and acknowledged by the article authors) that a bacterial infection could not be completely excluded given that one of the blood cultures was taken after initiation of antibiotic therapy, and no throat swab for bacterial culture was taken. The article authors also acknowledge that the case could be Kawasaki disease unrelated to SARS-CoV-2 vaccination however they report that the older age and lymphopenia are atypical for KD.*

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number	Reported event PTs	Case summary
Age/Sex	Medical history	*MAH comment*
Country of report	Concomitant medications	
		Rapporteur assessment comment: This MIS-C case is considered BC level 2b and possible related to Comirnaty exposure.

Table 2.Cases classified as BC level 2b; probable cases of MIS-C

AER number **Age/Sex** **Country of report**	**Reported event PTs** **Medical history** **Concomitant medications**	**Case summary** ***MAH comment***
[redacted] 20/male [redacted] Literature case report[10]	Drug ineffective, COVID-19, Multisystem inflammatory syndrome Obesity / Sickle cell trait Concomitant medications not reported	The patient had a medical history of sickle cell trait and obesity and had been "triple vaccinated" with BNT162b2. Two weeks before presentation he tested positive for COVID-19 and was asymptomatic. Ten days later he developed fevers and diarrhoea with dyspnoea developing the next day and he presented to the ED. On admission; temperature 39.3°C, heart rate 148 beats/min, BP 82/57 mmHg, respiratory rate 20/min and oxygen saturation 97% on high flow nasal cannula (FiO2 40%, 40L/min). Laboratory data showed WBC "25k", creatinine 2.1 mg/dL, lactate 8.0 mmol/l, ESR 130 mm/hr, CRP >300 mg/L, high-sensitivity troponin 759 ng/mL. SARS-CoV-2 PCR was negative. Pulmonary artery catheterisation suggested mixed distributive and cardiogenic shock. CT scan of chest, abdomen and pelvis demonstrated right middle lobe collapse. The patient had severe mixed cardiogenic and vasodilatory shock, hypoxaemic respiratory failure and oliguric kidney injury. On hospital day 2 he required intubation, extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy. The authors report that he had multi-organ failure and cytokine storm with unremarkable infectious and autoimmune workup and that the patient met the criteria for MIS-C. He received broad antibiotic cover, IVIG, steroids and anakinra. His cardiac function improved, he was decannulated from ECMO after 7 days and discharged to acute rehab on day 29 with complete cardiopulmonary and renal recovery. *MAH comment - This case does not report the latency from vaccination to the onset of the events. The BC diagnostic criteria for MIS include a time-frame of <12 weeks from SARS-CoV-2 infection/exposure/vaccination. In this patient the temporal association is with the symptomatic, PCR positive SARS-CoV-2 infection. Given that COVID-19 is the current known precipitant of MIS this is the most likely cause in this case.* *Rapporteur assessment comment:* This MIS-C case is considered BC level 2b and unlikely related to Comirnaty exposure due to a SARS-CoV-2 infection 2 weeks before presentation of complaints.

Rapporteur assessment comment:

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

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 9 potential new MIS-C cases. Of these, 3 were classified as BC level 1, 4 as BC level 2 (of which 1 case was reported and assessed in the previous interval period), 0 as BC level 3, 2 as BC level 4, and 0 as BC level 5.

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

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

MIS-A

Forty-two cases were in patients aged greater than or equal to 21 years and were classified in consideration of MIS-A. Four cases reported such insufficient information as to preclude BC classification.

Eight of the 42 cases were retrieved for BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) and three cases for BNT162b2 Bivalent (Original and Omicron BA.1).

Table 4 demonstrates the BC classification of the 38 cases classified in consideration of MIS-A:

Table 4. BC classification of potential MIS-A cases

BC level	Number of cases
1	0
2	0
3	0
4	15
5	23

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 42 potential new MIS-A cases (of which 3 cases after Comirnaty Original/Omicron BA.1, 8 cases Comirnaty Original/Omicron BA.4-5). Of these, 0 cases were classified as BC level 1, 0 as BC level 2, 0 as BC level 3, 15 as BC level 4, and 23 as BC level 5.

MAH's conclusion

In summary, 55 cases were analysed for potential MIS for the PSUR period 19 December 2022 through 18 June 2023.

Seven cases were classified as BC Level 1-3 MIS-C cases and there were no BC level 1-3 MIS-A cases. In three of the cases a temporal association with SARS-COV-2 infection was the more likely cause of the MIS-C than vaccination and in a further case positive for anti-nucleocapsid antibodies an anteceding SARS-CoV-2 infection as the cause cannot be ruled out. In two cases, from the same literature source[6], an atypical Kawasaki Disease or bacterial sepsis could not be excluded as differential diagnoses.

Considering the totality of the data, including the number of reports received in the context of the billions of doses of vaccine administered, the MAH does not consider that the currently available information supports a causal association between MIS-C/A and Comirnaty. No updates to current labelling or the

Risk Management Plan are warranted at this time. Routine pharmacovigilance on this topic will continue and further updates will be provided if warranted.

Rapporteur assessment comment:

MIS-C

During the reporting period, the MAH identified a total of 9 potential new MIS-C cases. Of these, 3 were classified as BC level 1, 4 as BC level 2 (of which 1 case was reported and assessed in the previous interval period), 0 as BC level 3, 2 as BC level 4, and 0 as BC level 5.

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

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

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

MIS-A

During the reporting period, the MAH identified a total of 42 potential new MIS-A cases (of which 3 cases after Comirnaty Original/Omicron BA.1, 8 cases Comirnaty Original/Omicron BA.4-5). Of these, 0 cases were classified as BC level 1, 0 as BC level 2, 0 as BC level 3, 15 as BC level 4, and 23 as BC level 5.

Cumulatively, two BC level 1 MIS-A cases (MIS-A BC level 1 case from the 3rd PSUR and 1 case from the 4th PSUR) are considered probably related with Comirnaty, due to the absence of other aetiologies or confounding. However, given the extensive exposure of Comirnaty in adults this is not considered unexpected and does not present a new safety concern.

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

The MAH should continue monitoring MIS-C/-A cases after Comirnaty exposure using routine pharmacovigilance and notify the PRAC Rapporteur immediately when unexpected numbers or (changes in) patterns of MIS-C/-A cases are reported.

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Dyspnoea; Palpitations, Tachycardia/Heart Rate Increase

Response to the PRAC request 5 from the 4th PSUR (EMEA/H/C/PSUSA/00010898/202212):

> *The MAH should present a case level analysis for all cumulative positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a TTO of <2 days. The MAH should discuss whether these events should be added in section 4.8 of the Comirnaty SmPC and PIL accordingly.*

MAH's response (Appendix 5.3 of the PSUR):

Methodology

A search of the safety database cumulatively through 18 June 2023 was conducted for all BNT162b2 vaccines (original and bivalent presentations) for cases where these events were reported after at least 2 unique doses of the vaccine: PTs (MedDRA v. 26.0): Dyspnoea, Palpitations, Tachycardia, Heart rate increased. These cases were considered the "positive rechallenge cases" per the PRAC request.

It is worth noting that the concept of dechallenge/rechallenge is typically more relevant to medications rather than preventative vaccines; consequently the safety database is configured in such a way that dechallenge/rechallenge data fields are not available for vaccination-associated ICSRs. Therefore, this analysis was performed retrieving the date of each vaccination dose and the onset date of the associated AE(s).

Rapporteur assessment comment:

The MAH's choice is not accepted to configure the safety database in such a way that dechallenge/rechallenge data fields are not available for vaccination-associated ICSRs [based on the MAH's rationale that the concept of challenge/rechallenge is 'typically more relevant to medications rather than preventative vaccines'].

Information regarding dechallenge/rechallenge in relation to (re)occurrence of the observed AEs is an essential aspect of causality assessment.

Although it is acknowledged that dechallenge information might be less relevant for vaccines, consistently observed positive rechallenges (i.e., after multiple primary/booster doses) do provide supportive evidence for a causal role of the vaccine.

Note that also for medications dechallenge/rechallenge information could be either relevant/informative, or not, depending on the PK/PD and suspected adverse drug reaction. Relevance should be decided on case-by-case basis. Not systematically/routinely documenting dechallenge/rechallenge information up-front based on the MAH's gross generalisation, would seriously hamper causality assessment, hence regulatory authority review.

Dyspnoea

Search criteria - PT: Dyspnoea.

Cumulatively through 18 June 2023, 67,974 cases reporting the PT Dyspnoea were retrieved. Of these, 1079 cases (1.6%) were positive rechallenge cases for 503 unique individuals. Of note, the 1079 cases were comprised of 1145 events of dyspnoea that were reported with 2 up to 5 doses of the vaccine. These cases originated from PM sources; 271 cases were MC and 808 NMC. Case details for the 1079 cases are available in Appendix 1 -Table 1 of the PSUR (not reproduced here).

Case data/demographics related to the 503 unique individuals:

- Reported gender: female (329), male (159) and unknown (15).
- Reported age in years (n = 471), range: 2-95, mean: 48.6, median: 49.0.
- Country most frequently reported (>3%): Germany (182), UK (52), Norway (50), Denmark (36), France (26), Sweden (23), Finland (19).
- Medical history (n = 245): the most frequently (> 8) reported relevant medical conditions included Asthma and Hypertension (37 each), Seasonal allergy (35), Hypersensitivity (19), Chronic obstructive pulmonary disease and Depression (13 each), Hypothyroidism, Migraine, and Pain (12 each), Allergy to animal (11), Drug hypersensitivity (10), Fibromyalgia, Hypercholesterolemia, and Mite allergy (9 each).
- COVID-19 Medical history (n = 35): COVID-19 (24), Suspected COVID-19 (11) and Post-acute COVID-19 syndrome (3).

Out of the 1145 events of dyspnoea involving 503 individuals, one third of the events (384, 33.5%) of the events was serious; 301 (26.3%) of the events were recovering/recovered (with and without sequelae).

Out of the 503 individuals, 89 individuals reported latency from each vaccine dose to dyspnoea for at least 2 doses. Latency in these individuals ranged from the day of vaccination to 501 days following vaccination.

The cases most likely to be stress or anxiety reactions to vaccination are those with a latency within 1-2 days of vaccination. There were 57 individuals with such a latency for at least one of the occurrences of dyspnoea, however 9 of these had disparate latencies for each vaccination dose (e.g., D1 latency 0 days and D2 latency 26 days), suggesting that a dissimilar condition was occurring after each dose despite the reported PT being the same. Most of the 57 individuals with latencies within 2 days of vaccination did not provide information on the duration of dyspnoea. When provided (n=18), the dyspnoea lasted from 15 minutes to 264 days.

There were 32 individuals with latencies >3 days from vaccination (range of 4 days to 501 days). A minority (9) individuals had latency of at least one of the dyspnoea events occur between 3 and 7 days from dosing but the remaining had larger latencies making it less likely a relationship between vaccination and the events was causal.

Out of the 503 individuals, 21 reported information on duration of at least 2 events of dyspnoea. Thirteen of the individuals also provided latency information and are listed below in Table 2. The remaining 8 reported the following durations (latency provided when available), as presented in Table 1:

Table 1. Dyspnoea: Individuals with Duration Data but Incomplete Latency Data

AER number*	Dose 1 Dyspnoea duration Latency (when provided)	Dose 2 Dyspnoea duration Latency (when provided)
[redacted]	1 week	1 week
	>7 months	>7 months
	4 days (Latency 11 days)	4 days
[redacted]	2 days	2 days**
	30 minutes	1 day (Latency 1 day)
	2 weeks	2 weeks
	8 days (Latency 2 days)	1 month
	1 week	1 week

*Due to case processing conventions, 1 individual may have >1 adverse event report
**Individual also reported dyspnoea with 2 day duration after Dose 3

Out of the 503 individuals, 13 reported both duration and latency of their events of dyspnoea:

Table 2. Dyspnoea: Individuals with Duration and Latency Data

AER number*	Dose 1 Latency/Duration	Dose 2 Latency/Duration
[redacted]	Same day/1 week	Same day/6 weeks
	Same day/30 minutes	Same day/60 minutes
	278 days/10 days	236 days/10 days
	2 days/25 days	Same day/8 days
	1 day/3 days	Same day/3 days
	1 day/8 days	Same day/6 days
	Same day/15 minutes	Same day/30 minutes
	Same day/9 days	Same day/9 days
	7 days/13 days	4 days/14 days
	Same day/9 months, 25 days	Same day/264 days
	5 days/23 days	8 days/26 days
	1 day/29 days	Same day/28 days
	Same day/1 day	1 day/1 day

*Due to case processing conventions, 1 individual may have >1 adverse event report

MAH's conclusion

Overall, of the individuals with recurrent dyspnoea following vaccination and sufficient data on latency and duration of the events, most events of dyspnoea had an onset close to the time of vaccination and lasting less than 2 weeks.

Rapporteur assessment comment:

Concerning dyspnoea, cumulatively retrieved were 67,974 post-marketing cases. Of these, 1079 cases (1.6%) were positive rechallenge cases for 503 unique individuals.

Out of the 503 individuals, 13 reported both duration and latency of their events of dyspnoea of which most events of dyspnoea had an onset close to the time of vaccination and lasting less than 2 weeks.

There were 57 individuals with a latency within 2 days for at least one of the occurrences of dyspnoea. Most (68%) of the 57 individuals with latencies within 2 days of vaccination did not provide information on the duration of dyspnoea.

Taking into account the relative low number of rechallenge/recurrent dyspnoea reports and the high Comirnaty exposure, the rechallenge/recurrent dyspnoea events are considered not unexpected and coincidence reports.

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

Palpitations

Search criteria - PTs: Palpitations.

Cumulatively through 18 June 2023, 37,311 cases reporting the PT Palpitations were retrieved. Of these, 173 (0.5%) were positive rechallenge cases. Of note, the 173 cases were comprised of 188 events of palpitations that were reported with 2 doses or with 3 doses of the vaccine. These 173 cases (188 events) involved 91 individuals. All cases originated from PM sources; 50 cases were MC and 123 NMC. Case details for the 173 cases are available in Appendix 1 -Table 2 of the PSUR (not reproduced here).

- Case data/demographics pertinent to the 91 unique individuals2:
- Reported gender: female (61), male (27) and unknown (3).
- Reported age in years (n = 86), range: 14-83, mean: 45.2, median: 46.5.
- Country from which at least 2 reports were received: Germany (33), UK (10), Sweden(8), US (6), Belgium (5), Finland, France (4 each), Austria (3), Denmark, Netherlands, Norway and Switzerland (2 each).
- Medical history (n = 43): the most frequently (> 2) reported relevant medical conditions included Seasonal allergy (7), Drug hypersensitivity, Hypertension (6 each), Allergy to animal, Asthma, Hypersensitivity, Pain (4 each), Chronic obstructive pulmonary disease, Mite allergy, and Obesity (3 each).
- COVID-19 Medical history (n = 5): COVID-19 (4), and Suspected COVID-19 (1).

Out of the 188 events of palpitations involving 91 individuals, the majority (130, 69.1%) of the events were non-serious; 66 (35.1%) of the events were recovering/recovered (with and without sequelae).

Out of the 91 individuals, only 20 provided latency data after each of the 2 doses. Latency in these individuals ranged from the day of vaccination to 251 days following vaccination.

There were 13 individuals with a latency within 1-2 days of vaccination for at least one of the occurrences of palpitations, however 1 of them had disparate latencies for each vaccination (D1 latency was the same

day as vaccination while D2 latency was 10 days), suggesting that a dissimilar condition was occurring after each dose despite the reported PTs being similar.

The 7 individuals with latencies farthest from dosing are further listed below:

- [redacted] D2, 73 days and D3, 39 days
- [redacted] D1, 21 days and D2, 69 days
- [redacted] D1, 4 days and D2, 13 days
- [redacted]: D1, 11 days and D2, 11 days
- [redacted] D2, 14 days and D3, 10 days
- [redacted] D1, 82 days and D2, 127 days
- [redacted] D1, 9 days and D2, 21 days

Out of the 91 individuals, only 33 provided palpitation duration data for both of the palpitation events. Two of the individuals also had latency information. The 3 individuals' events are in the table below:

Table 3. Palpitations: Individuals with duration data for both events

AER number*	Dose 1 Duration Latency (when available)	Dose 2 Duration Latency (when available)
[redacted]	1 week	1 week
	15 days Same day	7 days Same day
	1 hour Same day	1 hour Same day

*Due to case processing conventions, 1 individual may have >1 adverse event report

MAH's conclusion

Overall, the incomplete nature of the data does not allow better characterisation of the event or substantiate that palpitations are causally related to the vaccine.

Rapporteur assessment comment:

Concerning palpitations, cumulatively retrieved were 37,311 post-marketing cases. Of these, 173 (0.5%) were positive rechallenge cases for 91 unique individuals.

Out of the 91 individuals, only 33 provided palpitation duration data for both of the palpitation events, and 2 of the individuals also had latency information.

There were 13 individuals with a latency within 1-2 days of vaccination for at least one of the occurrences of palpitations.

The incomplete data of the retrieved palpitations cases hampered causality assessment.

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

Tachycardia and/or Heart rate increased

Search criteria - PTs: Tachycardia, Heart rate increased.

Cumulatively through 18 June 2023, 42,530 cases reporting the PTs Tachycardia and/or Heart rate increased were retrieved. Of these, 224 (0.5%) were positive rechallenge cases.

The 224 cases were comprised of 235 events of tachycardia (128) and heart rate increased (107) that were reported with 2, 3 or 4 doses of the vaccine. These 224 cases involved 106 individuals. All cases originated from PM sources; 38 cases were MC and 186 NMC.

Case details for the 173 cases are available in Appendix 1 -Table 3 of the PSUR (not reproduced here).

Case data/demographics pertinent to the 106 unique individuals:

- Reported gender: female (80), male (23) and unknown (3).
- Reported age in years (n = 96), range: 12-91, mean: 43.3, median: 41.5.
- Country from which at least 2 reports were received: Germany (40), UK (10), Belgium and US (7 each), France; Norway (6 each), Finland (5), Romania, Sweden (3 each), Greece, Netherlands, Slovakia, and Spain (2 each).
- Medical history (n = 51): the most frequently (> 2) reported relevant medical conditions included Seasonal allergy (10), Drug hypersensitivity (7), Hypertension, Mite allergy, (6 each), Asthma and Hypersensitivity (5 each), Allergy to animal (4), Diabetes mellitus, and Food allergy (3 each).
- COVID-19 Medical history (n = 4): COVID-19 (3), and Suspected COVID-19 (1).

Out of 106 individuals 68 provided latency information. Latency in those individuals ranged from days before vaccination to day 365, 38 individuals had a short latency of 0-2 days, indicating a higher possibility of stress related tachycardia. 19 individuals had latencies ≥15 days from dosing indicated an unlikely relationship to vaccination due to their distant temporality.

Fourteen individuals provided tachycardia/heart rate increased duration data. Four individuals had a duration of less than 2 days indicating a higher likelihood of anxiety /stress response to vaccination.

Out of the 14 individuals mentioned above, for 12 both latency and duration data are available:

AER number	Summary
[redacted]	Tachycardia day of vaccination after dose 1 and 2 lasting for 1 day each.
	Patient with lymphoma, heart rate increased 1 day after dose 3 lasting 3 days, went to hospital after dose 3, no findings, similar occurrence after dose 4.
	6 days after dose 1 lasting 1 day and 3 days after dose 2 lasting 1 day.
	1 day after dose 1 lasting 1 day (patient had tick borne encephalitis vaccine the day before) and occurring one day after dose 2 again.
	2 days after dose 1 lasting 1 day and 1 day after dose 2 lasting 1 day.
	Heart rate increased after dose 1 and again after dose 2 onset 4 days lasting for 10 days.
	1 day after dose 1 lasted for 13 months, again after dose 2 and 3 but no latency or onset provided.
	Heart rate increased after dose 1 no latency or duration provided and dose 2 onset same day lasting for 9 days.
	Patient with multiple allergies, onset same day lasting for about 13 months, patient stated "massive aggravation after dose 2 but no further info provided. 2.

[redacted]	Patient with Lyme disease, onset 4 days after dose 3 and 3 days after dose 2.
	Dose 1 AstraZeneca vaccine tachycardia for 2 days, dose 2 BNT162b2 tachycardia occurred the same day of vaccination and lasted about 2 months; dose 3 BNT162b2no latency and duration provided.
	Patient with Lyme disease and atrial fibrillation, 2 doses of AstraZeneca heart rate increased, as well as after D3 of BNT162b2 no latency or duration provided and after D4 of BNT162b2 latency 35 days after vaccination and duration of 12 days.

The overwhelming majority of the better described rechallenge cases above appear to be indicative of anxiety / stress related tachycardia.

MAH's conclusion

Overall, the incomplete nature of the data does not allow better characterization of the events tachycardia or increased heart rate or substantiate that they are causally related to the vaccine.

Rapporteur assessment comment:

Concerning tachycardia and/or heart rate increased, cumulatively retrieved were 42,530 post-marketing cases. Of these, 224 (0.5%) were positive rechallenge cases (comprised 235 events of tachycardia [128] and heart rate increased [107]) for unique 106 individuals.

Out of the 106 individuals, for only 12 both latency and duration data were available.

Out of the 106 individuals, 38 individuals had a short latency of 0-2 days.

The incomplete data of the retrieved tachycardia and/or heart rate increased cases hampered causality assessment.

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

MAH's overall conclusion

A further review of details at the case level for cumulative rechallenge/recurrent cases of dyspnea, palpitations and tachycardia/heart rate increased after vaccination was performed.

All times to onset and event durations were included. While many events were reported, a relatively small proportion of them were recurrent cases. A still smaller proportion of those contained adequate latency and duration data for assessment. Of these, the majority of reports have times to onset that are close to vaccination and durations that are short.

The further analysis revealed little new information and none with enough strength of evidence to add as adverse reactions to section 4.8 Undesirable effects of the Comirnaty SmPC. These events will continue to be monitored with routine pharmacovigilance.

Rapporteur assessment comment:

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

Issue solved

Hemophagocytic lymphohistiocytosis (HLH)

Response to the EMA request (21 Jul 2023):

> *It has come to our attention on accumulating literature articles on hemophagocytic lymphohistiocytosis (HLH) with COVID-19 vaccines, and more particularly on a new hypothesis of a possible involvement of Epstein-Barr Virus (EBV) reactivation. Some case reports describing EBV-positive HLH after COVID-19 vaccination have been recently published (Arand et al., 2023; Takana et al., 2023; Lin et al., 2022; Tang et al., 2021). We would ask to further discuss this topic in the upcoming PSUR, and particularly any new data from the literature.*

MAH's response (Appendix 5.5 of the PSUR)

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of defective apoptosis, a disruption of the regulatory pathway that terminates immune and inflammatory responses and results in excessive immune activation. HLH can be induced by genetic disorders (familial) or environmental causes. Familial HLH is rare, while environmental causes in adults include infection (most commonly EBV), autoimmunity, HIV infection and malignancy. HLH in adults may be confused with or misdiagnosed as sepsis, mainly due to similar clinical manifestations and the lack of specific clinical and laboratory findings for its diagnosis. HLH's immune dysregulation with unchecked inflammation leads to the typical clinical presentation of fever, cytopenia, splenomegaly, and/or hemophagocytosis; ferritin >500 mcg/L and soluble CD25 elevation. HLH is treated with immunosuppressive agents and/or chemotherapy. Treatment of pediatric HLH with multi-agent chemotherapy can be applied in adult patients, although the dose and type of drug need to be adjusted. It is highly recommended that allogenic hematopoietic stem cell transplantation should be used in patients who become reactivated or are refractory to the initial treatment as soon as possible to improve survival.[1,2]

Diagnostic criteria of hemophagocytic lymphohistiocytosis: HLH-2004.

Diagnosis will be established if one of either (1) or (2) is fulfilled
(1) Molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria shown below)
① Fever ≥38.5°C for ≥7 days
② Splenomegaly ≥3 finger breadth below the left subcostal margin
③ Cytopenias affecting ≥2 of 3 lineages in peripheral blood
Hemoglobin <9 g/L
Platelets $<100\times10^9$/L

Absolute neutrophil count <1.0×10⁹/L

④ Hypertriglyceridemia and/or hypofibrinogenemia

Fasting triglycerides ≥265 mg/dL, Fibrinogen ≤1.5 g/L

⑤ Hemophagocytosis in the bone marrow or spleen or lymph node

⑥ Low or absent NK cell activity (according to the local laboratory reference)

⑦ Ferritin ≥500 μg/L

⑧ Soluble CD25 (sIL-2 receptor) ≥2,400 U/mL

Rapporteur assessment comment:

Haemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis - UpToDate

Prompt treatment is critical, but the greatest barrier to a successful outcome is often a delay in diagnosis due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings. If left untreated, patients with HLH survive for only a few months, due to progressive multi-organ failure Treatment and prognosis of hemophagocytic lymphohistiocytosis - UpToDate

Literature

A cumulative search of literature was conducted through 23 July 2023, to identify articles describing BNT162b2 and the MedDRA PT Haemophagocytic lymphohistiocytosis in the Medline, Biosis and Embase database.

The search revealed 11 relevant case reports including Tanaka[3]. Lin[4] was included in the last signal evaluation. Two of the 4 articles cited by EMA PRAC, Arand[5] did not specify the COVID-19 vaccine and Tang[6], reported an inactivated COVID-19 vaccine case in China and will not be discussed further.

Rapporteur assessment comment:

A literature search revealed 11 relevant case reports which included Takana et al. (2023) sited by the EMA as one of the four recently published articles, please refer to case report 3 below.

The MAH stated that the publication of Lin et al. (2022) was included in the last signal evaluation. However, in the previous PSURs no evaluation of the publication of Lin et al. (2022) seems to be included. Lin et al (2022) reported a case of a 14 year old previously healthy girl with HLH after dose 1 (TTO 15 days). The authors concluded that the HLH could be the net result of both acute immunostimulation after COVID-19 vaccination and EBV infection and suggested that the immune activation after COVID-19 vaccination is likely to interfere with the adequate immune response to certain infectious pathogens, resulting in a hyperinflammatory syndrome. Therefore, the case is considered possible related to Comirnaty exposure.

The two remaining publications cited by the EMA, Arand et al. (2023) and Tang et al. (2021), were considered not relevant publications by the MAH because Arand et al. did not specify the mRNA COVID-19

vaccine and Tang et al. reported an inactivated COVID-19 vaccine case in China. For the study of Arand et al. this is not accepted because a mRNA COVID-19 vaccine was reported and therefore of relevance for Comirnaty: Literature case report of a 17 year old male with Epstein–Barr virus-associated HLH after dose 2 mRNA COVID-19 vaccine (TTO 2 weeks) which is considered possible related to mRNA COVID-19 vaccine exposure.

Case report 1: *Simpson et.al: A Case of a Relapsing Remitting Macrophage Activating Syndrome After Covid-19 Vaccine In a Teenager with UNC13D Heterozygous Variant of Uncertain Significance.*[7]

A 15-year-old previously healthy female developed fatigue, fevers, myalgia, chest pain, splenomegaly and lymphadenopathy 10 days after receiving her first Pfizer COVID-19 vaccine. Her symptoms recurred 10 days after receiving the second dose. Her myocarditis, MIS-C, and infectious work up was negative except for positive EBV IgG. Laboratory studies revealed anemia, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. She initially responded to decadron; however, her symptoms recurred with steroid taper. Bone marrow biopsy revealed hemophagocytosis. Whole exome sequencing (WES) revealed a heterozygous variant of uncertain significance in UNC13D c.962C>A (p.Thr321Asn). She had multiple re-admissions with significantly elevated inflammatory markers, including IL2-R, IL-18 and CXCL9. Each episode was complicated by an acute viral infection. She responded to high dose steroids, anti-IL-1, and JAK inhibitors; the weaning of decadron triggered flares. Per the authors, she continues to require increasing doses of the JAK inhibitor, baricitinib. The authors hypothesize she developed MAS due to a combination of genetic predisposition, prior EBV infection, and immune stress associated with the COVID-19 vaccine.

Rapporteur assessment comment:

Literature case report of a 15 year old female with Macrophage Activating Syndrome (MAS) after dose 1 (TTO 10 days) and dose 2 (recurrence, TTO 10 days) which was hypothesized to be developed due to a combination of genetic predisposition, prior EBV infection, and immune stress associated with the COVID-19 vaccine.

The term MAS is usually used when a hemophagocytic syndrome develops in children systemic juvenile idiopathic arthritis (sJIA, formerly called Still's disease, systemic onset JIA, or systemic onset juvenile rheumatoid arthritis. MAS should be thought of as HLH in the setting of a rheumatologic disorder rather than as a separate syndrome. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis - UpToDate

However, none of these conditions have been diagnosed in this reported patient despite extensive testing. Therefore, this case is considered not a HLH case. The (recurrence of) MAS complaints after dose 1 and dose 2, is likely caused by the combination of genetic predisposition and (prior) EBV infection rather than Comirnaty exposure.

The case is considered not valid for causality assessment concerning HLH and Comirnaty.

Case report 2: *Maarten et.al: Case report: Hemorrhagic fever with renal syndrome presenting as hemophagocytic lymphohistiocytosis.*[8]

A 49-year-old man presented to the emergency department following a week of night sweats and fever up to 39C. He complained of right upper quadrant pain, dyspnea, headache, photophobia, and diplopia. The patient was a metal worker and kept guinea pigs, hamsters and rabbits. No other animal contact was reported. Two weeks before presentation, he received a second dose of the BNT162b2 mRNA COVID-19

vaccine. There was no history of recent travel. He smoked actively, drank alcohol sporadically and used no drugs. There were no known allergies and the family history, including active or recent infections, was negative. He presented with hemorrhagic fever, type 1 respiratory insufficiency and acute kidney injury. Diagnostic work up showed a hyperinflammatory syndrome, hypertriglyceridemia, hemophagocytosis, very high ferritin and significantly elevated sCD25. He was diagnosed with hemophagocytic lymphohistiocytosis based on the HLH-2004 criteria. Serological testing indentified Puumala virus (a hantavirus) as the causal pathogen and the authors attributed this to the patient's hamsters. The patient was successfully treated with pulse corticosteroids, intravenous immunoglobins and supportive therapy.

Rapporteur assessment comment:

Literature case report of a 49 year old male with HLH after dose 2 (TTO 2 weeks) which was probably caused by Puumala virus (a hantavirus).

The case is considered unlikely related to Comirnaty exposure.

Case report 3: *Tanaka et.al: Epstein-Barr virus-associated lymphoproliferative disorders after BNT162b2 mRNA COVID-19 vaccination*.[3]

Epstein-Barr virus-associated lymphoproliferative disorders (EBV-LPD) is a rare disease characterized by persistent or recurrent inflammation accompanied by EBV infection of T or NK cells that is not self-limiting, and it is fatal, if untreated. After receiving the first dose of the BNT162b2 mRNA COVID-19 vaccine, a 79-year-old male in [redacted] presented to the hospital with a 2-week history of fever. Laboratory results indicated pancytopenia, elevated liver transaminase levels, hyperferritinemia, and hypofibrinogenemia. Computed tomography revealed hepatosplenomegaly, but lymphadenopathy was not observed. A bone marrow biopsy, a random skin biopsy, and a liver biopsy revealed no malignancy, but an infectious evaluation revealed EBV viremia (5.19 Log IU/ml). Flow cytometry and RT-PCR revealed that the EBV genome was localized in NK cells, suggesting the diagnosis of EBV-NK-LPD. He was treated with prednisolone, intravenous immunoglobulin, and etoposide, but the EBV-DNA load failed to decrease, and he died 2 months later. The authors conclude that although the mechanisms and risk factors for EBV-LPD after BNT162b2 mRNA COVID-19 vaccination remain unknown, it was possible that reactivation of EBV after COVID-19 vaccination may occur.

Rapporteur assessment comment:

Literature case report of a 79 year old male with lymphoproliferative disorders (EBV-LPD) after dose 1 (TTO 2 weeks) probably caused by persistent or recurrent inflammation accompanied by EBV infection.

Although the mechanisms and risk factors for EBV-LPD after Comirnaty exposure remain unknown, the authors concluded that reactivation of EBV after COVID-19 vaccination may be possible.

Therefore, the case is considered possible related to Comirnaty exposure.

Case report 4: *Calvaruso et.a: The First Case of Haemophagocytic Lymphohistiocytosis Triggered by the Booster Dose of Anti-SARS-CoV-2 Vaccine in a Patient with Thalassemia*.[9]

A 48-year-old woman in [redacted] affected by a transfusion-dependent thalassemia was hospitalized in the haematology unit presenting with intermittent fever, haepatosplenomegaly and pancytopenia, which developed a few days after the booster dose of anti-SARS-CoV-2 mRNA vaccine (BNT162b2). The investigations performed during hospitalization led to a diagnosis of HLH and IV dexamethasone was initiated. Cytomegalovirus, Epstein–Barr virus, parvovirus B19, hepatitis B virus, hepatitis C virus,

Leishmania spp., Rickettsia spp., Aspergillus spp., Bartonella spp., Borrelia burgdorferi, Brucella spp., Toxoplasma gondii, Plasmodium spp., human immunodeficiency virus 1-2 were negative. SARS-CoV-2 RNA was not detected on nasopharyngeal swabs. The patient responded well to treatment with i.v dexamethasone.

Rapporteur assessment comment:

Literature case report of a 48 year old women with HLH after booster dose (TTO 6 days) and affected by transfusion-dependent β-thalassemia. The underlying thalassemia is considered a confounding factor for the onset of fever and the worsening of anaemia with subsequent neutropenia and thrombocytopenia, although the clinical presentation compatible with HLH which was hypothesized by the authors to be likely triggered by the vaccination (even after the administration of first doses without adverse reactions).

The case is considered unlikely related to Comirnaty exposure.

Case report 5: *Sprute et.al: Correspondence to: hemophagocytic lymphohistiocytosis after SARS-CoV-2 vaccination*.[10]

The authors, responding to an inquiry, provided more information about a published case report. They did not provide an age of the patient nor what SARS-COV 2 vaccine the patient received. The patient's medical history was unremarkable for underlying diseases associated with HLH. The only pre-existing condition was a pilonidal disease which had been surgically drained 4 years prior. In addition to imaging and microbiological, viral and rheumatological diagnostic approaches listed in the case report, blood cultures were repeatedly negative and serological testing for Brucella spp., Chlamydia trachomatis, Coxiella burnetii, Echinococcus, Entamoeba histolytica, Leishmania, Treponema pallidum and Yersinia was unremarkable. Mycoplasma pneumoniae infection was excluded as trigger due to stable titers over time. The authors consider the SARS-CoV-2 vaccine as the most plausible trigger for HLH. No information was given regarding Epstein-Barr virus infection.

Rapporteur assessment comment:

Literature case report of patient with HLH of which the received SARS-COV 2 vaccine was not reported.

The case is considered not valid for causality assessment concerning HLH and Comirnaty.

Case report 6: *Ashizawa et.al: Macrophage activation syndrome after BNT162b2 mRNA vaccination successfully treated with corticosteroids*.[11]

A previously healthy 51-year-old woman in [redacted] developed high fever, headache, and atypical genital bleeding on the following day after a second dose of BNT162b2 vaccine. She presented to the hospital 5 days after the vaccination without history of contact with COVID-19 patients. On admission, laboratory tests revealed thrombocytopenia, elevated fibrin degradation products, elevated D-dimer, lactate dehydrogenase (LDH) and ferritin. No thrombosis, infarction, hemorrhage or abnormal opacity of lung field was present. A SARS-CoV-2 polymerase chain reaction, blood cultures, antinuclear antibody, rheumatoid factor, and cardiolipin antibodies were all negative. Argatroban and intravenous immunoglobulin were initiated due to the possibility of thrombotic thrombocytopenia which has been reported after the ChAdOx1 nCov-19 vaccine. However, her general condition and her laboratory test results such as LDH, ferritin, and transaminase levels deteriorated. Steroid pulse therapy (methylprednisolone 1g daily for 3 days) followed by oral prednisolone for the diagnosis of MAS triggered by SARS-CoV-2 vaccination was initiated. After the corticosteroid treatment, her symptoms and laboratory data improved without relapse. The authors did not provide any data regarding Epstein-Barr

virus infection. The authors state that there is no known association between SARS-CoV-2 mRNA vaccines and MAS.

Rapporteur assessment comment:

Literature case report of a 51 year old women with Macrophage Activating Syndrome (MAS) after dose 2 (TTO 5 days). No information was provided regarding EBV infection. HLH was not diagnosed and therefore, this case is considered not a HLH case.

The case is considered not valid for causality assessment concerning HLH and Comirnaty.

Case report 7: *Muench et.al: Macrophage activation syndrome in a patient with adult-onset Still's disease following first COVID-19 vaccination with BNT162b2*.[12]

The authors report the case of a twenty-year-old female in [redacted] with adult-onset Still's disease (AOSD), who developed MAS six days after receiving her first dose of BNT162b2 COVID-19 vaccine with ferritin levels of 136,680 µg/l (ref.: 13–150 µg/l). Treatment with methylprednisolone (250 mg/d intravenously) and intravenous immunoglobulins was started, and anakinra was increased to 3×100 mg/d subcutaneously. Initial treatment response was moderate with reduced but remaining fever, decreasing ferritin levels, and normalizing cell counts after four days. She eventually received additional cyclosporin to achieve stable remission (2×100 mg/d). After 2 weeks, she was discharged with her previous anakinra dose, cyclosporin and a steroid tapering regimen. Despite her immunosuppressive treatment, the first vaccination had shown positive antibody development against SARS-CoV-2. Her planned second vaccination with BNT162b2 was discussed by an interdisciplinary team and they recommended that she wait for a synthetic protein-based vaccine (e.g. NVX-CoV2373 (protein-based vaccine, Novavax)) to be approved by regulators, in the hope for a less inflammatory response. Follow-up over a period of 4 month showed disease control and no clinical signs of relapse.

Rapporteur assessment comment:

Literature case report of a 20 year old women with Macrophage Activating Syndrome (MAS) after dose 1 (TTO 6 days). Patient's history included adult-onset Still's disease which had been in stable condition for more than three months under maintenance therapy (anakinra and prednisolone). SARS-CoV-2 PCR test, as well as blood and urine cultures, were negative.

The diagnosed MAS should be thought of as HLH in the setting of a rheumatologic disorder rather than as a separate syndrome. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis - UpToDate

The case is considered possible related to Comirnaty exposure.

Case report 8: *Awan et.al: COVID-19 vaccination–related hemophagocytic lymphohistiocytosis presenting as acute liver failure*.[13]

In September 2021, a 33-year-old healthy man in the [redacted] with a past medical history of hyperlipidemia and seasonal allergies presented to the emergency department with fever, rash, malaise, elevated liver enzymes, and leukopenia. He had received his second dose of the Pfizer COVID vaccine on August 25, 2021, and 3 days later developed fever (102F), chills, and headaches. He was sent home for outpatient follow-up and eventually saw a hematologist for persistent cytopenia, believed to be a likely sequela of a viral infection. He tested negative for COVID-19, although serology was positive for COVID-19 antibodies due to vaccination. The patient continued to have intermittent fevers, body aches, and a 15-lb weight loss, eventually culminating in his first hospitalization on October 22, 2021, for fever of unknown origin

and acute liver injury. During this hospitalization, the patient had pancytopenia and elevated liver function tests (LFTs). Abdominal ultrasound revealed splenomegaly, and a bone marrow biopsy was unremarkable. Viral, fungal, protozoal, helminthic, and bacterial etiologies were ruled out. A liver biopsy revealed significant hepatic inflammation without any confirmatory etiology. At this point, rheumatology started the patient on prednisolone for adult-onset Stills disease (AOSD), with fever, myalgias/arthralgias, rash, splenomegaly, and elevated ferritin. The patient improved and was discharged home on prednisone 20 mg twice a day with gastroenterology follow up, as LFTs did not return to normal. On November 23, 2021, the patient followed up with a hepatologist; LFTs had improved remarkably. Rheumatology tapered his steroids to 40 mg and started to work on procurement of canakinumab. However, soon after steroid tapering, the patient developed arthralgias, rash, jaundice, and fever, again resulting in hospitalization on December 14, 2021, for management of AOSD flare-up. His LFTs and inflammatory markers continued to worsen despite being on methylprednisolone, anakinra, and intravenous immunoglobulin. Since he was no longer meeting the Cush and Fautrel criteria, the rheumatologists were not convinced he had AOSD. Due to lack of response to therapy, there was concern that he had secondary HLH. The H-score was 274, showing a >99% probability of HLH. Therefore, he was started on the HLH 2004 protocol (etoposide and dexamethasone). Repeat bone marrow biopsy on January 10, 2022, showed marrow consistent with HLH. He continued to worsen clinically. Due to severe liver dysfunction, etoposide was discontinued on January 13, 2022. His inflammatory markers, LFTs, and cytopenia continued to worsen, and ultimately, he was in multiorgan failure, after which he was transitioned to comfort care.

Rapporteur assessment comment:

Literature case report of a 33 year old men with HLH after dose 2 (TTO 3 days). Medical history included hyperlipidemia and seasonal allergies. A liver biopsy revealed significant hepatic inflammation without any confirmatory etiology. The patient was started on prednisolone for adult-onset Stills disease. Three months later due to lack of response to therapy, he was diagnosed secondary HLH and was started on the HLH 2004 protocol (etoposide and dexamethasone).

The case is considered possible related to Comirnaty exposure.

Case report 9: *Shimada et.al: A case of hemophagocytic lymphohistiocytosis after BNT162b2 COVID-19 (Comirnaty®) vaccination*.[14]

An 85-years-old [redacted] woman with a 10-year history of nephrosclerosis with hypertension presented to the hospital with a history of fever, temperature > 38°C for 7 days, and nonspecific fatigue. The patient was admitted 12 days after the first COVID-19 vaccination with Comirnaty®. Preliminary examination of the patient revealed the following findings: body temperature, 39°C; blood pressure, 120/80 mm Hg; heart rate 90 beats/minute, SpO2 90% to 95%. No palpable or superficial lymph nodes were observed. No abnormalities were found on auscultation. Laboratory data showed white blood cell 400 × 103/μL (Neut 0% Lymph 60%, Mono 34%, Blast 2%), Hb 8.1 g/dL, Plt 28.7 × 104/μL, C Reactive Protein 9.64 mg/dL. Other findings were elevated levels of serum lactate dehydrogenase, 904 U/L (124–222), soluble IL-2 R 1450U/mL (1–613), IL-6 37 pg/mL (<7), and ferritin 2284 ng/ml (10–80). Chest and abdominal computed tomography (CT) revealed no bilateral lung consolidation, pleural effusion, or splenopmegaly. Bone marrow aspiration was performed, and microscopic examination revealed agranulocytosis and anemia. The bone marrow aspirate show two histiocytes phagocytosing erythrocytes. On the second day of admission, pulsed intravenous (IV) methylprednisolone (500 mg/day for 3 consecutive days) and granulocyte-colony stimulating factor was started, followed by oral prednisolone (30 mg once daily). The patient's temperature normalized within 12 hours of steroid initiation, and concurrent symptomatic and biochemical improvements were observed.

Rapporteur assessment comment:

Literature case report of a 85 year old women with HLH after dose 1 (TTO 12 days). Medical history included the presence of chronic kidney disease (CKD) due to nephroscelorosis for 10 years with hypertension.

The case is considered unlikely related to Comirnaty exposure.

Case report 10: Sassi et.al: Haemophagocytosis and atypical vacuolated lymphocytes in bone marrow and blood films after SARS-CoV-2 vaccination.[15]

An 85-year-old man in [redacted] without co-morbidities presented with anorexia, asthenia and pruritus at an unspecified time after a first dose of Pfizer-BioNTech COVID-19 vaccine. His full blood count showed a normal haemoglobin concentration, severe thombocytopenia (platelet count 34x109/l), neutrophilia (neutrophil count 9.2x109/l), mild eosinophilia (eosinophil count 0.6x109/l) and lymphopenia (lymphocyte count 0.5x109/l). These anomalies had not been found on a blood count carried out a few days before administration of the vaccine. The reason for the previous bloodwork was not provided. Clinical examination showed neither organomegaly nor signs of bleeding. A bone marrow aspirate showed low cellularity with absence of megakaryocytes; myeloid and erythroid cells were present at all stages of maturation with a myeloid/erythroid ratio of 5:1. Eosinophils constituted 20% of nucleated cells. Haemophagocytosis was observed with scattered histiocytes engulfing nucleated cells and erythrocytes The authors reported that HLH secondary to the vaccine was suspected but diagnostic criteria were not met.

Rapporteur assessment comment:

Literature case report of a 85 year old men with haemophagocytosis after dose 3 (TTO not reported). HLH secondary to the vaccine was suspected but diagnostic criteria were not met.

The case is not considered valid for causality assessment concerning HLH and Comirnaty.

Case report 11: *Park et.al: A Case of Hemophagocytic Lymphohistiocytosis following Second Dose of COVID-19 Vaccination*.[16]

A 21-year-old man in [redacted] was transferred from another hospital with an uncontrolled high fever (above 39°C), pancytopenia, and an elevated total bilirubin concentration (10.27 mg/dL). He experienced general weakness, a fever, myalgia, and a non-pruritic skin rash. The patient had no known or related medical history and was in good physical condition before receiving the second dose of the BNT162b2 vaccine 2 weeks prior. He was started on empirical intravenous antibiotics (Tazoperan, piperacillin and tazobactam) for fever of unknown origin and steroid pulse therapy (intravenous methylprednisolone, 1.5 mg/kg/day) 4 days before the hospital transfer. Blood and urine cultures were negative. 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. There was no evidence of acute or active infection with cytomegalovirus; Epstein-Barr virus; parvovirus B19; hepatitis A, B, and C; human immunodeficiency virus (HIV); or Korean endemic viruses related to hemorrhagic fever with renal syndrome. Autoimmune antibody tests were negative. The patient subsequently received high-dose dexamethasone (20 mg/day for 7 days) and a 25% dose reduction on a weekly basis without etoposide or other treatment modalities. Nineteen days after steroid pulse therapy, the patient was discharged in good physical condition without any constitutional symptoms, with normal laboratory values and the

disappearance of the skin rash. After discharge, the patient received oral steroids, which were tapered weekly, and stopped after the third month of follow-up without any evidence of HLH relapse.

Rapporteur assessment comment:

Literature case report of a 21 year old men with HLH after dose 2 (TTO 2 weeks). The patient met the HLH criteria for both measures: he fulfilled all eight of the HLH-2004 diagnostic criteria and had an hemophagocytic syndrome (HS)core of 319 (In the validation set, the median HScore was 222 [IQR 202–284] for positive cases and 129 [IQR 77–152] for negative cases, Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the Hscore a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66[9]:2613–2620).

There was no clear precipitant of HLH other than the second dose of the BNT162b2 vaccine. The patient had no remarkable medical history, was not taking any medications, and had no active or recent bacterial or viral infection or autoimmune disease. After his diagnosis, the patient recovered entirely without relapse or sequelae with the administration of dexamethasone steroid pulse therapy with slow tapering.

The case is considered probable related to Comirnaty exposure.

MAH's literature summary

The ten new case reports of HLH in the literature do not provide significant new safety information that would support a causal association between vaccination with BNT162b2 and the development of HLH. Viruses such as Epstein-Barr-virus infection is a major contributor to the development of HLH, however the new literature case reports do not provide convincing evidence that COVID-19 vaccination leads to reactivation of Epstein-Barr virus which then triggers HLH.

Rapporteur assessment comment:

Through 23 Jul 2023, in total 14 case report publications were reported, 4 case reports cited by the EMA and 10 new other case reports retrieved by the MAH, of which:

- 1 case report was considered probable related to Comirnaty exposure;
- 5 case reports were considered possible related (including Lin et al. [2022], Tanaka et al. [2023], Arand et al. [2023] cited by the EMA);
- 3 case reports were considered unlikely related; and
- 5 case reports were considered not relevant cases (4 cases with no diagnosed HLH and 1 case reported an inactivated COVID-19 vaccine) for causality assessment concerning HLH and Comirnaty.

Safety database review

The Safety database was searched from 23 September 2022 (the DLP for the previous evaluation of HLH) to 23 July 2023 using the MedDRA (v. 26.0) PT: Haemophagocytic lymphohistiocytosis for all BNT162b2 vaccines. 19 cases were retrieved.

Fourteen (14) cases were female and 5 cases male, the mean age was 48.9 years (min 12 and max 88 years). There were 3 fatal reports. The top reporting countries were Japan (6), Germany (4), Australia (3) and United States (3). There were 10 spontaneous and 9 literature reports, all serious. Two reports were duplicates ([redacted] and [redacted]).

Six (6) cases were literature reports already reported in the literature section.[5,7,7,16,14,9] 5 cases contained insufficient information for a medical assessment. There were 7 remaining cases summarized below:

AE Number	Preferred Terms	Medical History / Concomitant Medications	Narrative
[redacted] 16 years / male Dose 3	Pyrexia, Hepatitis, Jaundice, Rash erythematous, Leukopenia, Thrombocytopenia, Skin exfoliation, Blister, Toxic epidermal necrolysis, Acute respiratory distress syndrome, Stevens-Johnson syndrome, Hypotension, Malaise, Myalgia, Decreased appetite, Chromaturia, Dizziness, Hepatic enzyme increased, Serum ferritin increased, C-reactive protein increased, Haemophagocytic lymphohistiocytosis, Dengue fever, Lip swelling, Lip erythema, Ocular hyperaemia	COVID-19 Jun 2022 CETIRIZINE / CHLORMEZANONE / DICLOFENAC / MOSAPRIDE / PIPRINHYDRINATE	16-year-old male received 3rd dose of BNT162b2 14 Sep 2022. The patient experienced fever, generalized malaise, muscle soreness, decreased appetite, tea-colored urine, erythematous papular skin rashes over anterior chest, dizziness on 23-Sep-2022, leukopenia, thrombocytopenia, elevated liver enzymes, elevated ferritin and mild elevated C-reactive protein, hemophagocytic lymphohistiocytosis, dengue fever on 26-Sep-2022, swelling lips, erythematous lips and red eye on 27-Sep-2022, scrotum desquamation, chest bullae formation, stevens-Johnson syndrome, toxic epidermal necrolysis on 28-Sep-2022, acute respiratory distress syndrome and hypotension on 29-Sep-2022, hepatitis and jaundice on 02-Oct-2022. *MAH comment: The dengue fever infection was the most likely cause of HLH.*
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. The dengue fever infection seemed to be the most likely cause of HLH.			
[redacted] 80 years, female Dose 3	Off label use, Interchange of vaccine products, Autoimmune hepatitis, Haemophagocytic lymphohistiocytosis, Encephalopathy, Renal failure	Hypertension AMLODIPINE / TELMISARTAN	She had received the ChAdOx1 vaccine 1 year prior and developed haemophagocytic lymphohistiocytosis, encephalopathy, renal failure 3 weeks after a second dose of BNT162b2. Laboratory tests show elevated liver function tests; Biopsy bone marrow showed hemophagocytic lymphangiohistiocytosis secondary due to her autoimmune hepatitis; Biopsy liver showed active periportal, notes: inflammation with prominent eosinophils and plasma cells, suggestive of autoimmune hepatitis. The patient date of death was unknown. Reported cause of death: "progressive encephalopathy", "renal failure". It was not reported if an autopsy was performed.

AE Number	Preferred Terms	Medical History / Concomitant Medications	Narrative
			MAH comment: This case is unlikely related to BNT162b2.
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. The HLH was secondary due to patient's autoimmune hepatitis.			
[redacted] 55 years / female Dose 2	Still's disease, Acute hepatic failure, Rash, Pyrexia, Arthralgia, Transaminases increased, Blood lactate dehydrogenase increased, C-reactive protein increased, Haemophagocytic lymphohistiocytosis, Polyserositis, Leukocytosis, Paraesthesia, Hypoaesthesia, Eosinophilia, Hot flush, Limb discomfort, Poor quality sleep, Depressed mood, Alopecia, Dyspepsia, Fatigue	Hashimoto's thyroiditis LEVOTHYROXINE	The individual received BNT162b2 (COMIRNATY), on 30Jun2021 as dose 2. One day later she developed tingling in her face. 6 weeks later she developed fever, arthralgia, leukocytosis, elevated liver function tests and Still disease 8 weeks later. In September low grade haemophagocytosis was noticed, the patient was treated and recovered. *MAH comment: Haemophagocytosis is likely related to the underlying Still's disease.*
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. The underlying Still's disease seemed to be the most likely cause of HLH.			
[redacted] 12 years / female Dose 3	Haemophagocytic lymphohistiocytosis, Splenomegaly, Neoplasm malignant, Pyrexia, Blood disorder	Orthokeratology and allergy to cedar pollen ATROPINE / CRYPTOMERIA JAPONICA POLLEN / NORETHISTERONE	On 03Dec2022, the individual received BNT162b2 dose 3. Influenza vaccination on 14Nov2022. She presented with pyrexia on 4Dec2022. Fever persisted and patient presented to hospital Dec 8th, Blood tests revealed low levels of white blood cells/platelets, high levels of AST, ALT, and LDH, high level of ferritin, and mild increases in CRP and sIL2-R. The patient was placed on follow-up on outpatient basis, but because of no improvement, the patient was hospitalized for detailed examination on 12 Dec2022. A post-admission contrast-enhanced MRI test showed mild hepatosplenomegaly but revealed no other malignant findings or obvious swollen lymph nodes. On aspiration bone marrow, haemophagocytosis images and activated macrophage were noted, while

AE Number	Preferred Terms	Medical History / Concomitant Medications	Narrative
			hematopoiesis was normal without malignant findings. Virus multi tests and antinuclear antibody showed negative results. These results led to a diagnosis of haemophagocytic syndrome, and from 16Dec2022, treatment with prednisolone 2 mg/kg/day was started. The subsequent course showed prompt fever resolution, and blood tests results showed improving tendency. Steroid dose was reduced and the patient recovered. *MAH comment: There is a plausible temporal relationship to vaccination.*
Rapporteur assessment comment: A case of 12 year old girl with HLH after dose 3 (TTO 1 day). Virus multi tests and antinuclear antibody showed negative results. The case is considered possible related to Comirnaty exposure.			
[redacted] 88 years / female Dose 5	Haemophagocytic lymphohistiocytosis, Interstitial lung disease, Pleurisy, Capillary leak syndrome, Pleural effusion, Pancytopenia, Pneumonia, Dyspnoea, Oedema peripheral, Pyrexia, Arthralgia	Pulmonary mycobacterium avium complex, variant angina	An 88 year old female with a history of pulmonary Mycobacterium avium complex developed haemophagocytic syndrome, Pleurisy and Interstitial pneumonia 3 months after dose 5 booster vaccination with BNT162b2. The patient was admitted to hospital and treated with steroids and diuretics however deteriorated further and passed away 5 weeks after admission. *MAH comment: The symptoms are likely related due to the underlying mycobacterium infection and the old age of the patient.*
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. The HLH is more likely related to the mycobacterium infection.			
[redacted] 18 years / female Dose unknown	Haemophagocytic lymphohistiocytosis, Histiocytic necrotising lymphadenitis	Medical history not reported	Woman developed haemophagocytic lymphohistiocytosis and Kikuchi's disease in Oct 2023 following administration of tozinameran for COVID-19 immunisation in Apr 2021 and Jul 2021. Thereafter, she developed morbilliform drug eruption during prophylactic treatment with cefuroxime. She presented to the

AE Number	Preferred Terms	Medical History / Concomitant Medications	Narrative
			emergency room with 3 weeks history of fever associated with sweating and painful swelling on the right side of her neck on 11 October 2021. She had poor appetite and lost 5kg. She visited her primary care physician, who prescribed an oral amoxicillin/clavulanic-acid. However, she showed no improvement over 5 days. Based on investigation results and pathological findings, she was diagnosed with haemophagocytic lymphohistiocytosis and Kikuchi's disease. Haemophagocytic lymphohistiocytosis and Kikuchi's disease was attributed to tozinameran. The woman was treated with dexamethasone. She improved dramatically and the fever subsided completely. She regained her appetite, the skin rash did not recur, the size of the cervical lymphadenopathy regressed and white cell counts rose to near normal. *MAH comment: There is a long latency (3 months) between vaccination and the occurrence of symptoms, in addition medical history nor concomitant medications were not provided.*
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. Due to the TTO of 3 months after dose 2 it is not likely that Comirnaty exposure was the cause of HLH.			
[redacted] 67 years / male Dose 5	Pulmonary alveolar haemorrhage, Haemophagocytic lymphohistiocytosis, Pyrexia, Haemoptysis	Medical history not reported	On 30 Mar 2023 (3 months 24 days after the vaccination), the patient experienced Pulmonary alveolar haemorrhage, Macrophage activation syndrome. On 03 Apr 2023 (3 months 28 days after the vaccination), the patient was admitted to the hospital. On 13 Apr 2023 (4 months 7 days after the vaccination), the patient discharged from hospital. On 13 Apr 2023 (4 months 7 days after the vaccination), the outcome of the event was recovering.

AE Number	Preferred Terms	Medical History / Concomitant Medications	Narrative
			MAH comment: The time to onset is very long suggesting alternative cause.
Rapporteur assessment comment: The case is considered unlikely related to Comirnaty exposure. Due to the TTO of 3 months after dose 2 it is not likely that Comirnaty exposure was the cause of HLH.			

Rapporteur assessment comment:

From 23 Sep 2022 to 23 Jul 2023, the MAH retrieved from the safety database 19 HLH cases, of which 2 case reports were duplicates, resulting in 18 unique case reports:

- 1 case report was considered possible related to Comirnaty exposure;
- 6 case reports were considered unlikely related;
- 6 case reports were already discussed in the literature section above;
- 5 cases reports contained insufficient information for a medical assessment.

Routine statistical reports

To support routine signal detection activities in addition to the non-statistical reports, the MAH generates statistical reports including EB05.

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

On cumulative review of the EB05 report (May 2023) for the relevant PT's, the obtained value for HLH was 0.75 for BNT162b2 and 0.6 for BNT162b2 BA4/5 and has not been reported for BNT162b2 BA1.

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

Rapporteur assessment comment:

The MAH stated that the EB05 is less than the EB05>2 threshold (May 2023), indicating no emerging statistical signal for HLH.

MAH's summary and conclusion

An updated literature and safety database search including routine statistical reports did not reveal any new significant safety information and a causal relationship between vaccination with BNT162b2 and the development of haemophagocytic lymphohistiocytosis or the reactivation of Epstein-Barr virus infection leading to the development of haemophagocytic lymphohistiocytosis cannot be concluded. The topic will be monitored using routine Pharmacovigilance.

Rapporteur assessment comment:

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by an overwhelming systemic inflammatory reaction. The aberrant activation of macrophages, natural killer cells, and cytotoxic T cells leads to the overproduction of cytokines, especially interleukin (IL)-1, IL-2, IL-6, and tumor necrosis

factor-alpha, as well as hemophagocytosis of hematopoietic cells in the bone marrow. The resulting tissue/organ destruction means that the disease is life-threatening. Multisystem inflammatory syndrome in children (MIS-C), also a disorder caused by the dysregulated immune system, is associated with SARS-CoV-2 infection. MIS-C is similar to HLH in increased T-cell activation and plasma cytokines/chemokines, but differs in the extent of the stimulation. Patients with MIS-C usually present with cardiac problems including myocarditis and often involve gastrointestinal disorders. Patients with HLH experience an unremitting high fever, cytopenia, coagulopathy, hepatic dysfunction, and organomegaly, with or without lymphadenopathies. If not treated appropriately, the patient's condition may rapidly deteriorate to terminal multiorgan failure and subsequent death. Therefore, early diagnosis and urgent treatment are critical for survival. HLH can be classified as either familial, characterized by genetic defects causing lymphocyte cytotoxicity, or acquired/secondary HLH (sHLH), usually triggered by infection, autoimmune disease, or malignancy.[16]

Literature

In total 14 case report publications were reported, 4 case reports cited by the EMA and 10 new other case reports retrieved by the MAH, of which:

- 1 case report was considered probable related to Comirnaty exposure;
- 5 case reports were considered possible related (including Lin et al. [2022], Tanaka et al. [2023], and Arand et al. [2023] cited by the EMA);
- 3 case reports were considered unlikely related; and
- 5 case reports were considered not relevant cases (4 cases with no diagnosed HLH and 1 case reported an inactivated COVID-19 vaccine) for causality assessment concerning HLH and Comirnaty.

Post-marketing

From MAH's safety database 19 HLH cases were retrieved, of which 2 case reports were duplicates, resulting in 18 unique case reports:

- 1 case report was considered possible related to Comirnaty exposure;
- 6 case reports were considered unlikely related;
- 6 case reports were already discussed in the literature section above;
- 5 cases reports contained insufficient information for a medical assessment.

Cumulatively, 1 HLH case (women 21 years old) is considered probably related with Comirnaty (due to the absence of other aetiologies or confounding) and 6 HLH cases (women 12, 14, 20 years old; men 17, 33, 79 years old) are considered possible related. However, given the extensive exposure of Comirnaty this is not considered unexpected and does not present a new safety concern at the moment.

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

However, the MAH should continue to closely monitor HLH and all new (literature) cases of HLH including a WHO-UMC causality assessment per case and age-stratified observed/expected analyses using 21- and 42-day risk intervals, should be reported in the next PSUR. **Request for next PSUR**

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Pemphigus and Pemphigoid

Introduction/background

In December 2022, a signal assessment report was issued by the EMA (PAM-SDA-061) on Comirnaty and pemphigus and pemphigoid. Following submission of a signal evaluation report, the MAH received an adopted PRAC recommendation on 14 April 2023 that stated:

> *Having considered the available evidence from EudraVigilance, literature, the data submitted by the MAH and the analysis by EMA of real-world data, the PRAC has concluded that the current evidence is insufficient to establish a causal relationship between Comirnaty and pemphigus or pemphigoid. The MAH should continue to monitor these topics in PSURs.*
>
> *In the next PSUR (DLP 18 June 2023), the MAH should perform a review of all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to Comirnaty, including data from clinical trials, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an O/E analysis and provide all case narratives within this review.*

Rapporteur assessment comment:

Please also refer to the closed signal procedure Pemphigus and Pemphigoid (EPITT 19859).

Appendix 5.6 of the PSUR has been created to review the new emerging data on pemphigus and pemphigoid.

Autoimmune bullous dermatoses in the pemphigus family cause loss of cell-to-cell adhesion (acantholysis) in the mucocutaneous membranes due to antibodies against proteins on the cell surface of keratinocytes (e.g., desmogleins). It is rare and may be idiopathic or drug-induced but also seems to have a relationship with certain HAL class II genes as evidenced by its higher prevalence in individuals of Mediterranean and Ashkenazi decent. Subtypes include pemphigus vulgaris, pemphigus foliaceus, IgA pemphigus and paraneoplastic pemphigus. It is largely a disease of adults but may also affect children and the male-to-female ratio worldwide is about equal. Diagnosis is based on histopathology and direct immunofluorescence of the specimen and is supported by the presence of pathogenic antibodies in the serum.[1]

The bullous form of pemphigoid is also an autoimmune condition and thought to involve autoantibodies directed against hemidesmosomes that attach basal keratinocytes with the basement membrane at the dermal-epidermal junction. Risk factors for this condition are also thought to include hereditary predisposing factors such as HLA types in addition to infections and certain drugs. Pemphigoid has a tendency to occur in elderly males (>70 years) and is no longer considered a rare dermatologic disease in the elderly. Its incidence varies from 2.4 to 21.7 new cases/million/year–and prevalence has been increasing. Diagnosis is based on the presence of clinical features, direct immunofluorescence of tissue (linear deposits of IgG or C3 along the epidermal basement membrane) and serum autoantibodies against BP180 and/or BP230 antigens.[2,3]

Rapporteur assessment comment:

Pemphigus and pemphigoid are rare autoimmune blistering diseases of the skin and/or mucous membranes.

Pemphigus affects the epidermis and causes lesions and blisters that are easily ruptured.

Pemphigoid affects a lower layer of the skin, between the epidermis and the dermis, creating tense blisters that do not break easily. Sometimes pemphigoid may look like hives or eczema without blisters. Over-active immune system leads to skin cells separating from each other, fluid collecting between skin layers and blisters formation.

Clinical trial data

There is no new placebo-controlled clinical trial data from the large pivotal Pfizer-run clinical studies C4591001 and C4591007 that were previously presented. The pemphigus/pemphigoid AEs reported had either occurred after placebo or with times to onset longer than ~3 months after receipt of BNT162b2 vaccine.

Safety database

Methodology

Utilizing PSUR criteria, MAH's safety database was searched cumulatively through 18 June 2023 for BNT162b2, BNT162b2/BNT162b2 OMI BA.1 and BNT162b2/BNT162b2 OMI BA.4-5 cases coded with any of the following PTs (MedDRA version 26.0): Benign familial pemphigus; Linear IgA disease; Mucous membrane pemphigoid; Ocular pemphigoid; Paraneoplastic pemphigus; Pemphigoid; Pemphigus; Pemphigus disease area index. Cases included in the previous signal evaluation performed by the MAH (end date 15 Nov 2022) were excluded from the search.

As of 23 June 2023, there were 52 cases of pemphigoid and 35 cases of pemphigus retrieved for review.

Results – Pemphigus

The 35 serious cases of pemphigus were from spontaneous reports (22) and literature (13); all were reported for BNT162b2 (original) except 1 report coincident with administration of Bivalent BNT162b2 (Original + Omicron BA.4/BA.5). They were reported from Germany (7), Italy (5), France and Japan (4 each), Canada (3), Greece, Morocco and UK (2 each) and Portugal, South Africa, Thailand, Tunisia, Turkey and US (1 each) in a relatively equal number of males (18) and females (17) ranging in age from 17 to 86 years of age (mean 55.6). Most reports described patients between 31 and 74 years of age. The outcome of the cases was reported as recovered/recovering (with or without sequelae) in 45.7%, not recovered in 28.6% and unknown in 25.7% of reports. There were no fatal cases.

As requested by EMA, narratives of all the cases are provided in Appendix 5.6.1 of the PSUR (not reproduced here).

Of the 35 cases, 18 did not mention the means to a clear diagnosis of pemphigus (e.g., cutaneous or mucosal biopsy). Due to this lack of reassurance of the diagnosis of interest, these cases are considered unclassifiable and not further discussed.

Of the remaining 17 cases with biopsies, 2 describe the occurrence of pemphigus long after vaccination (70 and 95 days, respectively) and are therefore considered unlikely to be associated with Comirnaty.

Details of the remaining 15 cases (13 unique patients) are in the table below. These could be considered "possible or better" if the WHO-UMC case causality assessment for medication is applied[4], however it should be recognized that for AEFIs, it is seldom possible to achieve a straightforward answer about causality at the individual case level and causality assessment must also occur at the population level.[5]

Table 1. Remaining Pemphigus Cases (n = 15)

	AER **Age (years)/Sex** **Country** **Reporter**	**Dose** **Time to Onset**	**Medical History** **Medications**	**Summary** ***MAH Comment***
1	[redacted][a] 73/Male [redacted] Literature case report (unpublished)	Dose 1 22 days	Not reported Not reported	Erosions were reported on the trunk 22 days after D1 and at an unspecified time after D2, new erosions occurred on the trunk, face and limbs. Skin biopsy showed acantholysis and IgG and C3 deposition between

Table 1. Remaining Pemphigus Cases (n = 15)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
2	[redacted][a] 73/M [redacted] Literature case report (unpublished)	Dose 2 Not specified		epidermal cells; Antibodies to desmoglein 1 were positive. Recovering following prednisone, cyclosporin then rituximab. *Lack of clinical detail (medical history and current meds); Unclear if 2nd report of pemphigus was continuation of 1st episode; event temporality to vaccination may be coincidental. More data for a proper assessment would be needed.*
	Rapporteur assessment comment: Case of a 73 year old men with pemphigus after dose 1 and dose 2 (TTO 22 days). Not clear if the complaints after the dose 2 are recurrence or continuation of the pemphigus after dose 1. The case is considered possible related to Comirnaty exposure.			
3	[redacted][b] 53/Male [redacted] Physician	Dose 2 25 days	High cholesterol; Hypertension; Glaucoma Indapamide; perindopril, ezetimibe	D1 with Comirnaty. Skin lesions after D2 not described but biopsy showed acantholysis and C3 depositions. Negative antibodies to desmoglein. Was on azathioprine and tapering dose of steroids at time of D3 and 1 month later had worsening lesions requiring an increase in steroids and use of rituximab; not recovered at time of report *ACE inhibitors have been associated with pemphigus; decrease in steroids following 1st episode may have also played role in 2nd report; 2nd report may have been continuation of 1st episode rather than separate incident*
4	[redacted][b] 52/Male [redacted] Physician	Dose 3 33 days		
	Rapporteur assessment comment: Case of a 52 year old men with pemphigus after dose 2 and dose 3 (TTO 25 days and 33 days respectively). It is not clear if the complaints after the dose 3 are recurrence or continuation of the pemphigus after dose 2. The case is considered possible related to Comirnaty exposure.			
5	[redacted] 69/Female [redacted] Physician	Dose 1 Same day as vaccination	Pemphigus vulgaris; osteoporosis Not reported	Long history of pemphigus (last flare in 2015); mouth and genital lesions assessed as possible relapse of PV by dermatologist; biopsy showed direct immunofluorescence; antibodies to desmoglein 1 present *History of pre-COVID-19 vaccination PV raises question of whether the vaccine induces flares; however, TTO of same day as dose 1 seems very soon for a causal connection*

Table 1. Remaining Pemphigus Cases (n = 15)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
Rapporteur assessment comment: Case of a 69 year old women with (a relapse of) pemphigus after dose 1 and dose 3 (TTO same day vaccination). The case is considered unlikely related to Comirnaty exposure, due to a TTO on the same day of the vaccination.				
6	[redacted] 86/Male [redacted] Literature case report	Dose 2 1 day	Metastatic pharyngeal and gastric cancer Not reported	D1 with Comirnaty. Biopsy showed intraepidermal blister and IgG deposition on keratinocytes but no C3; serum antibodies to desmoglein 1 and 3 present. Skin lesions improved with IV steroids; pharyngeal and gastric cancer found during examination; oncologic treatment was declined *The presence of metastatic cancer introduces an alternative potential cause for pemphigus*
Rapporteur assessment comment: Case of a 86 year old men with pemphigus after dose 2 (TTO 1 day). The case is considered unlikely related to Comirnaty exposure, due to the latent hypopharyngeal and gastric cancer that manifested vaccination and could be an alternative for pemphigus.				
7	[redacted] 20/Male [redacted] Non-HCP	Dose 2 14 days	Reported to have no relevant medical history Not reported	D1 with Comirnaty. Skin biopsy showed irregular acanthosis with eosinophilic exocytosis and DD included drug eruption, viral exanthem and urticarial vasculitis. Reportedly no relevant medical history by narrative alludes to a previous similar incident in 2020 (pre-COVID-19 vaccination). *Unclear picture of overall pathological process specifically with multiple other PTs coded (including Herpes simplex). More information would be helpful for a proper assessment.*
Rapporteur assessment comment: Case of a 20 year old men with pemphigus after dose 2 (TTO 14 days). The case is considered unassessable for causality assessment with Comirnaty.				

Table 1. Remaining Pemphigus Cases (n = 15)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
8	[redacted] 50/Female [redacted] Literature case report	Dose 2 15 days	"No specific medical history" Not reported	D1 with Comirnaty. Extensive post-bullous erosions on the trunk, back and scalp with no mucosal involvement. Biopsy with intraepidermal eosinophils, IgG/C3 intercellular deposition and unspecified antibodies "indicating foliaceous pemphigus;" recovered completely with oral steroids after 3 weeks. *The patient was not reported to have a relevant medical history and no other exposures were described that the condition could be attributed to.*
Rapporteur assessment comment: Literature case report of a 50 year old women with pemphigus after dose 2 (TTO 15 days). The case is considered possible related to Comirnaty exposure.				
9	[redacted] 58/Female [redacted] Literature case report	Dose 1 31 days	Depression Not reported	Biopsy showed acantholysis with diffuse perivascular dermal lymphocytic and eosinophilic infiltration; IgG and C3 on epidermal cells; no mention of desmoglein antibodies; treated with steroids and recovering. *Concomitant medication use was not reported; timing is questionable; more information would be helpful for a proper assessment*
Rapporteur assessment comment: Literature case report of a 58 year old women with pemphigus after dose 1 (TTO 31 days). The case is considered possible related to Comirnaty exposure.				
10	[redacted] 74/Male [redacted] Non-HCP	Dose 2 18 days	Hypertension; stroke; BPH s/p gamma radiation therapy; GERD; mesothelioma; pancreatic calcification Urapidil; esomeprazole; febuxostat; irbesartan/HCTZn ebivolol;	D1 COVID-19 vaccine manufacturer was reported as unknown. Skin biopsy "in favor of" acantholytic dyskeratosis in context of acantholytic actinic keratosis; Antibodies to desmoglein 1 and 3 reported; corticosteroid treatment did not improve but resolved with rituximab. *Unclear contribution of mesothelioma (no malignancy per se noted) and unspecified vaccine for D1, however diagnosis appears consistent with pemphigus in patient on multiple medications, including an angiotensin receptor blocker.*
Rapporteur assessment comment: Case of a 74 year old men with pemphigus after dose 2 (TTO 18 days). The case is considered possible related to Comirnaty exposure.				

Table 1. Remaining Pemphigus Cases (n = 15)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
11	[redacted]* 38/Female [redacted] Physician	Dose 4 2 days	Asthma; zinc and iron deficiencies; hysterectomy Tranexamic acid (beauty purposes)	D1-D3 COVID-19 vaccine manufacturer was reported as unknown; only oral mucous membrane affected – biopsy showed "viral inclusion body without malignant features" and no mention of acantholysis. Antibodies to "DS-1 and DS-3" were negative; recovered with steroid administration but had lasting intraoral discomfort and taste abnormality. *Patient did not have classic pemphigus biopsy findings or serum antibodies. Unspecified D1, D2, D3 COVID-19 vaccines; there is some doubt to the accurate diagnosis and cause. More data would be helpful for a proper assessment*
Rapporteur assessment comment: Case of a 38 year old women with pemphigus after dose 4 (TTO 2 days). The case is considered unassessable for causality assessment with Comirnaty.				
12	[redacted] 40/Female [redacted] Non-HCP	Dose 2 37 days	Polycystic kidney disease Not reported	D1 was Comirnaty. Biopsy of palate was not described nor was any lab work; treated with steroids, azathioprine and rituximab; outcome reported as unknown. *Patient with possible pemphigus symptoms over 1 month after D2; the lack of biopsy or lab data to support diagnosis leaves an incomplete picture for assessment*
Rapporteur assessment comment: Case of a 40 year old women with pemphigus after dose 2 (TTO 37 days). The case is considered unlikely related to Comirnaty exposure due to a TTO of over a month.				
13	[redacted] 70/Male [redacted] Literature case report	Dose 3 7 days	Hypertension, High cholesterol Not reported	D1 and D2 were Sinovac 6 months prior with no reported incident. Flaccid blisters and crusting observed on thighs and in axillary and inguinal folds; mucus membranes spared. Biopsy showed intraepidermal acantholysis and IgG and C3 deposits on keratinocytes; serum positive for elevated antibodies to desmoglein 1 and negative for anti-desmoglein 3; diagnosed with pemphigus foliaceus; recovered following treatment with prednisone and clobetasol ointment. *Heterologous COVID-19 vaccine for D1 and D2 introduces complexity; lack of description of antihypertensive leaves potential for confounder (e.g., ACE-I). The endemic nature of pemphigus in the patient's region [redacted] with non-pathogenic anti-desmoglein 1 antibodies found in healthy subjects as cited by the authors, also a potential contributing factor.*

Table 1. Remaining Pemphigus Cases (n = 15)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
Rapporteur assessment comment: Literature case report of a 70 year old men with pemphigus after dose 3 (TTO 7 days). The case is considered unlikely related to Comirnaty exposure due to confounding (endemic nature of pemphigus in the patient's region).				
14	[redacted] 43/Female [redacted] Literature case report	Dose 2 7 days	Atypical psychosis Aripiprazole, quetiapine	D1 COVID-19 vaccine manufacturer was reported as unknown; the patient was referred to dermatology after being diagnosed with cellulitis and taking ciprofloxacin and amoxicillin clavulanate for a bullous eruption of the right lower extremity appearing over 1 week. She was diagnosed with linear IgA disease; biopsy showed subepidermal cleavage and blister with dermal perivascular inflammatory infiltrate of primarily lymphocytes and a linear pattern of IgA immunodeposits at basement membrane zone; no blood immunoglobulins or C3 detected; no mucosal involvement; doppler exam found slow venous flow pattern in the vena saphena magna; recovering following unspecified treatment. *The reported venous flow abnormality and initial treatment with antibiotics for cellulitis introduce the possibility of confounding by (or contribution of) other medication to pemphigus.*
Rapporteur assessment comment: Literature case report of a 43 year old women with pemphigus after dose 2 (TTO 7 days). The case is considered unlikely related to Comirnaty exposure due to antibiotics use that could be a plausible cause for pemphigus.				
15	[redacted] 78/Male [redacted] Literature case report	Dose 3 Unspecified	High cholesterol; arrhythmia (pacemaker), glaucoma Not reported	D1 and D2 COVID-19 vaccine manufacturer was reported as unknown; Biopsy of oral mucosa was described as compatible with PV and antibodies to desmoglein 3 were positive; he recovered after treatment with prednisone and rituximab. *Concomitant medications for current conditions are not noted; the evolution of the skin abnormalities occurred over 4 months with an unclear time to onset following the patient's 3rd COVID-19 vaccination. More information would be needed for a proper assessment.*
Rapporteur assessment comment: Literature case report of a 78 year old men with pemphigus after dose 3 (TTO not reported). The case is considered unassessable for causality assessment with Comirnaty.				

Table 1. Remaining Pemphigus Cases (n = 15)				
	AER **Age (years)/Sex** **Country** **Reporter**	**Dose** **Time to Onset**	**Medical History** **Medications**	**Summary** ***MAH Comment***
[a] Case [redacted] and [redacted] are same individual. [b] Case [redacted] and [redacted] are same individual. *Vaccine (D4) = Bivalent BNT162b2 (Original + Omicron BA.4/BA.5)				

Rapporteur assessment comment:

From 15 Nov 2022 through 23 Jun 2023, 35 cases of pemphigus concerning 33 unique cases were retrieved from MAH's safety database of which:

- 5 cases were considered possible related to Comirnaty exposure;
- 7 cases were considered unlikely related; and
- 21 cases were considered unassessable.

Results - Pemphigoid

The 52 serious cases of pemphigoid were from spontaneous reports (42) and literature (10). There were 42 cases reported for BNT162b2 (original), 7 for Bivalent BNT162b2 (Original + Omicron BA.4/BA.5) and 3 reported for Bivalent BNT162b2 (Original + Omicron BA.1).

They were reported from Australia (9), UK (8), Japan and France (7), Germany and US (6 each), Estonia (2) and Belgium, Greece, Portugal, Spain, Sweden, Thailand and Turkey (1 each) in a larger number of females (35) than males (16) – one report did not provide sex data. The patients ranged in age from 31 to 90 years of age (mean 68.9). The largest age group was 75 years and older (21, 40.4%) and the next largest was 65-74 (17, 32.7%); this is consistent with the known epidemiology of pemphigoid.

Case outcome was reported as recovered/recovering (with or without sequelae) in 52%, not recovered in 36.5% and unknown in 11.5% of reports. There were no fatal cases.

As requested by EMA, narratives of all the cases are provided in MAH's documentation, Appendix 5.6.2 of the PSUR (not reproduced here).

Of the 52 cases, 25 did not mention the means to a clear diagnosis of pemphigus (e.g., skin biopsy and/or serum antibodies). Due to the lack of assuredness of the diagnosis of interest, these cases are considered unclassifiable and not further discussed. Of note, among those 25 cases, there were 2 patients who described similar events following >1 COVID-19 vaccination.

Of the remaining 27 cases, 21 were reported to have biopsies and the remaining 6 described serum antibody testing. One of the 27 cases will not be further discussed because it was discussed among the pemphigus cases above. Four additional cases are also not further discussed because they are assessed as unlikely to be associated with vaccine: 2 that lacked information about time to onset of pemphigoid following vaccination and 2 that reported very distant times to onset, 190 days and 215 days, respectively.

Two cases ([redacted] and [redacted]) describing a woman in her 70s in [redacted] had very similar details and confirmed as duplicates during this assessment. They are noted by an asterisk in Table 2.

Four cases described 2 unique patients who reported pemphigoid after each of 2 doses of Comirnaty (see table for details).

Details of the remaining 22 cases are in the table below. These could be considered "possible or better" if the WHO-UMC case causality assessment for medication is applied[6], however it should be recognized that for AEFIs, it is seldom possible to achieve a straightforward answer about causality at the individual case level and causality assessment must also occur at the population level.[7]

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
1	[redacted] 90/Female [redacted] Literature	Dose 1 6 days	Primary biliary cirrhosis, HTN, AF Amlodipine, warfarin,	1 week after D1 the patient was reported to have an itchy rash of the trunk and extremities and left leg swelling. At an unspecified time after
2	[redacted] 90/Female [redacted] Literature	Dose 2 Unspecified	bisoprolol, bendroflumethiazide, ursodeoxycholic acid,	D2, the rash was reported to worsen; she was hospitalized, histology showed a chronic eczematous process, and she was discharged on oral steroids. Approximately 2 months after D2 she was re-hospitalized with blisters now on the palms and soles. She was found to have circulating anti-BMZ IgG autoantibodies and a biopsy showed linear C3 deposition along the BMZ. Outcome was unknown. *The patient's diagnosis was made only with the 2nd biopsy. The use of a thiol-containing medication complicates assessment due to its association with pemphigoid.*

Rapporteur assessment comment:

Literature case report of a 90 year old women with pemphigoid after dose 1 and dose 2 (TTO 6 days and not reported respectively). The complaints after dose 2 are considered a continuation of the pemphigoid complaints after dose 1.

The case is considered possible related to Comirnaty exposure.

3	[redacted] 80/Female [redacted] Non-HCP	Dose 1 2 days	Unspecified cardiac disorder, HTN Amlodipine, ramipril,	Onset of bullous pemphigoid was reported to occur 2 days after D1 with the appearance of small fluid-filled pimples on the back and thighs that
4	[redacted] 80/Female [redacted] Non-HCP	Dose 2 1 day	levothyroxine	subsided somewhat after 2 weeks. After D2 the rash and blisters worsened. A biopsy over 2 months later was reported to be consistent with bullous pemphigoid. She was treated with steroids and remains under control if she does not consume several medication and food additives thought to worsen the reaction (e.g., PEG, macrogol, propylene glycol, certain unspecified foods) *The history of multiple foods and medications that cause exacerbations of the patient's skin condition do not point to the vaccine as a sole cause. The use of amlodipine raises another potential cause of BP*

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
Rapporteur assessment comment: Case of a 80 year old women with pemphigoid after dose 1 and dose 2 (TTO 2 days and 1 day respectively). The complaints after dose 2 are considered a continuation of the pemphigoid complaints after dose 1. The case is considered possible related to Comirnaty exposure.				
5	[redacted] 33/Male [redacted] Physician	Dose 1 and 2 Within 1 month of D1; worsening after D2	Not reported Not reported	Patient had D1 in June and reported itching and blistering of the lower legs in July which spontaneously subsided. He received D2 in Aug and in Sep had increased blistering that again spontaneously subsided. Serum tests and biopsy approximately 4 months after D2 showed antibodies against BP180 and IgG for BP180 and C3 along the BMZ along with subepidermal blistering. Recovered *The patient's young age makes this an unusual diagnosis, and the lack of medication history does not allow for a complete understanding of all potential exposures. More data would be needed for a proper assessment*
Rapporteur assessment comment: Case of a 33 year old men with pemphigoid after dose 1 and dose 2 (TTO 2 days and 1 day respectively). The complaints after dose 2 are considered a continuation of the pemphigoid complaints after dose 1. Medical history and medications are not reported. The case is considered unassessable for causality assessment with Comirnaty.				
6	[redacted] 74/Female [redacted] Physician	Dose 1 Unspecified but within 1 month	Previous COVID-19, Basal cell cancer, Ampulla of Vater cancer, seasonal and drug hypersensitivities Not reported	Within 1 month (timing not specified) of D1, the patient had a histological diagnosis of BP with positive anti-BP180 antibodies. She was recovering and is still using topical corticosteroids. *The patient's cancer history and lack of detail on chemotherapy along with her history of multiple drug allergies do not allow for a complete assessment of all potential exposures and bring up other possible contributors to the pemphigoid*
Rapporteur assessment comment: Case of a 74 year old women with pemphigoid after dose 1 (TTO within 1 month). The case is considered unlikely related to Comirnaty due to a history of recurrent bullous pemphigoid.				
7	[redacted] 66/Female [redacted] Physician	Unspecified (booster)	DM, Allergies, Tobacco user, Asthma	At an unspecified time following a booster vaccine (dose not specified), tense blisters developed on the 4 limbs. A biopsy was eventually

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
		Unspecified but within 1 month	Metformin, linagliptin	performed and was consistent with BP. Serum antibodies to BP180 were positive. She was hospitalized and had not recovered at the time of the report. *The presence of a gliptin in the patient's medication list is a potential additional or alternative cause of BP. Manufacturer of previous COVID-19 doses was not reported.*
Rapporteur assessment comment: Case of a 66 year old women with pemphigoid after dose 1 (TTO within 1 month). The case is considered unlikely related to Comirnaty due to a history of recurrent bullous pemphigoid.				
8	[redacted] 89/Male [redacted] Physician	3 Unspecified but within 1 month	DM, HTN, Tobacco user Linagliptin, mitiglinide, voglibose, pravastatin, benidipine, olmesartan	At an unspecified time following a booster vaccine (dose not specified), tense blisters developed on the 4 limbs. Diagnosis was made by serum antibodies to BP180. He was hospitalized and administered steroids. He had not recovered at the time of the report. *The presence of a gliptin in the patient's medication list is a potential additional or alternative cause of BP. Manufacturer of previous COVID-19 doses was not reported.*
Rapporteur assessment comment: Case of a 89 year old men with pemphigoid after dose 3 (TTO within 1 month). The case is considered possible related to Comirnaty.				
9	[redacted] 87/Male [redacted] Non-HCP	4 (MODERNA) Approximately 1 month	AF, Ischemic cardiac disease, Cerebral microangiopathy, COPD Amiodarone, fluindione, zopiclone, lercanidipine, alprazolam, oxazepam, macrogol	At the time of D4 with Moderna vaccine, the patient had an unspecified acute infection causing subacute diarrhea (he was treated with ciprofloxacin). Approximately 1 month later he was hospitalised with a bullous rash and found to have positive serum antibodies to BP230 and BP180 but a biopsy without direct immunofluorescence. He was recovering with topical treatment. *The coinciding infection and use of cipro complicates assessment of this case. As does the use of a COVID-19 vaccine from another manufacturer following 3 previous Comirnaty vaccines.*
Rapporteur assessment comment: Case of a 87 year old men with pemphigoid after dose 4 (Spikevax)(TTO approximately 1 month).				

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
The case is considered unlikely related to Comirnaty.				
10	[redacted] 70/Male [redacted] Non-HCP	Dose 1 (AZ) and Dose 3 (PFE/BNT) 6 weeks after Dose 1 and Dose 3	Bullous pemphigoid, hypothyroidism, DM, Drug hypersensitivity Insulin, metformin, pravastatin, tamsulosin, irbesartan, levothyroxine, duloxetine,	The patient was reported to have a rash and spots 6 weeks following D1 (AstraZeneca vaccine) which was treated with antihistamines; 6 weeks after D2 (AZ vaccine) the rash became itchy and was described as "nodular prurigo," it worsened despite topical steroids and he was referred to a dermatologist. Six weeks following D3 (Comirnaty) he developed blisters on his feet, legs thighs and hands. Biopsy was consistent with BP and he was treated with systemic steroids then methotrexate. He was not recovered. *The patient's use of an ARB and 2 different COVID-19 vaccines complicates assessment of this case.*
Rapporteur assessment comment: Case of a 70 year old men with pemphigoid after dose 1 (Vaxzevria), dose 2 (Vaxzevria) and dose 3 (Comirnaty) (TTO 6 weeks after dose 1). The complaints after dose 3 (Comirnaty) are considered a continuation of the pemphigoid complaints after dose 1 (Vaxzevria). The case is considered unlikely related to Comirnaty.				
11	[redacted] 71/Male [redacted] Literature	Dose 2 40 days	Bullous pemphigoid, SLE, HLH, DM Prednisone Unspecified dipeptidyl peptidase 4 inhibitors ('gliptin')	Patient with non-active bullous SLE at the time of vaccination (dose # not specified) was reported to have conversion to dipeptidyl peptidase 4 inhibitors-associated bullous pemphigoid 40 days after vaccination despite a long history of being on a gliptin. The biopsy showed IgM and C3 deposition in the BMZ and serum Anti BP180 antibodies were not detected. *The time to onset complicates assessment of the case and use of a gliptin provides a plausible alternative cause of the BP.*
Rapporteur assessment comment: Case of a 71 year old men with pemphigoid after dose 2 (TTO 40 days). The case is considered unlikely related to Comirnaty due to the relative long TTO and underlying diseases.				
12	[redacted]* 72/Female [redacted] Non-HCP	Dose 3 30 days	HTN, Autoimmune gastritis, Autoimmune thyroiditis, Celiac disease, Monoclonal gammopathy Not reported	This patient was reported to have pemphigoid diagnosed by serum antibodies against BP180, 30 days following her 3rd dose of Comirnaty. She had not recovered at the time of the report. *The medical history limits assessment of this case as there appears to be a*

Table 2. Remaining Pemphigoid Cases (n = 22)

AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
			significant propensity for autoimmune disorders.
Rapporteur assessment comment: Case of a 72 year old women with pemphigoid after dose 3 (TTO 2 weeks to 30 days). The case is considered unlikely related to Comirnaty due to underlying diseases.			
13 [redacted]* 73/Female [redacted] Physician	Dose 3 2 weeks	HTN, Autoimmune gastritis, Autoimmune thyroiditis, Celiac disease, Monoclonal gammopathy Not reported	This patient developed itching about 2 weeks after her 3rd dose of Comirnaty. About 4 weeks after D3 she had new blisters on her skin and mucous membranes. She was found to have antibodies against BP180. *The medical history limits assessment of this case as there appears to be a significant propensity for autoimmune disorders.*
Rapporteur assessment comment: Same case as described above, number 12.			
14 [redacted] 79/Female [redacted] Literature	Dose 2 3 days	HTN, Obesity, Severe bullous pemphigoid None	Patient with a medical history of severe bullous pemphigoid with no concomitant medications developed a severe case of BP after D2 of Comirnaty. She was hospitalized and treated with IVIG for 5 days, steroids and mycophenolate with resolution. *This patient was reported to have BP in the past and also HTN despite no concomitant medications being noted. These factors bring the possibility of confounding factors; more information would be helpful for assessment.*
Rapporteur assessment comment: Literature case report of a 79 year old women with pemphigoid after dose 2 (TTO 3 days). Medical history included severe bullous pemphigoid. The case is considered possible related to Comirnaty.			
15 [redacted] 74/Female [redacted] Literature	Dose 1 21 days	Reported to have no relevant history Not reported	Patient, who was reported to have a two-month history of a burning sensation in her mouth, then developed blood-filled vesicles in the oral cavity 21 days after D1 of Comirnaty. Biopsy showed subepithelial separation and IgG and C3 at the BMZ. *The oral symptoms preceding vaccination are suspicious for a process beginning prior to vaccination.*
Rapporteur assessment comment:			

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
Literature case report of a 74 year old women with pemphigoid after dose 1 (TTO 21 days). The case is considered unlikely related to Comirnaty due to that the complaints started before vaccination.				
16	[redacted] 75/Female [redacted] Physician	Dose 4 2 weeks	DM, Cardiac failure, Prurigo Not reported	Patient with significant medical history but no medications reportedly developed BP 2 weeks following D4. The manufacturer of the previous COVID-19 vaccine was not known. The patient had serum antibodies positive for BP180 approximately 5 months after the blisters began. The reporter states that is was unclear with the onset of the disease occurred and the patient had been diagnosed with SJS the year before (2022). *The unclear chronology of events and the lack of medication reported limit assessment of this case. Further, it is unclear if she had exposure to COVID-19 vaccines other than Comirnaty. More information would be needed for a proper assessment*
Rapporteur assessment comment: Case of a 75 year old women with pemphigoid after dose 4 (TTO 2 weeks). The case is considered unassessable for causality assessment with Comirnaty.				
17	[redacted] 84/Male [redacted] Physician	Dose 2 2 days	Renal cancer, bladder cancer, basal cell cancer Not reported	Patient with multiple malignancies reported to have a skin biopsy due to undescribed lesions that occurred 2 days following D2. The biopsy showed superficial dermal inflammation and keratinocytic necrosis along with linear deposits of IgG and C3 along the BMZ. *The assessment of a relationship between vaccination and pemphigoid is complicated by the potential contribution of the malignancies and treatment (not reported). Further, it is unclear if he had exposure to COVID-19 vaccine other than Comirnaty for D1.*
Rapporteur assessment comment: Case of a 84 year old men with pemphigoid after dose 2 (TTO 2 days). The case is considered unlikely related to Comirnaty due to underlying diseases/treatments.				
18	[redacted] 69/Male [redacted] Non-HCP	Dose 4 14 days	Previous COVID-19 Not reported	Patient with previous COVID-19 and medications not reported was reported to have biopsy-confirmed BP with onset 14 days after D4 of Comirnaty. He was recovering.

Table 2. Remaining Pemphigoid Cases (n = 22)

	AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary ***MAH Comment***
				There is lack of clinical detail in this case and more information would helpful for a proper assessment, however no alternative cause of pemphigoid is noted.
Rapporteur assessment comment: Case of a 69 year old men with pemphigoid after dose 4 (TTO 14 days). The case is considered possible related to Comirnaty.				
19	[redacted] 41/Female [redacted] Literature	Dose 1 14 days	DM Vildagliptin	Patient reported itchy bullous lesions on trunk, extremities and palms that began 2 weeks following D1 of Comirnaty. She had a biopsy showing subepidermal blisters and eosinophilic infiltration along with linear deposition of IgG and C3 on the BMZ. She was started on systemic steroids and the lesions resolved in the 2nd week of treatment. *The presence of a gliptin in the medication list complicates assessment of this case as it is an alternative potential cause of BP*
Rapporteur assessment comment: Case of a 41 year old women with pemphigoid after dose 1 (TTO 14 days). The case is considered possible related to Comirnaty.				
20	[redacted] 41/Female [redacted] Non-HCP	Dose 2 14 days	Reported to have no relevant history None	This patient was reported to have oral mucosa and genital blisters develop 2 weeks after her 2nd dose of Comirnaty. Blisters developed all over her body except for her face. After approximately 6 months she sought medical attention and was found to be ANA positive; other (unspecified) immunology tests were reported to be positive; no biopsy was reported. She was told she had BP and has been treated with IVIG, steroids, mycophenolic acid and antibiotics. Outcome is not known. *The patient is young for BP and diagnostic tests confirming BP are not provided. The length of time from vaccination to diagnosis is particularly long, making it plausible that the reported chronology of events may not be accurately recalled.*
Rapporteur assessment comment: Case of a 41 year old women with pemphigoid after dose 2 (TTO 14 days).				

Table 2. Remaining Pemphigoid Cases (n = 22)

AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
The case is considered unlikely related to Comirnaty due to the relative long time (6 months) between complaints (recall bias) and diagnosis pemphigoid.			
21 [redacted] 87/Female [redacted] Physician	Dose 5 10 days	Dementia, osteoporosis, hyponatremia, neurogenic bladder None	Patient with complicated medication history including neurological pathology was reported to develop blistering and peeling skin on the face and extremities approximately 10 days after a 5th dose of COVID-19 vaccine (Comirnaty). The patient's previous COVID-19 vaccines were Comirnaty except for D4 which was the Moderna vaccine. She was found to have an eosinophil count of 44.3% and anti BP180 antibodies. She was treated with oral prednisone and had not recovered at the time of the report. *While there is a temporal association with the 5th vaccine, the lack of a medication list and the presence of dementia (which has been correlated with BP) makes this case difficult to assess as it brings the possibility of other contributors.*
Rapporteur assessment comment: Case of a 87 year old women with pemphigoid after dose 5 (TTO 10 days). The case is considered possible related to Comirnaty.			
22 [redacted] 37/Female [redacted] Non-HCP	Dose 3 1 day	Factor V Leiden mutation, Hashimoto thyroiditis, endometriosis, previous COVID-19 Con influvax; levothyroxine, tinzaparin	The patient was seen by emergency dermatology <1 week after giving birth, having been prescribed a topical steroid for acral lesions thought to be possible erythema multiforme 2 days prior. She was on thromboprophylaxis during her pregnancy. She had tense blisters on her legs and arms. She reported that the soles of her feet were affected 1 day after D3 of Comirnaty which was approximately 3 months prior. There was no itchiness. She was found on biopsy to have subepidermal blisters, epidermal detachment and isolated eosinophils; her serum was positive for Anti-BP180 antibodies. She was started on steroids and was recovering with f/u to the dermatologist planned. *This young patient has a complex medical history including an autoimmune disorder and previous COVID-19. Further, she received a concomitant influenza vaccine at the time of the Comirnaty vaccine. In addition, thromboprophylaxis during recent pregnancy included unspecified medication. These factors serve as*

Table 2. Remaining Pemphigoid Cases (n = 22)

AER Age (years)/Sex Country Reporter	Dose Time to Onset	Medical History Medications	Summary *MAH Comment*
			potential alternative causes of the skin lesions.

Rapporteur assessment comment:

Case of a 37 year old women with pemphigoid after dose 3 (TTO 1 day).

The case is considered unlikely related to Comirnaty due to potential alternative causes of the skin lesions.

* [redacted] and [redacted] confirmed as duplicate cases during this assessment.

Rapporteur assessment comment:

From 15 Nov 2022 through 23 Jun 2023, 52 cases of pemphigoid concerning 49 unique cases were retrieved from MAH's safety database of which:

- 7 cases were considered possible related to Comirnaty exposure;
- 14 cases were considered unlikely related; and
- 28 cases were considered unassessable.

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

On cumulative review of the EB05 report for the PT's were as follows:

Table 3. Routine EB05

PT	BNT162b2	BNT162b2/BNT162b2 BA.1	BNT162b2/BNT162b2 BA.4/BA.5
Pemphigus	1.0	-	-
Pemphigoid	1.2	0.6	0.6
Benign familial pemphigus	0.7	-	-
Paraneoplastic pemphigus	-	-	-
Ocular pemphigoid	-	-	-
Pemphigus disease area index	-	-	-
Mucous membrane pemphigoid	0.6	-	-
Linear IgA disease	0.14	-	-

The EB05 is less than the EB05>2 threshold, thus indicating no emerging statistical signal for the selected PTs.

Literature

Methodology

A search of literature was conducted from 15 Dec 2022 to 20 Jun 2023 to identify any new articles describing BNT162b2 and the MedDRA PT's pemphigus, pemphigoid, benign familial pemphigus, paraneoplastic pemphigus, ocular pemphigoid, pemphigus disease area index, mucous membrane pemphigoid and linear IgA disease in the Medline, Biosis and Embase database.

Results

There were 5 relevant articles, case reports are included in the post marketing section except for one case literature report added to the safety database after database lock and described below.

Article 1: Cowan Timothy L., Huang Cheng, Murrell Dédée F: Autoimmune blistering skin diseases triggered by COVID-19 vaccinations: An Australian case series. Frontiers in Medicine, VOLUME=9, YEAR=2023

At a single academic blistering disease centre in Sydney, Australia, a retrospective review was conducted, identifying 59 patients with AIBD seen between February 2021 and November 2022. According to the authors, four patients had induction of bullous pemphigoid (1 BNT162b2, 3 AstraZeneca), three patients had a flare of preexisting bullous pemphigoid (2 BNT162b2, 1 AstraZeneca), one patient had induction of pemphigus (BNT162b2), and two patients had a flare of pre-existing pemphigus vulgaris (BNT162b2). Five of the 10 cases described did not have a known measurement of disease activity prior to vaccination. Two reported flares occurred shortly after the vaccination (5 and 6 days, respectively) while the remaining patients were reported to have flares from 15 to 123 days (mean 61.3 days) after vaccination.

Article 2: Martora, F., Ruggiero, A., Battista, T., Fabbrocini, G. and Megna, M. (2023), Bullous pemphigoid and COVID-19 vaccination: Management and treatment reply to 'Bullous pemphigoid in a young male after COVID-19 mRNA vaccine: A report and brief literature review' by Pauluzzi et al. J Eur Acad Dermatol Venereol, 37: e35-e36. https://doi.org/10.1111/jdv.18503.

The Dermatology Centre of the University of Naples Federico II in Italy collected data on 43 patients with BP who had three COVID-19 vaccine doses (BNT162b2 and mRNA-1273 were the vaccines administered). In the majority of the cases (90.6%), no disease worsening or onset of new lesions was observed. In the remaining 4 (10.4%) cases, patients experienced disease worsening 5– 8 days after the vaccination. Notably, all subjects were previously treated with oral corticosteroids ± azathioprine and they were all under control before undergoing vaccination. The patients who had a worsening of the disease were managed without significant complications and completed their vaccine schedule.

Article 3: Solimani, F., Mesas-Fernández, A., Bodner, E., Carevic-Neri, M., Hasheminasab, M., Jakovljevicova, T., Philipp, A., Nast, A., Worm, M., Hilke, F.J., Meier, K. and Ghoreschi, K. (2023), Clinical and immunological impact of booster immunization with recombinant mRNA vaccines for SARS-CoV-2 in patients with pemphigus and bullous pemphigoid. J Eur Acad Dermatol Venereol, 37: e695-e697. https://doi.org/10.1111/jdv.18967.

The authors followed clinical and immunological parameters in patients with pemphigus (n=9), BP (n=4) and healthy individuals (HI) up to 4 weeks after booster immunization with either BNT162b2 or mRNA1273. Cytofluorimetric analysis revealed an increase in Th1 and Th17.1 cells in patients with pemphigus at 4 weeks after booster vaccination, whereas Th17 cells concomitantly decreased. Th2 cells showed no significant changes. The authors observed a similar trend in the BP group but not in HI. Intracellular cytokine expression 2 and 4 weeks after booster immunization, showed pemphigus patients had a significant increase in interferon-ɣ production in T memory cells. Serum levels of interferon-ɣ, IL-4, IL-17A and IL-6 were not or minimally affected at weeks 2 and 4 after vaccination.

Disease activity, as determined by the Autoimmune Bullous Skin Disorder Intensity Score, remained stable in all patients. The authors concluded that the study reports initial evidence, that mRNA booster vaccines elicit a robust and specific anti spike protein humoral reaction and T- cellular activity without

influencing disease activity in pemphigus and BP. Importantly, booster vaccinations with BNT162b2 or mRNA1273 only minimally influenced autoantibody titres specific for DSG1/3 or BP180/230. Concomitant immunosuppressive drugs as studied except for rituximab up to 3 months prior to vaccination were reported to have little effect on the antibody titres and possible relevance to avoiding disease reactivation.

Article 4: Özgen, Z, Aksoy, H, Akın Çakıcı, Ö, et al. COVID-19 severity and SARS-Cov-2 vaccine safety in pemphigus patients. Dermatologic Therapy. 2022; 35(5):e15417. doi:10.1111/dth.15417

This multicenter study included 247 patients with pemphigus from three tertiary dermatology clinics with the specialized outpatient clinic for autoimmune blistering diseases in Turkey. Patients were asked standardized questions in person or via telephone calls. Also, demographic data were collected from patients' files. Two hundred forty-four of 247 patients took the survey between August and September 2021. Total 175 of 244 (71.7%) patients were vaccinated against COVID-19. The percentage of vaccine types were 36.9, 34.4, and 0.4 to Sinovac, Pfizer-BioNTech, and Oxford AstraZeneca, respectively. Total number and percentage of patients who experienced pemphigus flare after vaccination was 18 (10.3%). Fifteen of 18 experienced flares after the first vaccine administration, and three of 18 after the second administration. Total seven of 18 flares were with Sinovac, and 11 of 18 were with Pfizer-BioNTech. Patients who needed further treatment or treatment change after a vaccination-induced flare was 7 (38.8%). Additionally, one patient other than the study group developed pemphigus vulgaris after the first administration of the Pfizer BioNTech SARS COV-2 vaccine during this period.

Article 5: Oguz Topal, I, Tokmak, A, Kurmuş, GI, et al. Skin manifestations following anti-COVID-19 vaccination: A multicentricstudy from Turkey. J Cosmet Dermatol. 2023; 22: 354- 363. doi:10.1111/jocd.15570

The study included patients aged ≥18 years, who presented to 13 different dermatology clinics in Turkey between July 2021 and September 2021 after developing dermatological events following the administration of the COVID- 19 vaccine. A total of 269 patients [116 women (43.1%), 153 men (56.9%)] were included in the study. It was observed that the dermatological events that most frequently developed after vaccination were urticaria (25.7%), herpes zoster (24.9%), maculopapular eruption (12.3%), and pityriasis rosea (4.5%). Bullous pemphigoid (BP) development was more common in the inactivated vaccine group than in the mRNA vaccine group (1.86% and 0.37%, respectively).

Case report: (Chen, H.-C., Ma, S.-H., Wang, L.-H., Chang, Y.-T. and Wu, C.-Y. (2023), Pemphigus aggravation following Pfizer-BioNTech vaccination: A case report and review of literature. Int J Rheum Dis, 26: 1187-1190. https://doi.org/10.1111/1756-185X.14581

A 39-year-old man with a history of hypertension presented 1 week following dose 1 of Pfizer-BioNTech (BNT) COVID- 19 vaccine. Two months prior to admission, he had experienced unhealed oral ulcers and crusted erosions over the scalp, which were relatively stable under topical treatment at a local clinic. However, within 1 week of COVID-19 vaccination, painful vesicles and erosions progressed rapidly over his trunk and limbs. The patient was transferred to the emergency department due to progressive disease. Examination revealed coalescing erosions and scattered flaccid blisters over the patient's trunk and limbs, involving a total body surface area of approximately 30%. Diffuse oral mucosal erosions and bilateral injected conjunctiva with purulent discharge were also observed. A skin biopsy performed under the suspicion of pemphigus vulgaris (PV) revealed intraepidermal acantholysis. Direct immunofluorescence examination revealed intercellular deposits of immunoglobulin G in the epidermis. The patient was transferred to the burn unit due to extensive involvement (initial Pemphigus Disease Area Index score, 73). High- dose methylprednisolone (1 mg/kg/d) and subsequent rituximab (2 1000-mg doses 2 weeks apart) were initiated due to severe and uncontrolled disease status. However, despite aggressive immunosuppressants use, new blisters and erosions developed after rituximab administration.

Thus, azathioprine (200 mg/d) was initiated (2 weeks after rituximab infusion). After serial treatment, the disease activity was controlled, and the erosions gradually healed. The patient was discharged and followed-up at the outpatient department with low-dose azathioprine (100 mg/d) and methylprednisolone (8 mg/d) for maintenance. Due to concerns of pemphigus flares, the patient declined to receive a second dose of the SARS-CoV-2 vaccine.

Rapporteur assessment comment:

Literature case report of a 39 old man with pemphigus after dose 1 (TTO 1 week). Within 1 week of vaccination, painful vesicles and erosions progressed rapidly over his trunk and limbs. However, two months prior to admission, he had experienced unhealed oral ulcers and crusted erosions over the scalp which is considered a more likely cause of the pemphigus and not the Comirnaty exposure.

This case is considered unlikely related to Comirnaty exposure.

MAH's literature summary

Although case reports of pemphigus / pemphigoid reactivation and new occurrence of pemphigus / pemphigoid conditions have been observed, the updated literature search did not reveal any significant new safety information.

Rapporteur assessment comment:

The MAH stated that above described literature case reports of pemphigus, pemphigoid were already included in the post-marketing section above.

One additional literature case report was considered unlikely related to Comirnaty exposure.

Observed to expected analyses

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 147 pemphigus cases and 359 pemphigoid cases reported cumulatively through 15 May 2023 globally. Age-specific O/E ratios are restricted to the US/EEA because exposure data is available at this level of detail for these regions.

Table 4. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Pemphigus Through 15 May 2023

Stratification	Observed Cases	Time at risk (PY)	Background Rate Per 100,000 PY[a]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
28-day							
US/EEA							
Males							
<5 years	0	59,003	0.00	0.0	-	-	-
5-11 years	0	1,085,526	0.00	0.0	-	-	-
12-17 years	0	1,951,959	0.00	0.0	-	-	-
18-24 years	0	2,780,167	0.00	0.0	-	-	-
25-49 years	9	11,965,249	0.15	17.9	0.50	0.23	0.95

50-59 years	7	6,184,907	0.34	20.7	0.34	0.14	0.70
60-69 years	10	6,282,378	0.37	23.2	0.43	0.21	0.79
70+ years	11	8,745,036	0.37	32.4	0.34	0.17	0.61
Females							
<5 years	0	65,240	0.11	0.1	-	-	-
5-11 years	0	1,218,557	0.11	1.3	-	-	-
12-17 years	1	2,194,342	0.11	2.4	0.41	0.01	2.31
18-24 years	0	3,126,025	0.11	3.4	-	-	-
25-49 years	14	13,477,813	0.17	23.4	0.60	0.33	1.01
50-59 years	5	7,007,422	0.22	15.1	0.33	0.11	0.77
60-69 years	9	7,148,734	0.26	18.6	0.48	0.22	0.92
70+ years	12	9,934,756	0.26	25.8	0.46	0.24	0.81
Overall, monovalent (any)	78	76,659,992	0.17	130.3	0.60	0.47	0.75
Overall, bivalent (any)	0	6,567,121	0.17	11.2	-	-	-
Overall Global (any dose)	115	178,717,988	0.17	303.8	0.38	0.31	0.45

a. The background rate source is Bastuji-Garin et al., 1995.[8] Source age group of 15-24 years used for <5, 5-11, 12-17, and 18-24; average of 25-34, 35-44, and 45-54 used for 25-49 years, average of 45-54 and 55+ used for 50-59 years; 55+ used for 60-69 and 70+ years.
CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States.

Table 5. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Pemphigoid Through 15 May 2023

Stratification	Observed Cases	Time at risk (PY)	Background Rate Per 100,000 PY[a]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
28-day							
US/EEA							
Males							
<5 years	0	59,003	0.50	0.3	-	-	-
5-11 years	1	1,085,526	0.50	5.4	0.18	0.00	1.03
12-17 years	0	1,951,959	0.50	9.8	-	-	-
18-24 years	1	2,780,167	0.50	13.9	0.07	0.00	0.40
25-49 years	6	11,965,249	0.50	59.8	0.10	0.04	0.22
50-59 years	7	6,184,907	1.50	92.8	0.08	0.03	0.16
60-69 years	17	6,282,378	3.70	232.4	0.07	0.04	0.12
70+ years	62	8,745,036	26.52	2319.2	0.03	0.02	0.03
Females							

<5 years	0	65,240	0.50	0.3	-	-	-
5-11 years	0	1,218,557	0.50	6.1	-	-	-
12-17 years	1	2,194,342	0.50	11.0	0.09	0.00	0.51
18-24 years	0	3,126,025	0.50	15.6	-	-	-
25-49 years	11	13,477,813	0.50	67.4	0.16	0.08	0.29
50-59 years	13	7,007,422	1.50	105.1	0.12	0.07	0.21
60-69 years	12	7,148,734	3.70	264.5	0.05	0.02	0.08
70+ years	52	9,934,756	26.52	2634.7	0.02	0.01	0.03
Overall, monovalent (any)	178	76,659,992	4.25	3258.0	0.05	0.05	0.06
Overall, bivalent (any)	5	6,567,121	4.25	279.1	0.02	0.01	0.04
Overall Global (any dose)	274	178,717,988	4.25	7595.5	0.04	0.03	0.04

a. The background rate source is Langan et al., 2008.[10] Source age group of <50 years used for <5, 5-11, 12-17, 18-24, and 25-49; 50-59 used for 50-59; 60-69 used for 60-69; and average of 70-74, 75-79, 80-84, 85-89, and 90+ for 70+ years.
CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States.

Based on the selected background rates and the estimated number of exposure person-years through 15 May 2023, O/E ratios were well below one for both pemphigus and pemphigoid in a 28-day risk window. This suggests that the number of observed cases may not be higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines.

Rapporteur assessment comment:

All O/E ratios were well below one for both pemphigus and pemphigoid in a 28-day risk window.

MAH's summary and conclusion

The risk of development of pemphigus and pemphigoid is most likely multifactorial; conditions with unclear etiologies are likely to be hypothesized to be related to a known occurrence when one can be identified (e.g., new exposure). While this may be a logical step, temporal proximity to vaccine exposure is not sufficient to conclude causality. While well-described individual cases without alternative etiologies have been used in pharmacovigilance to justify causal relationships between vaccines/medications and adverse events, it remains unclear if this is a reasonable approach when a vaccine has been administered to an unprecedented number of diverse individuals globally. Population level evidence needs to be considered.

Nonetheless, this review of additional safety database cases does not provide information different from the previous review; most cases either lack important information or describe additional factors that may be contributory to the development of the event. Likewise, the new literature does not clearly support that pemphigus/pemphigoid is caused by vaccination. Additionally, the updated age and sex-stratified observed to expected analyses for the vaccines suggest that the observed number of cases of potential pemphigus and pemphigoid are not higher than expected in the absence of COVID-19 vaccination. Overall, the available data is insufficient to conclude a causal association between BNT162b2 vaccination and pemphigus/pemphigoid.

Rapporteur assessment comment:

<u>Pemphigus</u>

From the previous pemphigus signal procedure (EPITT 19859), through 15 Nov 2022, there were identified 2 probable cases, 8 possible cases, and 6 unlikely/unassessable cases among the 16 pemphigus cases with diagnostic tests.

From 16 Nov 2022 through 23 Jun 2023, 36 cases of pemphigus concerning 34 unique cases were retrieved from MAH's safety database of which:

- 5 cases were considered possible related to Comirnaty exposure;
- 8 cases were considered unlikely related; and
- 21 cases were considered unassessable.

Overall, through 23 Jun 2023:

- 2 pemphigus cases were considered probable related to Comirnaty exposure;
- 13 pemphigus cases were considered possible related;
- 35 pemphigus cases were considered unlikely related/unassessable.

Pemphigoid

From the previous pemphigoid signal procedure (EPITT 19859), through 15 Nov 2022, there were identified 7 probable cases, 22 possible cases, and 93 unlikely/unassessable cases among the 122 pemphigoid cases with diagnostic tests.

From 16 Nov 2022 through 23 Jun 2023, 52 cases of pemphigoid concerning 49 unique cases were retrieved from MAH's safety database of which:

- 7 cases were considered possible related to Comirnaty exposure;
- 14 cases were considered unlikely related; and
- 28 cases were considered unassessable.

Overall, through 23 Jun 2023:

- 7 pemphigoid cases were considered probable related to Comirnaty exposure;
- 29 pemphigoid cases were considered possible related;
- 135 pemphigoid cases were considered unlikely related/unassessable.

Literature

The updated pemphigus/pemphigoid literature search did not reveal any significant new safety information.

O/E analyses

All O/E ratios were well below one for both pemphigus and pemphigoid in a 28-day risk window.

In conclusion based on provided data, MAH's conclusion is endorsed that there is not sufficient evidence to conclude a causal association between Comirnaty and pemphigus/pemphigoid. The MAH should continue monitoring pemphigus/pemphigoid cases after Comirnaty exposure using routine pharmacovigilance and notify the PRAC Rapporteur immediately when unexpected numbers or (changes in) patterns of pemphigus/pemphigoid cases are reported.

Issue solved

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2.2.1. Evaluation of closed signals

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined not to be risks	
Myositis	Following receipt of an EMA PRAC adopted recommendation (EMA/PRAC/3178/2023) for this signal on 12 January 2023, myositis and vaccination with BNT162b2 (original and bivalent) was evaluated by the MAH. Evaluation consisted of the review of non-clinical data that showed common occurrence of injection site reactions but no microscopic evidence of any inflammatory process in muscle sites beyond the injection site on necroscopy (e.g., gastrocnemius, tongue, heart). The

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	clinical study database for 4 completed and 7 ongoing Pfizer-run clinical studies was searched for relevant reports per the MedDRA search strategy for myositis. Three cases were retrieved, all assessed by the investigators as not related: One report of dermatomyositis in the pivotal study of >44,000 participants (C4591001) occurring on day 44 after dose 3 of BNT162b2; 1 report of worsening dermatomyositis in a study of immunocompromised participants (C4591024) in a 6-year-old with a history of juvenile dermatomyositis occurring 76 days after dose 2 of BNT162b2; also in C4591024, 1 report of myositis in a 4 year-old with a history of renal transplantation occurring 74 days after dose 3 of BNT162b2. The literature search retrieved 10 articles (1 was a pre-print) that were mostly retrospective cohort studies in patients with inflammatory myopathies who were surveyed or otherwise assessed for flares following vaccination. Some studies reported new cases of myositis and flares of underlying disease in a minority of patients, but most authors acknowledged that it was not possible to assume a causal association based on their results. Indeed, the potential mechanisms for as association hypothesized by the authors were not uniform. The MAH's safety database disproportionality analysis was unremarkable and a review of the 1017 cases retrieved were of variable quality. There were 16 cases (15 individuals) without alternative aetiologies that had temporality with vaccination. The O/E ratios in some age groups and risk windows were greater than 1 suggesting that the number of reported cases may be higher than expected compared to unvaccinated persons, however, the risk windows for myositis following Comirnaty vaccines are unclear, and the caveats of the O/E analyses, including the use of several risk windows, one background rate, the unknown degree of underreporting, the small number of observations in some age stratifications and the possibility of the numerator including patients with a medical history of idiopathic inflammatory myopathies (IIM) (that was not reported in the case), need to be weighed in consideration. Overall, in the context of the >4 billion doses of BNT162b2 original and bivalent shipped since Dec 2020, the totality of the data did not allow a causal link to be concluded. In the 2nd adopted PRAC recommendation (12 May 2023), the PRAC agreed that a causal association between Comirnaty and myositis could not be concluded, and no update to the product information and/or the risk management plan was warranted. MAH's response (Appendix 5 of the PSUR) to the PRAC's request included in the signal AR (PAM-SDA-063, EPITT: 19883) *to explore the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand the occurrence of myositis in a broad population and provide proposals to obtain more recent background incidence rates (during the pandemic/immunization campaigns)*:

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	The MAH was requested to explore the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand the occurrence of myositis in a broad population and provide proposals to obtain more recent background incidence rates (during the pandemic/immunization campaigns). The MAH is conducting an updated literature review to identify recently published studies on IIM incidence rates prior to and/or during the COVID-19 pandemic. In addition, the MAH is conducting a feasibility for analysis of annual incidence rates for IIM in the Optum Clinformatics closed claims database for the timeframe 01 January 2019 to most current data available. The proposed definition for IIM cases would include ICD-10-CM diagnosis codes for myositis and be based on an algorithm for case identification in healthcare databases that has been used in published papers. In future O/E analyses of myositis, the MAH proposes to include updated O/E analyses based on pre-COVID-19 published background rates, as well as IIM incidence rates from the healthcare database during 2019 and during the COVID-19 era. Additional Note: PRAC also recommended to include myositis in ongoing PASSs in the pharmacovigilance plan (C4591009; C4591010; C4591011; C4591012; C4591021). The MAH confirms that myositis will be added as an endpoint to C4591009 and C4591021. Due to the end of data collection in June 2023 for a planned final study report in December 2023 for C4591012 myositis will not be added to that PASS. Because PRAC recommended that C4591010 be removed from the RMP at the next regulatory opportunity, when study termination commences it will preclude the addition of myositis as a PASS endpoint. Due to the significant operational challenges experienced with C4591011, myositis will not be added to that PASS.
Rapporteur assessment comment: Please refer to the Myositis signal procedure (EPITT 19883) which concluded closely monitor Idiopathic inflammatory myopathies (IIM)/autoimmune myositis, and IIM flares through routine pharmacovigilance and evaluation as an AESI in ongoing PASS(s). MAH's proposal is agreed, that future O/E analyses of myositis will be based on pre-COVID-19 published background rates, as well as IIM incidence rates from the healthcare database during 2019 and during the COVID-19 era. Myositis will be added to as an endpoint to PASS C4591009 and PASS C4591021.	
Pemphigus and Pemphigoid	Following receipt of an EMA PRAC adopted recommendation (EMA/PRAC/868335/2022) for this signal on 01 December 2022, pemphigus/pemphigoid was evaluated by the MAH. On 14 Apr 2023, the PRAC concluded that the current evidence was insufficient to establish a causal relationship between Comirnaty and pemphigus or pemphigoid. They requested that within PSUR 5 the MAH perform a review of new

Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	emerging data on pemphigus and pemphigoid; this can be found in Appendix 5.6 of the PSUR (not reproduced here). The outcome of this updated review does not change the MAH previous assessment which concluded that there is insufficient evidence for a causal association between Comirnaty and pemphigus/pemphigoid.
Rapporteur assessment comment: Please refer to the previous pemphigus/pemphigoid signal procedure (EPITT 19859) and the assessment of appendix 5.6 of the PSUR reporting MAH's review of new emerging data on pemphigus and pemphigoid, in section 2.2 'Signal evaluation' above, concluding that there is not sufficient evidence to conclude a causal association between Comirnaty and pemphigus/pemphigoid.	

2.2.2. Signal evaluation plan for ongoing signals

Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Menstrual irregularities[a]	Following closure of the EMA PRAC signal Heavy menstrual bleeding and Amenorrhea, the MAH determined that the broader concept of menstrual irregularities (not limited to HMB and Amenorrhea) should be evaluated. See appendix 5.7 of the PSUR (not fully reproduced here): ***MAH's summary and conclusion of the repeated review of menstrual irregularities*** A repeated review of menstrual irregularities was undertaken in order to ensure an up to date understanding of the adverse event reports received and accumulating medical literature. The difficulties of discerning causality of menstrual irregularities to the vaccine have been discussed in other documents, including in Pfizer/BNT's signal evaluation documents produced for the EMA PRAC, and include that menstrual irregularities are common and may be multifactorial in etiology. Menstrual irregularities were not widely reported in the large pivotal clinical trial study in adults and no imbalance between BNT162b2 and placebo groups was noted. The spontaneously reported cases are mostly non-medically confirmed and non-serious without trends toward events of clinical significance. There are notable differences in regional reporting of menstrual irregularities, with the bulk of reports from the UK and Western European countries and significantly fewer from the US, Australia and Japan, which are countries with robust pharmacovigilance systems and which account for an overall high proportion of ICSRs received in the Pfizer safety database. This observation may indicate that non-causal factors may be playing a role in

	reporting. With such widespread global administration of primary doses of BNT162b2, many ICSRs have been received and even what may historically be considered a large number of ICSRs for a vaccine, cannot be considered similarly with the COVID-19 vaccine in the pandemic setting where the number of doses administered worldwide was unprecedented. Careful review of the accumulating literature focusing on the highest quality studies, provided reassurance that menstrual abnormalities reported following vaccination do not appear to be clinically consequential. Study observations have included: weak/small observations of temporary changes in menstrual cycle length, inconsistent (some point toward, and others do not) changes in the length of reported menses, inconsistent (some point toward, and others do not) observations of heavier than usual menstrual bleeding. Overall, based on the strength and quality of evidence and lack of clear mechanism, a causal association between Comirnaty and menstrual irregularities is not supported at this time and no changes to the core data sheet or core safety concerns is warranted. To improve detailed data collection in the COVID-19 vaccine clinical studies, Pfizer has created specific case report forms to use if menstrual irregularities are reported and Pfizer will continue to monitor menstrual irregularities with routine pharmacovigilance.

Rapporteur assessment comment:

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

In the current 5th PSUR, the MAH reported the results of a repeated review of menstrual irregularities (not limited to heavy menstrual bleeding and amenorrhoea) through 31 Mar 2023 for post-marketing cases (731 serious medically confirmed cases with a reasonable latency between 1-90 days post vaccination) and through 11 Jul 2023 for relevant literature (6 high quality articles). Based on provided data, MAH's conclusion is endorsed that a causal association between Comirnaty and menstrual irregularities is not supported at this time and that the MAH should continue to monitor menstrual irregularities through routine pharmacovigilance.

Of note, after DLP of this PSUR a safety signal concerning postmenopausal haemorrhage after COVID-19 mRNA vaccine (nucleoside-modified) was started, confirmed and is ongoing, please refer to procedure EPITT 19989.

Sensorineural hearing loss[a]	Following receipt of a request by TGA (Australia) for an "updated signal analysis" on this topic in the next PSUR, the MAH re-opened this signal and provides a full evaluation in Appendix 5.4 of the PSUR (not fully reproduced here): ***MAH's summary and conclusion of the updated signal analysis sensorineural hearing loss***

	Data from the pivotal Pfizer led COVID-19 vaccine clinical studies, post-authorization safety database and medical literature were reviewed for this evaluation. In addition, O/E analyses were reviewed. Participants in the placebo-controlled, blinded periods of the clinical studies reported a low number of hearing loss events in the vaccination group and placebo group, with no meaningful difference between the 2 groups. The spontaneously reported cases are of variable quality. While there are individual cases that report events temporally close to the time of vaccination(s) and provide detailed information without alternative explanations for hearing loss, the nature of SNHL and its myriad etiologies is such that the possibility of coincidental occurrence versus causality of the vaccine cannot be discounted. The number of vaccine doses administered globally, and the subsequent number of adverse event reports received for the vaccine are unprecedented in the field of pharmacovigilance. The vast numbers call into question the traditional use of individual "sentinel" cases to determine a causal relationship and raise the importance of population level data. Overall, the literature does not support an increased risk of SNHL following vaccination with Comirnaty. No signal of disproportionate reporting has been observed in the Pfizer safety database for any of the Preferred Terms included in the safety database search. The O/E analyses (through 15 May 2023) on deafness and SNHL supports that the reports of hearing loss and tinnitus in the stratified populations and doses are not greater than would be expected as background occurrences. Considering the totality of the data available, a causal association between Comirnaty and sensory neural hearing loss is not supported, this topic will be monitored using routine pharmacovigilance.

Rapporteur assessment comment:

A review of hearing loss was included in the previous 3rd PSUR in which PRAC endorsed the MAH conclusion that a causal association between Comirnaty and hearing loss or tinnitus could not be concluded (procedure EMEA/H/C/PSUSA/00010898/202206).

In the current 5th PSUR, the MAH reported the results of an updated review of sensorineural hearing loss requested by TGA (Australia) through 18 Jun 2023 including literature (13 articles), post-marketing cases (BC level 1: 132 cases; BC level 2: 9; BC level 3: 1; BC level 4: 205; BC level 5: 72 cases) and O/E analyses (all O/E ratios well below 1). Based on provided data, MAH's conclusion is endorsed that a causal association between Comirnaty and sensorineural hearing loss is not supported at this time and that the MAH should continue to monitor sensorineural hearing loss through routine pharmacovigilance.

Retinal vascular occlusion	Prompted by a literature article entitled *Risk assessment of retinal vascular occlusion after COVID-19 vaccination* by Li Jing-Xing et al. (Li J-X, Wang Y-H, Bair H, Hsu S-B, Chen C, Wei JC-C, et al. Risk assessment of retinal vascular

	occlusion after COVID-19 vaccination. npj Vaccines. 2023;8[1]:64) the MAH has undertaken an evaluation of this signal; the evaluation is ongoing.

Rapporteur assessment comment:

The ongoing evaluation of retinal vascular occlusion by the MAH is awaited.

a. Closed after DLP as no risk.

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Evaluation of important identified risks

Myocarditis and Pericarditis

There were 1014 potentially relevant cases of Myocarditis and Pericarditis: 711 cases reported myocarditis and 379 cases reported pericarditis (in 76 of these 1014 cases, both myocarditis and pericarditis were reported):

Myocarditis

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

Overall - All ages

- Clinical Trial Data
    - Number of cases: none, no cases were retrieved in the PSUR#4.
- Post-Authorisation Data
    - Number of cases: 711 (original [622], bivalent Omi BA.1 [50], bivalent Omi BA.4/BA.5 [49]; 1.0% of 74,102 cases of the total PM dataset), compared to 1287 cases (0.5%) retrieved in the PSUR#4.
    - Reported relevant PTs: Myocarditis (595), Myopericarditis (116), Carditis (5), Eosinophilic myocarditis (4), Chronic myocarditis (3), Giant cell myocarditis (2).
    - Relevant event outcome: fatal (35), resolved/resolving (220), resolved with sequelae (43), not resolved (170), unknown (257).

Pericarditis

Search criteria: Autoimmune pericarditis; Immune-mediated pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Overall - All ages

- Clinical Trial Data
    - Number of cases: none; no cases were retrieved in the PSUR#4.

- Post-Authorisation Data
    - Number of cases: 379 (original [322], bivalent Omi BA.1 [36], bivalent Omi BA.4/BA.5 [28]; 0.5% of 74,102 cases of the total PM dataset), compared to 796 cases (0.3%) retrieved in the PSUR#4.
    - Reported relevant PTs: Pericarditis (376), Pericarditis constrictive (3), Pleuropericarditis (2).
    - Relevant event outcome: fatal (6), resolved/resolving (120), resolved with sequelae (17), not resolved (106), unknown (132).

Literature

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

O/E analysis

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

- 14-day risk window:
    - Males 5+ years
    - Females 5+ years
    - Overall, monovalent dose 1, dose 2, and additional doses
    - Overall
- 21-day risk window:
    - Males 5+ years
    - Females 12+ years
    - Overall, monovalent dose 1, dose 2, and additional doses
    - Overall

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

- 14-day risk window:
    - Males 12-24 years
    - Females 12+ years
    - Overall, monovalent dose 1 and dose 2
    - Overall
- 21-day risk window:
    - Males 12-24 years
    - Females 12-49 years
    - Overall, monovalent dose 2
    - Overall

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

MAH's 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 is communicated in the BNT162b2 CDS, in:

- Section 4.4, Special warnings and precautions for use - General recommendations, which includes information on appropriate action to be taken, as follows: "Very rare cases of myocarditis and

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

- Section 4.8, Undesirable effects as adverse drug reaction in the post authorisation experience.
- Appendices A and B of the BNT162b2 CDS.

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

Rapporteur assessment comment:

During the interval period, 1,014 potentially relevant cases of myocarditis and pericarditis were retrieved: 711 cases reporting myocarditis and 379 cases reporting pericarditis. In 76 of these 1014 cases, both myocarditis and pericarditis were reported.

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

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

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

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

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

2.3.2. Evaluation of important potential risks

In the PSUR#4, the MAH, based on the review of clinical trial data, cumulative PM data, individual review of cases, and real world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease (VAED/VAERD) from the list of the safety concerns. In the AR of the PSUR#4 (EMEA/H/C/PSUSA/00010898/202212), the PRAC agreed to remove VAED/VAERD from the list of safety concerns in both RMP and PSUR.

Rapporteur assessment comment:

Please refer regarding the assessment of the Comirnaty EU-RMP version 10.1 to the ongoing procedure EMEA/H/C/005735/II/0188/G which include the removal of VAED/VAERD from the list of safety concerns.

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

Adverse events of special interest (AESIs)

Rapporteur assessment comment: The MAH stated that, no new safety issues/signals or reporting pattern changes were detected concerning the cardiovascular AESIs, haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity. Consequently these topics are not discussed in this section.

Response to the PRAC request 1 from the 4th PSUR (EMEA/H/C/PSUSA/00010898/202212):

> *For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition; HIV infection should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

MAH's response:

No new safety issue/signal or reporting pattern change was identified upon review of the incremental data for the AESIs in subjects with Malnutrition; HIV infection. Therefore, this topic is not discussed in the PSUR.

Rapporteur assessment comment: Noted.

Anaphylactic AESIs

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

Clinical trial data

- Number of cases: none, compared to 1 case (0.32%) retrieved in the PSUR#4.

Post-authorisation data

- Number of cases: 188 (original [101], bivalent Omi BA.1 [24], bivalent Omi BA.4/BA.5 [63]; 0.25% of 74,102 cases, the total PM dataset), compared to 421 cases (0.15%) retrieved in the PSUR#4.
- Reported relevant PTs: Anaphylactic reaction (146), Anaphylactic shock (43), Anaphylactoid reaction (7).
- Relevant event outcome fatal (4), resolved/resolving (109), resolved with sequelae (7), not resolved (16), unknown (60). In 4 cases (reporting 4 relevant events with fatal outcomes), the reported causes of death were Anaphylactic reaction (3), Dyspnoea (2), Anaphylactic shock, Blood pressure decreased, Cardiac failure acute, Cerebrovascular accident, Depressed level of consciousness, Respiratory rate decreased, Shock (1 each). All cases involved elderly subjects (Age range: 77 to 102 years). Medical history was provided in 3 cases and included PTs under the SOC Cardiac disorders (4 events), Metabolism and nutrition disorders, Nervous system disorders (3 events each), Gastrointestinal disorders, Social circumstances, Surgical and medical procedures, Vascular disorders (2 events each), Endocrine disorders, Psychiatric disorders, Renal and urinary disorders (1 event each).

Analysis Original versus Bivalent Vaccines

The majority of the anaphylaxis cases were reported after administration of the original vaccine (52%) rather than the bivalent Omi BA.4/BA.5 vaccine (35.7%); the PT most frequently reported was Anaphylactic reaction (70% versus 86%). Few cases of anaphylaxis were reported after the administration of bivalent Omi BA.1, therefore a meaningful comparison of the PTs reported with the other 2 vaccines was not possible.

O/E analysis

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

The MAH has conducted unadjusted observed versus expected analyses for the 9,112 cumulative cases of anaphylaxis reported through 18 June 2023. Anaphylaxis cases were identified using the following PTs: anaphylactic shock, anaphylactic reaction, anaphylactoid shock, and anaphylactoid reaction. A background rate of 1.31 anaphylaxis cases per million vaccine doses was assumed.

Considering the current status of the vaccination schedule and the availability of only partial data published worldwide and on the ECDC websites for doses of BNT162b2 vaccines (original and bivalent) administered in the EU-EEA countries, the number of doses administered from those shipped was estimated by applying the same administration percentage used in the previous PSUR (76%). Therefore, an estimated 3,507,956,339 doses (76% of shipped doses) were administered.

Expected counts were determined by multiplying the number of doses administered by the expected rates per dose.

An O/E ratio of 1.983 (95% CI 1.942, 2.024) was observed for BNT162b2 compared to the background rate for anaphylaxis cases observed in the US. This rate has steadily declined each reporting period from the 9.47 (95% CI, 8.61, 10.40) first reported in Summary Monthly Safety Report 2 (through 31 January 2021) and has remained consistent with that reported in the most recent PSUR. The reason for the decline is unknown but could reflect decreased reporting, changes in the accuracy of the exposure estimate, or changes in population being vaccinated.

MAH's conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

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

COVID-19 AESIs

This AESI with the MedDRA search criteria - SMQ COVID-19 (Narrow and Broad) OR PTs Ageusia; Anosmia* was foreseen as a way to monitor for possible cases of VAED/VAERD. Because, as agreed by EMA, VAED/VAERD has been removed as a safety concern (Important potential risk) after >2.5 years of surveillance, COVID-19 will no longer be considered an AESI for discussion in the PSUR, however, discussion of lack of efficacy cases will continue as per PSUR requirements.

*: Due to MedDRA upgrade to version 26.0: 3 PTs (Asymptomatic COVID-19, Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease) have been removed.

Clinical trial data

- Number of cases: 2 (original [2]; 2.4% of 82 cases, the total CT dataset), compared to 4 cases (1.3%) retrieved in the PSUR#4. None of the events were related to BNT162b2.

Post-authorisation data

- Number of relevant cases: 7738 (original [5398], bivalent Omi BA.1 [309], bivalent Omi BA.4/BA.5 [2031], BNT162b2 multivalent NOS [45]; 10.4% of 74,102 cases, the total PM dataset), compared to 57,462 cases (20.3%) retrieved in the PSUR#4.
- Time to event onset: n=3667, range: <24 hours to 798 days, median: 167 days.
- Duration of relevant events: n=550, range: 24 hours to 713 days, median: 9 days.
- Relevant event outcome: fatal (52), resolved/resolving (1784), resolved with sequelae (126), not resolved (1152), unknown (4852).
    - Fatal cases (52): In 52 cases (reporting 55 relevant events of which 52 relevant events reported a fatal outcome), the reported causes of death (≥2) included COVID-19 (26), Drug ineffective (22), COVID-19 pneumonia, Vaccination failure (15 each), Respiratory failure (7), Suspected COVID-19 (6), Acute respiratory distress syndrome (5), Dyspnoea, Interchange of vaccine products (4 each), Cardiac arrest, Multiple organ dysfunction syndrome, Pyrexia (3 each), Cardiac failure, Coronavirus infection, Pneumonia, Shock (2 each).

Long COVID

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

Clinical trial data

- Number of cases: none; no cases were retrieved in the PSUR#4.

Post-authorization data

- Number of relevant cases: 156 (original [139], bivalent Omi BA.1 [8], bivalent Omi BA.4/BA.5 [9]; 0.2% of 74,102 cases, the total PM dataset), compared to 178 cases (0.06%) retrieved in the PSUR#4.
- Subjects' gender: female (103), male (50) and unknown (3).
- Subjects' age in years: n = 135, range: 14–86, mean: 46.3, median: 46.0. When the subjects' age group was provided (n=137), there were 7 paediatric, 113 adults, and 17 elderly subjects.

Analysis Original versus Bivalent Vaccines

The majority of the long COVID-19 cases was reported after administration of the original vaccine (89%), therefore a meaningful comparison of the PTs reported in the 3 vaccines groups was not possible.

O/E analysis

The current age-stratified observed to expected analysis for ageusia/anosmia in the 12-17 years age group using the 21-day risk window had a O/E ratio >1 (1.162; 95% CI 0.927, 1.439) compared to the previous PSUR. Of note, the background rates used in the O/E analyses were updated for ageusia/anosmia, using the new ACCESS publication[1], which reports one combined incidence rate for <19

years and therefore may over- or underestimate background incidence for some pediatric age-groups. The confidence intervals included 1 so are therefore not statistically significant, however, the AE reports for that age group were reviewed:

There were 84 cases in which either ageusia (71 events), anosmia (48 events) or both were reported (total of 522 AEs). The cases were reported between 17 April 2021 and 22 November 2022 and largely described primary dosing (dose 1 or 2). Most cases were in females (63.1%) compared to males (35.7%) and the mean age was 15.2 years. Cases were mostly non-serious (65.5%); 57 (67.9%) were non-medically confirmed and 27 (32.1%) were medically confirmed. Countries contributing at least 10% of the cases were the UK (20.2%), the US (16.7%) and France (10.7%). Outcome was recovered (with or without sequelae) or recovering in the 39.3% of the cases, not recovered in 46.4% of cases and unknown in 14.3% of the cases. All reports were for BNT162b2 (original).

Concomitant medications were reported in only 13 cases while 11 reported medical histories of COVID-19 or suspected COVID-19 and 3 reported concurrent COVID-19. Only 4 cases were reports of anosmia alone and 7 cases were reports of ageusia alone. Upon review of the cases, the only notable trend apart from temporality to vaccination was the co-reporting of adverse events reflective of systemic reactogenicity events and in many cases symptoms of what may also reflect upper respiratory infections in this age populations. The most common co-reported events were pyrexia (32.1%), headache (31.0%), cough (22.6%), fatigue (19.0%), nausea (13.1%), oropharyngeal pain (11.9%), dyspnoea (11.9%), malaise (11.9%) and myalgia (10.7%).

Overall, the information does not represent a new significant finding or signal. Reports of anosmia and ageusia will continue to be reviewed by routine pharmacovigilance.

[1]: Willame C, Dodd C, Durán CE, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023;41(1):251-262. doi:10.1016/j.vaccine.2022.11.031

MAH's conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue and long COVID-19 will be discussed in the next PSUR if warranted.

Rapporteur assessment comment:

The age-stratified observed to expected analysis for ageusia/anosmia in the 12-17 years age group using the 21-day risk window showed a O/E ratio of 1.162 (95% CI 0.927, 1.439) which is elevated compared to the previous PSUR (O/E ratio <1). The confidence interval included 1 and therefore considered not statistically significant. As a reason for the elevated O/E ratio the MAH stated that the background rates used in the O/E analyses were updated for ageusia/anosmia, using the new ACCESS publication, which reports one combined incidence rate for <19 years and therefore may over- or underestimate background incidence for some pediatric age-groups.

However, the AE reports (84 cases in which either ageusia [71 events], anosmia [48 events] or both) for that 12-17 years age group were reviewed and did not represent a new significant safety finding or signal.

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

The MAH stated that the MedDRA search criteria - SMQ COVID-19 (Narrow and Broad) OR PTs Ageusia; Anosmia was foreseen as a way to monitor for possible cases of VAED/VAERD. Because VAED/VAERD has been removed as an important potential risk, COVID-19 will no longer be considered an AESI for discussion in the PSUR. This is endorsed, routine pharmacovigilance is considered sufficient.

Immune-mediated/autoimmune AESIs

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

Clinical Trial Data

- Number of cases: none, compared to 9 cases (2.9%) retrieved in the PSUR#4.

Post-authorization data

- Number of cases: 3215 (original [2846], bivalent Omi BA.1 [138], bivalent Omi BA.4/BA.5 [248]; 4.3% of 74,102 cases of the total PM dataset), compared to 6155 cases (2.2%) retrieved in the PSUR#4.
- Most frequently (≥2%) reported relevant PTs: Hypersensitivity (413), Psoriasis (177), Polymyalgia rheumatica (160), Autoimmune disorder (156), Dermatitis (86), Thrombocytopenia (79), Alopecia areata (77), Myositis (69), Hyperthyroidism (65), Autoimmune thyroiditis, Hypothyroidism (64 each), and Graves' disease (63).
- Relevant event outcome: fatal (38), resolved/resolving (823), resolved with sequelae (240), not resolved at the time of reporting (1497), and unknown (1092).
    - Fatal cases (46): In 46 cases (reporting 38 relevant events with a fatal outcome), the reported causes of death (≥3) included Interstitial lung disease, Thrombocytopenia (6 each), Multiple organ dysfunction syndrome, Myocarditis (5 each), Cardiac arrest, Pneumonia (4 each), Acute respiratory failure, Cerebral haemorrhage, COVID-19, Death, Dyspnoea, and Shock (3 each). Most (30 of 43 cases that provided age) of the fatal cases involved elderly subjects. When the medical history was provided (28 cases), significant medical conditions reported in more than 2 cases included Hypertension (11), Dyslipidaemia, Type 2 diabetes mellitus (4 each), Chronic kidney disease, Hospitalisation, and Renal failure (3 each).

Analysis Original versus Bivalent Vaccines

PM: original (2846), bivalent Omi BA.1 (138), bivalent Omi BA.4/BA.5 (248).

Among the frequently (≥2%) reported Immune-mediated/autoimmune AESIs by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:

- PTs *Hypersensitivity, Dermatitis, Myositis* were reported at a higher frequency in patients administered bivalent Omi BA.1 when compared to subjects administered original and bivalent Omi BA.4/BA.5 (Hypersensitivity [21.0% in bivalent Omi BA.1 vs 12.6% in original and 11.3% in bivalent Omi BA.4/BA.5], Dermatitis [8.7% in bivalent Omi BA.1 vs 2.5% in original and 2.4% in bivalent Omi BA.4/BA.5], and Myositis [5.8% in bivalent Omi BA.1 vs 1.9% in original and 2.8% in bivalent Omi BA.4/BA.5]).
- PTs *Psoriasis, Autoimmune disorder, Alopecia areata, Hyperthyroidism, and Autoimmune thyroiditis* were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (Psoriasis [5.7% in original vs 3.6% in bivalent Omi BA.1 and 4.4% in bivalent Omi BA.4/BA.5], Autoimmune disorder [5.1% in original vs 2.2% in bivalent Omi BA.1 and 2.8% in bivalent Omi BA.4/BA.5], Alopecia areata [2.6% in original vs 1.5% in bivalent Omi BA.1 and 0.8% in bivalent Omi BA.4/BA.5], Hyperthyroidism [2.1% in original vs none in bivalent Omi BA.1 and 0.8% in bivalent

Omi BA.4/BA.5], and Autoimmune thyroiditis [2.1% in original vs none in bivalent Omi BA.1 and 1.6% in bivalent Omi BA.4/BA.5]).

- PTs *Polymyalgia rheumatica, and Thrombocytopenia* were reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to subjects administered original (Polymyalgia rheumatica [9.4% in bivalent Omi BA.1 and 9.7% in bivalent Omi BA.4/BA.5 vs 4.4% in original], and Thrombocytopenia [3.6% in bivalent Omi BA.1 and 4.4% in bivalent Omi BA.4/BA.5 vs 2.2% in original]).
- PT *Hypothyroidism* was reported at a higher frequency in subjects administered original and bivalent Omi BA.4/BA.5 when compared to subjects administered bivalent Omi BA.1 (2.1% in original and 1.6% in bivalent Omi BA.4/BA.5 vs 0.7% in bivalent Omi BA.1).
- PT *Graves' disease* was reported at a higher frequency in subjects administered original and bivalent Omi BA.1 when compared to subjects administered bivalent Omi BA.4/BA.5 (2.0% in original and 2.9% in bivalent Omi BA.1 vs 0.8% in bivalent Omi BA.4/BA.5).

O/E analysis

- O/E analysis through 15 May 2023 was performed for Acute disseminated encephalomyelitis (ADEM)(narrow definition), ADEM and encephalitis (broad definition), Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus. All O/E ratios were <1, except for ADEM narrow definition in the 18-24 years, 25-49 years, and 50-59 years age groups using the 21-day risk window (table 4) and in the 25-49 years age group using the 42-day risk window (table 5):

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.000	-	0.135	0.016, 0.486	0.493	0.263, 0.843	**1.016**	**0.525, 1.775**	**1.870**	**1.466, 2.352**	**1.473**	**0.970, 2.143**	0.749	0.437, 1.200	0.816	0.491, 1.274
ADEM and encephalitis, broad definition	0.000	-	0.071	0.029, 0.147	0.149	0.097, 0.218	0.098	0.062, 0.145	0.119	0.100, 0.139	0.062	0.047, 0.081	0.042	0.031, 0.054	0.042	0.034, 0.052

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.000	-	0.089	0.011, 0.322	0.364	0.204, 0.601	0.741	0.405, 1.243	**1.235**	**0.976, 1.542**	0.882	0.581, 1.284	0.433	0.252, 0.694	0.547	0.343, 0.828
ADEM and encephalitis, broad definition	0.000	-	0.047	0.019, 0.097	0.110	0.074, 0.157	0.074	0.049, 0.106	0.088	0.075, 0.102	0.043	0.033, 0.055	0.029	0.022, 0.036	0.027	0.022, 0.033

MAH's conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

For ADEM (narrow definition), the age stratified O/E ratios of more age groups (18-24 years, 25-49 years, and 50-59 years using the 21-day risk window and 25-49 years using the 42-day risk window) were >1 compared to the previous 4th PSUR (25-49 years age group using the 21-day risk window: O/E ratio 1.10 (95% CI [0.85, 1.40]). Furthermore, in this PSUR for the age group 25-49 years using the 21-day risk window the O/E was 1.87 (95% CI 1.47, 2.35), which is considered statistically significant.

Therefore, the MAH is requested to further discuss in detail the results of the O/E analyses concerning acute disseminated encephalomyelitis (ADEM, narrow definition) with focus on the age group 25-49 years, and perform a cumulative review of (literature) cases reporting ADEM after Comirnaty exposure using ADEM Brighton Collaboration case definition and WHO-UMC causality assessment per case, and an updated cumulative O/E analysis, if applicable. The MAH should evaluate whether ADEM should be added as an ADR in the Comirnaty PI. **Request for supplementary information**

Multisystem Inflammatory Syndrome in Children / Adults

Search criteria: *PTs Cytokine release syndrome; Distributive shock; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Systemic inflammatory response syndrome.*

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR#4.

Post-authorization data

- Number of relevant cases: 55 (original [45], bivalent Omi BA.1 [3], bivalent Omi BA.4/BA.5 [8]; 0.07% of 74,102 cases in the total PM dataset), compared to 92 (0.03%) retrieved in PSUR#4.
- Relevant PTs: Multiple organ dysfunction syndrome (22), Multisystem inflammatory syndrome (15), Multisystem inflammatory syndrome in children (7), Multisystem inflammatory syndrome in adults (5), Systemic inflammatory response syndrome (4), Distributive shock (3).
- Relevant event outcome: fatal (16), resolved/resolving (14), not resolved (11), unknown (15).
    - Fatal cases (15). In 15 fatal cases (reporting 16 relevant events with fatal outcome), the reported causes of death were coded to Multiple organ dysfunction syndrome (14), Renal failure and Thrombosis (4 each), Septic shock (3), Pancreatitis acute, Cardiogenic shock, Cerebrovascular accident, Necrosis ischaemic, Confusional state, Pulmonary embolism, COVID-19 pneumonia, Sepsis, Thrombocytopenia, Cerebral infarction, Cardiac arrest, Infarction and Ischaemic stroke (2 each). Of 15 cases, 11 involved elderly subjects. When the medical history was provided (12 cases), the most frequently (≥2) reported medical conditions included Hypertension (4), Type 2 diabetes mellitus (3), Cholecystectomy, Diverticulitis, Dyslipidaemia, Glomerulonephritis, Hypothyroidism and Obesity (2 each).

Analysis Original versus Bivalent Vaccines

PM: original (45 cases), bivalent Omi BA.1 (3 cases), bivalent Omi BA.4/BA.5 (8 cases). There were no paediatric patients administered bivalent vaccines.

Among the three groups, the PT Multiple organ dysfunction syndrome was the most frequently reported: there were 17 cases in the original group, 4 cases in the bivalent Omi BA.4/BA.5 group and 2 cases in the bivalent Omi BA.1 group.

The remaining relevant PTs were distributed as follows:

- PT *Multisystem inflammatory syndrome* was reported in cases involving patients administered the original vaccine (13 cases) and the bivalent Omi BA.4/BA.5 vaccine (2 cases);
- PTs *Multisystem inflammatory syndrome in children and Systemic inflammatory response syndrome* were reported exclusively in cases involving patients administered the original vaccine (7 cases and 4 cases, respectively);

- PT *Multisystem inflammatory syndrome in adults* was reported in cases involving patients administered the original vaccine (3 cases) and the bivalent Omi BA.4/BA.5 vaccine (2 cases);
- PT *Distributive shock* was reported in cases involving patients administered the original vaccine (2 cases) and the bivalent Omi BA.1 vaccine (1 case).

O/E analysis

- O/E analysis was performed for Multisystem inflammatory syndrome: For the MIS analysis, the 21-24 years age group using the 21-day risk window meets the signal criteria with an O/E ratio greater than ; however the results are not statistically significant as the 95% confidence intervals include 1. For all other age groups and risk windows, the O/E ratio is less than 1. This result is consistent with the analyses in the most recent PSUR.

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

		21-Day Risk Window					42-Day Risk Window				
Stratification	Bkgd Rate[a,9]	Obs Cases	PY	Exp Cases	O/E Ratio	95% CI	Obs Cases	PY	Exp Cases	O/E Ratio	95% CI
Age											
<5 years	2.77	2	107,635	3.0	0.671	0.081, 2.423	2	157,393	4.4	0.459	0.056, 1.657
5-11 years	2.77	14	1,968,738	54.5	0.257	0.140, 0.431	15	2,974,318	82.4	0.182	0.102, 0.300
12-17 years	2.77	37	3,492,152	96.7	0.382	0.269, 0.527	50	5,453,801	151.1	0.331	0.246, 0.436
18-20 years	1.50	8	2,109,075	31.6	0.253	0.109, 0.498	11	3,375,051	50.6	0.217	0.108, 0.389
21-24 years	0.23	9	2,812,100	6.5	**1.392**	**0.636, 2.642**	9	4,500,069	10.4	0.870	0.398, 1.651
25-49 years	0.58	65	21,096,203	122.4	0.531	0.410, 0.677	76	34,131,249	198.0	0.384	0.302, 0.481
50-59 years	1.47	37	10,785,214	158.5	0.233	0.164, 0.322	45	18,001,769	264.6	0.170	0.124, 0.228
60-69 years	3.38	48	10,802,000	365.1	0.131	0.097, 0.174	62	18,681,983	631.5	0.098	0.075, 0.126
70+ years	7.42	130	15,030,672	1,115.3	0.117	0.097, 0.138	164	25,968,815	1,926.9	0.085	0.073, 0.099
Gender											
Males	2.36	184	32,026,475	755.8	0.243	0.210, 0.281	229	53,096,323	1,253.1	0.183	0.160, 0.208
Females	2.36	167	36,177,313	853.8	0.196	0.167, 0.228	206	60,148,124	1,419.5	0.145	0.126, 0.166
Vaccine											
Monovalent (any dose)	2.36	345	63,265,291	1,493.1	0.231	0.207, 0.257	426	103,437,114	2,441.1	0.175	0.158, 0.192
Bivalent BA.1	2.36	2	591,317	14.0	0.143	0.017, 0.518	3	1,181,657	27.9	0.108	0.022, 0.314
Bivalent BA.4/5	2.36	4	4,347,181	102.6	0.039	0.011, 0.100	6	8,625,675	203.6	0.029	0.011, 0.064

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

MAH's conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

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

The results of the O/E analyses for multisystem inflammatory syndrome showed an O/E ratio above 1 for the age group 21-24 years using the 21-day risk window, (O/E ratio 1.39, 95% CI 0.64;1.64) which is considered not statistically significant (same results as in the previous 4th PSUR).

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

Myocarditis and Pericarditis AESIs

Rapporteur assessment comment:

Please refer to section 2.3.1 'Evaluation of important identified risks' of this assessment report.

Neurological AESIs (including demyelination)

Search Criteria: *SMQ Generalised convulsive seizures following immunisation (Narrow) OR SMQ Demyelination (Narrow and Broad) OR PTs Ataxia; Cataplexy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Meningitis viral; Miller Fisher syndrome; Narcolepsy; Neuropathy peripheral; Polyneuropathy.*

Clinical Trial Data

- Number of cases: 2 (original [1], blinded therapy [1]; 2.4% of 82 cases in the total CT dataset), compared to 8 cases (2.6%) retrieved in the PSUR#4. None of these SAEs were assessed as related to original/blinded therapy.

Post-authorization data

- Number of relevant cases: 1263 (original [1040], bivalent Omi BA.1 [80], bivalent Omi BA.4/BA.5 [149], BNT162b2 Multivalent NOS [4]; 1.7% of 74,102 cases in the total PM dataset), compared to 2597 cases (0.9%) retrieved in the PSUR#4. Please note that in some cases the subject received more than vaccine formulation.
- Most frequently (> 2% of cases) reported relevant PTs: Seizure (212), Neuropathy peripheral (149), Polyneuropathy (139), Guillain-Barre syndrome (130), Epilepsy (115), Fibromyalgia (110), Multiple sclerosis (93), Myelitis transverse (65), Trigeminal neuralgia (51), Ataxia (43), Generalised tonic-clonic seizure, Myokymia (33 each), Optic neuritis (31), Multiple sclerosis relapse (26)
- Relevant event outcome: fatal (14), resolved/resolving (299), resolved with sequelae (127), not resolved (562), unknown (420).
    - Fatal cases (13). In 13 cases (reporting 14 relevant events with fatal outcome), the reported causes of death included Seizure (5), Guillain-Barre syndrome, Status epilepticus (3 each), Epilepsy (2), and Demyelination (1). Over half (7 of 13 cases) of the fatal cases involved elderly subjects. When the medical history was provided (10 cases), medical conditions reported in 2 or more cases included Hypertension (5), Epilepsy, Non-tobacco user, and Tobacco user (2 each). The subjects in all 10 cases reported a history of other neurologic disorders (PTs Cerebral palsy, Cerebrovascular accident, Dementia, Encephalopathy, Generalised tonic-clonic seizure, Haemorrhage intracranial, Hemiparesis, Hydrocephalus, Paraparesis, and Seizure; 1 each) and 6 reported a history of cardiac disorders (PTs Atrial fibrillation, Cardiac arrest, Cardiac valve sclerosis, Coronary artery disease, Myocardial infarction, Myocardial ischaemia; 1 each).

Analysis Original versus Bivalent Vaccines

PM: original (1035), bivalent Omi BA.1 (79), and bivalent Omi BA.4/BA.5 (149).

Among the frequently (≥2%) reported Neurological AESIs (including demyelination) by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:

- PTs Polyneuropathy, Multiple sclerosis, Myelitis transverse, Myokymia, Optic neuritis, and Multiple sclerosis relapse were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5

PT	Original	Bivalent Omi BA.1	Bivalent Omi BA.4/BA.5
Polyneuropathy	**12.1%**	6.3%	6.0%
Multiple sclerosis	**8.3%**	1.3%	4.0%
Myelitis transverse	**5.7%**	1.3%	3.4%
Myokymia	**3.1%**	0	0.7%
Optic neuritis	**3.0%**	0	0
Multiple sclerosis relapse	**2.4%**	0	0.7%

- PT Trigeminal neuralgia was reported at a higher frequency in subjects administered bivalent Omi BA.1 when compared to subjects administered original and bivalent Omi BA.4/BA.5
- PTs Seizure was reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to subjects administered original (34.2% in bivalent Omi BA.1 and 25.5% in bivalent Omi BA.4/BA.5 vs 14.2% in original).
- PT Generalised tonic-clonic seizure was reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to original (6.3% in bivalent Omi BA.1 and 5.4% in bialent Omi BA.4/BA.5 vs 1.9% in original).
- PT Fibromyalgia was reported at a higher frequency in subjects administered original and bivalent Omi BA.1 when compared to subjects administered bivalent Omi BA.4/BA.5 (9.9% in original and 7.6% in bivalent Omi BA.1 vs 1.3% in bivalent Omi BA.4/BA.5).
- PT Guillain-Barre syndrome was reported at a higher frequency in subjects administered bivalent Omi BA.4/BA.5 when compared to subjects administered original and bivalent Omi BA.1 (24.8% in bivalent Omi BA.4/BA.5 vs 8.3% in original and 8.9% in bivalent Omi BA.1).

O/E analysis

- O/E analysis was performed for Generalized convulsive, Fibromyalgia, Guillain-Barré syndrome, Meningitis, Narcolepsy, Multiple sclerosis and Polyneuropathy. All O/E ratios were <1, except for multiple sclerosis in the age groups 12-17 years and 70+ years using the 21 day risk window, and in the age group 12-17 years using the 42 day risk window:

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Multiple sclerosis	NA	NA	NA	NA	**1.822**	**0.996, 3.057**	0.542	0.409, 0.704	0.285	0.264, 0.307	0.281	0.245, 0.321	0.461	0.386, 0.546	**1.441**	**1.025, 1.971**

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Multiple sclerosis	NA	NA	NA	NA	**1.667**	**1.018, 2.574**	0.429	0.335, 0.542	0.208	0.194, 0.223	0.193	0.170, 0.218	0.318	0.271, 0.372	0.963	0.702, 1.288

The age-stratified observed to expected analysis for multiple sclerosis in 2 age groups using the 21-day risk window and in one age group using the 42-day risk window had a ratio > 1 compared to the previous PSUR. Of note, the background rate used in the O/E analyses were updated using a published paper that provided age-specific estimates covering all ages.[1]

While the overall O/E was <1 and consistent with previous PSURs, the results for the 12-17 age group (1.822; 95% CI 0.996, 3.057) and 70+ years age group (1.441; 95% CI 1.025, 1.971) group are above 1 using the 21-day risk window and for the 12-17 year age group (1.667; 95% CI 1.018, 2.574) using the 42-day and the 95% CIs did not include 1. The age-groups reported in the background publication do not align exactly with the PSUR age groupings and may underestimate the background rates for certain groups, however, the AE reports for these age groups were reviewed:

The MedDRA search strategy for the AESI Multiple sclerosis is comprised of the PTs Multiple sclerosis, Multiple sclerosis relapse and Optic neuritis.

12- to 17-year-olds

There were 13 cases reporting at least one of these PTs for the 12–17-year age group (7 events of multiple sclerosis/multiple sclerosis relapse and 8 events of optic neuritis) using the 21-day risk window. The cases were reported between 23 August 2021 and 19 April 2022 and largely described primary dosing (dose 1 or 2). Most cases were in females (84.6%) compared to males (15.4%) and the mean age was 15.4 years. Latency ranged from the day of vaccination to 40 days after vaccination (mean 10.3 days). The cases were all categorized as serious; nine (9) of the cases were medically confirmed and 4 were non-medically confirmed. Cases were from Taiwan, EU and North America. All reports were for BNT162b2 (original). Out of the 13 cases, 5 provided a description of MRIs with abnormalities consistent with demyelination, however only 1 of these reported an lumbar puncture with IgG oligoclonal bands (and in this case the patient's neurological symptoms were reported as starting 11 days prior to dose 1). The remaining 8 described no diagnostic test results or tests (e.g., MRI, ophthalmological exams) that were normal.

There were 20 cases reporting at least one of these PTs for the 12–17-year age group using the 42-day risk window. Seven of the 20 cases were included in the 21-day risk window group above. The remaining 13 cases were reviewed and 1 was determined by this reviewer to be a duplicate of one of the 21-day risk window cases. In another case the patient was found to be 36 years old. The remaining 11 cases (6 events of multiple sclerosis and 6 events of optic neuritis) were all for BNT162b2 (original) and were reported between 17 March 2021 and 09 February 2023, largely describing primary dosing (dose 1 or 2). Six of the patients were female and 5 male and they ranged in age from 13 to 17 years (1 with no age reported). Latency ranged from 4 days to 2.5 months and 1 case described a history of multiple sclerosis. All 11 cases were from the EU and were serious; 7 were medically confirmed (4 non-medically confirmed). Upon review, one case described papilledema and macular edema and was determined by the reporter to not be optic neuritis. Of the remaining 10 cases, 1 described concurrent COVID-19 and 1 described information that was more consistent with anti-myelin oligodendrocyte glycoprotein occurring in conjunction with an upper respiratory infection and 5 provided no supportive diagnostic information. The remaining 3 cases provided some diagnostic imaging that was potentially supportive of the adverse event of interest (described MRI scans with lesions or otherwise consistent with inflammatory optic neuropathy or demyelination).

70 + year olds

There were 39 cases reporting at least one of the PTs for the 70+ year age group (17 events of multiple sclerosis relapse, 12 events of multiple sclerosis and 11 events of optic neuritis).

The cases were reported between 22 February 2021 and 15 February 2023. Most cases were in females (33, 84.6%) compared to males (6, 15.4%); ages ranged from 70 to 81 years (mean 73.6). The cases were all categorized as serious; 14 (35.9%) were medically confirmed and 25 (64.1%) were non-medically confirmed. Cases were from the EU (31) and the US (8). All reports were for BNT162b2 (original). The majority of the reports (28, 71.8%) provided no diagnostic information supportive of multiple sclerosis or optic neuritis; 1 of the 28 cases reported concurrent COVID-19. The remaining 11

cases had MRIs consistent with demyelination, optic neuritis or multiple sclerosis or had ophthalmological exams that were suspicious for or diagnostic of optic neuritis; except 1 case that described a patient whose ophthalmologist diagnosed ischemic optic neuritis. The remaining 10 cases occurred after doses 1, 2 or 3 with a latency ranging from the same day of vaccination to 26 days (unspecified latency in 2 cases). Of the 10 reports providing medical history, 4 had medical histories of either multiple sclerosis or optic neuritis. Outcomes were recovered or recovered with sequelae in 6, not recovered in 3 and unknown in 1 report.

Upon review, many of the cases in these age groups do not clearly describe the diagnoses of interest for monitoring the AESI of multiple sclerosis. The available information does not support a new significant finding or signal. Multiple sclerosis will continue to be monitored with routine pharmacovigilance.

[1]: Alonso, A., Jick, S. S., Olek, M. J., & Hernán, M. A. (2007). Incidence of multiple sclerosis in the United Kingdom : findings from a population-based cohort. Journal of neurology, 254(12), 1736–1741. https://doi.org/10.1007/s00415-007-0602-z.

MAH's conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

For multiple sclerosis it is noted that in the O/E analyses, the O/E ratio was >1 for the 12-17 age group (1.822; 95% CI 0.996, 3.057) and 70+ years age group (1.441; 95% CI 1.025, 1.971) group using the 21-day risk window and for the 12-17 year age group (1.667; 95% CI 1.018, 2.574) using the 42-day risk window. These are considered (borderline) statistically significant and is new compared to the previous 4th PSUR. However, based on the provided data, the review of the cases reporting multiple sclerosis did not support new significant safety information concerning multiple sclerosis and Comirnaty exposure.

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

Pregnancy related AESIs

Rapporteur assessment comment:

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

Glomerulonephritis and Nephrotic syndrome AESIs

Search Criteria: *HLT Glomerulonephritis and nephrotic syndrome (all path).*

Clinical Trial Data

- Number of cases: none; no cases were retrieved in PSUR#4.

Post-authorization data

- Number of cases: 103 (original [93], bivalent Omi BA.1 [3], bivalent Omi BA.4/BA.5 [8]; 0.07% of 74,102 cases, the total PM dataset), compared to 198 (0.07%) retrieved in PSUR#4. Please note that in 1 case the subject received more than vaccine formulation.

- Most frequently reported relevant PTs: Nephrotic syndrome (35), IgA nephropathy (19), Granulomatosis with polyangiitis (16), Glomerulonephritis membranous (11), Glomerulonephritis minimal lesion (8), Glomerulonephritis (6), Focal segmental glomerulosclerosis (5), Glomerulonephritis rapidly progressive, Microscopic polyangiitis (4 each), C3 glomerulopathy, Glomerulonephritis membranoproliferative (2 each), Anti-glomerular basement membrane disease, Nephritic syndrome, and Primary coenzyme Q10 deficiency (1 each).
- Relevant event outcome: fatal (3), resolved/resolving (31), resolved with sequelae (8), not resolved (37), unknown (36).
    - Fatal cases (3). In 3 cases (reporting 3 relevant events with fatal outcome), the reported causes of death were coded to Granulomatosis with polyangiitis (2) and Nephrotic syndrome (1). Medical history was provided in all 3 cases and included Fluid retention, Haemodialysis, and Glomerulonephritis and Renal failure (1 each).

Analysis Original versus Bivalent Vaccines

PM: original (92), bivalent Omi BA.1 (3), and bivalent Omi BA.4/BA.5 (8). The number of cases for bivalent Omi BA.1, and bivalent Omi BA.4/BA.5 (5 and 8, respectively) are too small to all for a meaningful comparison to the occurrence of Glomerulonephritis/nephrotic syndrome in cases treated with BNT162b2.

O/E analysis

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

MAH's conclusion

No new significant safety information has emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:
No new important safety concern could be identified for glomerulonephritis and nephrotic syndrome AESIs.

Stroke

Search criteria: *HLT Central nervous system haemorrhages and cerebrovascular accidents (All path); Cerebrovascular venous and sinus thrombosis (Primary Path).*

Clinical trial data

- Number of cases: 2 (original, BNT162b2 [B.1.1.7 + B.1.617.2] [1 each]; 2.4% of 82 cases in the total CT dataset), compared to 11 cases (3.5%) retrieved in the PSUR#4. Both these SAEs were assessed as unrelated to BNT162b2.

Post-authorisation data

- Number of cases: 764 (original [571], bivalent Omi BA.1 [52], bivalent Omi BA.4/BA.5 [141]; 1.0% of 74,102 cases in the total PM dataset), compared to 1132 cases (0.4%) retrieved in the PSUR#4.
- Most frequently (≥10) reported relevant PTs: Cerebrovascular accident (357), Cerebral infarction (107), Ischaemic stroke (86), Cerebral haemorrhage (57), Cerebral venous sinus thrombosis (40), Cerebral ischaemia (24), Subarachnoid haemorrhage (23), Cerebral thrombosis (18),

Embolic stroke (17), Cerebellar infarction, Haemorrhagic stroke (13 each), Brain stem infarction, Ischaemic cerebral infarction (10 each).

- Relevant event outcome: fatal (92), resolved/resolving (175), resolved with sequelae (154), not resolved (193), unknown (287).
    - Fatal cases (78). In 78 cases (reporting 92 relevant events with fatal outcome), the reported causes of death (≥3) were coded to the PTs Cerebrovascular accident (24), Cerebral haemorrhage (15), Ischaemic stroke (12), Cerebral infarction (8), Cerebral thrombosis (7), Subarachnoid haemorrhage (5), Haemorrhage intracranial (3).

Analysis Original versus Bivalent Vaccines

PM: original (571), bivalent Omi BA.1 (52), and bivalent Omi BA.4/BA.5 (141).

- Among the frequently (≥3%) reported stroke related events by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:
    - PTs Cerebral ischaemia and Cerebral venous sinus thrombosis were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (Cerebral ischaemia [3.5% in original vs none in bivalent Omi BA.1 and 2.8% in bivalent Omi BA.4/BA.5], Cerebral venous sinus thrombosis [6.5% in original vs none in bivalent Omi BA.1 and 2.1% in bivalent Omi BA.4/BA.5]).
    - PT Cerebral haemorrhage was reported at a higher frequency in subjects administered bivalent Omi BA.4/BA.5 (11.3%) when compared to subjects administered original (6.8%) and bivalent Omi BA.1 (3.8%). No significant difference observed in the other most frequently reported events among these groups.

O/E analysis

- O/E analysis was performed for Cerebral venous sinus thrombosis, Ischemic stroke and Hemorrhagic stroke. O/E ratios for ischemic stroke and hemorrhagic stroke were well below 1.

  For the CVST analysis using the low background rate (Table 12), males and females 18-24 and 25-49 years, as well as overall monovalent dose 1 and dose 2, meet the signal criteria with an O/E ratio greater than 1 in either the 21-day and/or 42-day risk windows. However, the 95% CIs for some age groups included 1, indicating that the result is not statistically significant. For all other stratifications using the low background rate, the O/E ratio is less than 1. Using the mid-range background rate (Table 13), all stratifications have an O/E ratio less than 1. These results are consistent with the analyses in the most recent PSUR.

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

Stratification	Low Bkgd rate[a,17]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95% CI[b]	Obs Cases	PY	Exp Cases	O/E Ratio	95% CI
Males <5 years	0.45	0	51,170	0.2	0.000	-	0	74,639	0.3	0.000	-
Males 5-11 years	0.45	0	928,026	4.2	0.000	-	0	1,400,319	6.3	0.000	-
Males 12-17 years	0.45	5	1,644,917	7.4	0.675	0.219, 1.576	6	2,565,678	11.5	0.520	0.191, 1.131
Males 18-24 years	0.42	12	2,317,797	9.7	**1.233**	**0.637, 2.153**	14	3,704,401	15.6	0.900	0.492, 1.510
Males 25-49 years	0.40	59	9,926,605	39.7	**1.486**	**1.131, 1.917**	78	16,040,004	64.2	**1.216**	**0.961, 1.517**
Males 50-59 years	1.24	31	5,060,070	62.7	0.494	0.336, 0.701	42	8,432,397	104.6	0.402	0.289, 0.543
Males 60-69 years	1.25	21	5,056,672	63.2	0.332	0.206, 0.508	31	8,730,439	109.1	0.284	0.193, 0.403
Males 70+ years	1.51	28	7,041,219	106.3	0.263	0.175, 0.381	41	12,148,446	183.4	0.224	0.160, 0.303
Females <5 years	0.97	0	56,465	0.5	0.000	-	0	82,753	0.8	0.000	-
Females 5-11 years	0.97	0	1,040,713	10.1	0.000	-	0	1,573,999	15.3	0.000	-
Females 12-17 years	0.97	5	1,847,235	17.9	0.279	0.091, 0.651	7	2,888,123	28.0	0.250	0.100, 0.515
Females 18-24 years	0.97[c]	42	2,603,378	25.3	**1.663**	**1.199, 2.248**	48	4,170,719	40.5	**1.186**	**0.875, 1.573**
Females 25-49 years	0.26	140	11,169,598	29.0	**4.821**	**4.055, 5.689**	172	18,091,245	47.0	**3.657**	**3.131, 4.246**
Females 50-59 years	1.55	56	5,725,144	88.7	0.631	0.477, 0.819	69	9,569,373	148.3	0.465	0.362, 0.589
Females 60-69 years	0.75	38	5,745,328	43.1	0.882	0.624, 1.210	44	9,951,543	74.6	0.590	0.428, 0.791
Females 70+ years	1.07	56	7,989,453	85.5	0.655	0.495, 0.851	64	13,820,369	147.9	0.433	0.333, 0.553
Overall, monovalent dose 1	0.76	165	23,062,069	175.3	0.941	0.803, 1.097	188	23,062,069	175.3	**1.073**	**0.925, 1.237**
Overall, monovalent dose 2	0.76	266	22,347,739	169.8	**1.566**	**1.384, 1.766**	326	44,690,162	339.6	0.960	0.858, 1.070
Overall, monovalent dose 3+	0.76	58	17,855,483	135.7	0.427	0.325, 0.553	96	35,684,884	271.2	0.354	0.287, 0.432
Overall, bivalent BA.1	0.76	2	591,317	4.5	0.445	0.054, 1.608	2	1,181,657	9.0	0.223	0.027, 0.804
Overall, bivalent BA.4/5	0.76	2	4,347,181	33.0	0.061	0.007, 0.219	4	8,625,675	65.6	0.061	0.017, 0.156

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

Stratification	Mid Bkgd rate[a,b,17,18]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95% CI[c]	Obs Cases	PY	Exp Cases	O/E Ratio	95% CI
Males <5 years	0.45	0	51,170	0.2	0.000	-	0	74,639	0.3	0.000	-
Males 5-11 years	0.45	0	928,026	4.2	0.000	-	0	1,400,319	6.3	0.000	-
Males 12-17 years	0.45	5	1,644,917	7.4	0.675	0.219, 1.576	6	2,565,678	11.5	0.520	0.191, 1.131
Males 18-24 years	1.10	12	2,317,797	25.5	0.471	0.243, 0.822	14	3,704,401	40.7	0.344	0.188, 0.576
Males 25-49 years	1.50	59	9,926,605	148.9	0.396	0.302, 0.511	78	16,040,004	240.6	0.324	0.256, 0.405
Males 50-59 years	1.71	31	5,060,070	86.5	0.358	0.243, 0.509	42	8,432,397	144.2	0.291	0.210, 0.394
Males 60-69 years	3.97	21	5,056,672	200.7	0.105	0.065, 0.160	31	8,730,439	346.6	0.089	0.061, 0.127
Males 70+ years	6.22	28	7,041,219	438.0	0.064	0.042, 0.092	41	12,148,446	755.6	0.054	0.039, 0.074
Females <5 years	0.97	0	56,465	0.5	0.000	-	0	82,753	0.8	0.000	-
Females 5-11 years	0.97	0	1,040,713	10.1	0.000	-	0	1,573,999	15.3	0.000	-
Females 12-17 years	0.97	5	1,847,235	17.9	0.279	0.091, 0.651	7	2,888,123	28.0	0.250	0.100, 0.515
Females 18-24 years	4.71	42	2,603,378	122.6	0.343	0.247, 0.463	48	4,170,719	196.4	0.244	0.180, 0.324
Females 25-49 years	2.85	140	11,169,598	318.3	0.440	0.370, 0.519	172	18,091,245	515.6	0.334	0.286, 0.387
Females 50-59 years	2.05	56	5,725,144	117.4	0.477	0.360, 0.620	69	9,569,373	196.2	0.352	0.274, 0.445
Females 60-69 years	1.70	38	5,745,328	97.7	0.389	0.275, 0.534	44	9,951,543	169.2	0.260	0.189, 0.349
Females 70+ years	1.35	56	7,989,453	107.9	0.519	0.392, 0.674	64	13,820,369	186.6	0.343	0.264, 0.438
Overall, monovalent dose 1	2.34	165	23,062,069	539.7	0.306	0.261, 0.356	188	23,062,069	539.7	0.348	0.300, 0.402
Overall, monovalent dose 2	2.34	266	22,347,739	522.9	0.509	0.449, 0.574	326	44,690,162	1,045.7	0.312	0.279, 0.347
Overall, monovalent dose 3+	2.34	58	17,855,483	417.8	0.139	0.105, 0.179	96	35,684,884	835.0	0.115	0.093, 0.140
Overall, bivalent BA.1	2.34	2	591,317	13.8	0.145	0.018, 0.522	2	1,181,657	27.7	0.072	0.009, 0.261
Overall, bivalent BA.4/5	2.34	2	4,347,181	101.7	0.020	0.002, 0.071	4	8,625,675	201.8	0.020	0.005, 0.051

MAH's conclusion

No new significant safety information have emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

It is noted that for cerebral venous sinus thrombosis the O/E analysis results for the 18-24 and 25-49-year age groups (in both males and females) using the low background rate for both the 21-day and 42-day risk windows (O/E ratios >1) are consistent with the previous 3rd and 4th PSURs.

Using the mid-range background rate all O/E ratios were below 1.

No new important safety concern could be identified for stroke.

Sudden death

Search criteria – *PT Sudden Death*

Clinical Trial Data

- Number of cases: none; no cases were retrieved in PSUR#4.

Post-authorization data

- Number of cases: 23 (original [11], bivalent Omi BA.1 [4], bivalent Omi BA.4/BA.5 [8]; 0.03% of 74,102 cases, the total PM dataset), compared to 48 (0.02%) retrieved in PSUR#4.
- MC cases (18), NMC cases (5).
- Country/region of incidence: Japan (10), Germany (7), Spain, UK (2 each), France, and Italy (1 each).
- Subjects' gender: female (8), and male (15).
- Subjects' age in years: n=19, range: 14–93, mean: 72.5, median: 80.0.
- Medical history (n=14); the most frequently (≥2) reported relevant medical conditions included Hypertension (6), Atrial fibrillation, Cerebral infarction, and Diabetes mellitus (2 each).
- COVID-19 Medical history: none.
- Co-suspect medications (n=2); the reported relevant co-suspect medications included influenza vaccine inact split 4V (2).
- Number of relevant events: 23.
- Relevant event seriousness: serious (23), non-serious (0).
- Time to event onset: n=18, range: 0-571 days, median: 9 days.

Analysis original versus bivalent vaccines

There are no differences in reporting proportion between cases involving administration of original vaccine (11 cases) compared to cases involving administration of bivalent vaccines (12 cases, of which 4 bivalent Omi BA.1 and 8 bivalent Omi BA.4/BA.5).

O/E analysis

O/E analysis was performed for Sudden death, see appendix 5.8 of the PSUR.

Rapporteur assessment comment:

In appendix 5.8 of the PSUR the results of the O/E analysis performed for Death (PT *Fatal clinical outcome*) is presented. All O/E ratios are well below 1.

MAH's conclusion

No new significant safety information has emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:

No new important safety concern could be identified for sudden death.

Thromboembolic AESIs

Search criteria: *HLGT (All path) Embolism and thrombosis (excluding PTs reviewed as Stroke AESIs) OR PT Coagulopathy.*

Clinical trial data

- Number of cases: 1 (Original [1]; 1.2% of 82 cases in the total CT dataset), compared to 5 cases (1.6%) retrieved in the PSUR#4. The case was assessed as unrelated to BNT162b2.

Post-authorisation data

- Number of cases: 1217 (original [968], bivalent Omi BA.1 [89], bivalent Omi BA.4/BA.5 [160]; 1.6% of 74,102 cases in the total PM dataset), compared to 2064 cases (0.7%) retrieved in the PSUR#4.
- Most frequently (>50 occurrences) reported relevant PTs: Pulmonary embolism (388), Thrombosis (339), Deep vein thrombosis (211).
- Relevant event outcome: fatal (105), resolved/resolving (377), resolved with sequelae (119), not resolved (396), unknown (462).
    - Fatal cases (82). In 82 cases (reporting 105 relevant events with fatal outcome), the reported causes of death (≥3 occurrences) were coded to the PTs Pulmonary embolism (34), Thrombosis (21), Deep vein thrombosis (10), Embolism (9), Coronary artery thrombosis, Pulmonary thrombosis (5 each), Thrombosis with thrombocytopenia syndrome (4), Disseminated intravascular coagulation, Intracardiac thrombus (3 each). Most (48 of 82 cases) of the fatal cases involved elderly subjects. When the medical history was provided (56 cases), the most frequently (≥5 occurrences) reported medical conditions included the PTs Hypertension (25), Type 2 Diabetes mellitus (9), Atrial fibrillation, Dyslipidaemia, Obesity (7 each), Chronic kidney disease (5).

Analysis original versus bivalent vaccines

PM: original (968), bivalent Omi BA.1 (89), and bivalent Omi BA.4/BA.5 (160). No significant difference observed in the most frequently (≥5%) reported events among these groups.

O/E analysis

- O/E analysis was performed for Arterial thromboembolism, Deep vein thrombosis, Disseminated intravascular coagulation, Thrombotic thrombocytopenia syndrome and Venous thromboembolism. All O/E ratios were below 1.

MAH's conclusion

No new significant safety information has emerged based on the review of these cases, and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Rapporteur assessment comment:
No new important safety concern could be identified for thromboembolic AESIs.

MAH's overall AESI conclusion

Considering that the review of the cases reporting AESIs identified no new significant safety information, the MAH proposes to include and discuss AESIs in future PSURs only if the reporting pattern changes and/or significant new safety information is evident.

At this time, the BNT162b2 vaccines have been administered to an unprecedented number of individuals worldwide and approximately 30 months of clinical trial safety data review, post-authorization surveillance and signal management activities have elapsed. The safety profile of the COVID-19 vaccine is well-characterized, however surveillance will continue.

Based on regulatory authority feedback, knowledge gained about the product safety profile, and the recognition that AESIs for products will evolve over time as knowledge about a product's safety profile grows, it is appropriate to review the AESI/TME list and revise it as needed to stay current and improve surveillance. Pfizer will continue to utilize and refine the AESI list as appropriate for signal detection activities (including O/E analyses) and in preparation for safety aggregate reports. At present, the AESI list is synonymous with the targeted medical event (TME) list which is a MedDRA-based list of >1900 unique PTs, leading to more of a SOC-based approach of aggregate case review. Commensurate with the safety profile of the vaccine, the future AESI list will reflect specific medical conditions coupled with appropriate MedDRA-derived search strategies for each AESI.

Rapporteur assessment comment:

MAH' s proposal is agreed to include and discuss AESIs in future PSURs only if the reporting pattern changes and/or significant new safety information is evident.

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. **Request for next PSUR**

Response to the PRAC request 2 from the 4th PSUR (EMEA/H/C/PSUSA/00010898/202212):

> *For future PSURs in the section 'Evaluation of Other Risks (not categorised as important)', the reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

MAH's response:

No new safety issue/signal or reporting pattern change was identified upon review of the incremental data for the reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions. Therefore, these topics are not discussed in the PSUR.

Rapporteur assessment comment:

Noted.

Evaluation of special situations

Rapporteur assessment comment:

The MAH stated that, no new safety issues/signals or reporting pattern changes were detected concerning the overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect. Consequently these topics are not discussed in this section.

Response to the PRAC request 3 from the 4th PSUR (EMEA/H/C/PSUSA/00010898/202212):

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.

MAH's response:

No new safety issue/signal or reporting pattern change was identified upon review of the incremental cases reporting fatal outcome; therefore, "Death" has not been included in the section 16.3.4. Evaluation of Special Situations of the PSUR.

Rapporteur assessment comment:
Noted.

Lack of therapeutic efficacy

Search Criteria: PTs Drug ineffective, Vaccination failure.

Clinical trial data

- There was no lack of efficacy cases in the clinical trial dataset for both this reporting period and for the reporting period of PSUR#4.

Post-authorization data

- Number of cases: 7048 (original [4896], bivalent Omi BA.1 [196], bivalent Omi BA.4/BA.5 [1956]) (9.5% of 74,102 cases, the total PM dataset), compared to 56,095 cases (19.8%) in PSUR#4.
- The increase in the reporting proportion of LOE cases was multifactorial:
    - A high number of cases were reported from Austria (40,496 cases in the current PSUR), as compared to the previous PSURs (31,629 cases in PSUR #3, 9009 cases in PSUR #2 and 204 cases in PSUR #1) due to the active solicitation of LOE cases, including retrospective cases, by the Austrian Board of Health starting from August 2021. Additionally, reviewing Austria cases, it is notable that these case reports, although received during the current reporting period, were reflective of events that had occurred during earlier vaccination campaigns with BNT162b2 Original.
    - In addition, the epidemiology of the virus has changed since December 2021 in that the Omicron variant has become predominant in most regions. The majority of the LOE cases received during the current reporting interval involved the monovalent vaccine, the efficacy of which against Omicron variants is less than against the previous dominant variants of concern. The first approval of BNT162b2 bivalent vaccine was received in US on 02 Sep 2022.
    - Of note, there are BNT162b2 LOE reports created from AE reports received for Nirmatrelvir/Ritonavir (Paxlovid®) based on the BNT162b2 vaccine history reported in the cases (AEs reported for Paxlovid in individuals with COVID 19 following vaccination with BNT162b2 will be appropriately databased as LOE cases for BNT162b2 as well).

SARS-CoV-2 Variants (48 cases)

- In 48 of the 7048 cases, information on SARS-CoV-2 variants was provided:
    - Delta variant (10 cases),
    - Omicron variant (40 cases).

Literature

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

MAH's conclusion

No new safety signals have emerged based on a review of these cases.

Rapporteur assessment comment: No new important safety concern could be identified for lack of therapeutic efficacy. 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. **Request for next PSUR**

Update on special populations

Rapporteur assessment comment: The MAH stated that, no new safety issues/signals or reporting pattern changes were detected concerning the use in frail patients with co-morbidities, and/or interactions with other vaccines. Consequently these topics are not discussed in this section.

Response to the PRAC request 4 from the 4th PSUR (EMEA/H/C/PSUSA/00010898/202212):

> *For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

MAH's conclusion: 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 this section.

Rapporteur assessment comment: Noted.

Use in paediatric population

Paediatric subjects <5 years of age

Clinical trial data

- Number of cases: 41 (blinded therapy [17], original [13], and bivalent Omi BA.4/BA.5 [11] originated from clinical studies C4591007, C4591007-OPENLABEL, C4591048-SSA, and C4591048-SSB; 50% of 82 cases, the total CT dataset), compared to 62 cases (20.1%) retrieved in the PSUR#4. All events were assessed as unrelated to blinded therapy, BNT162b2, or bivalent Omi BA.4/BA.5.

Post-authorisation data

- Number of cases: 396 (original [294], bivalent Omi BA.1 [2], bivalent Omi BA.4/BA.5 [176]; 0.5% of 74,102 cases in the total PM dataset), compared to 606 cases (0.2%) retrieved in the PSUR#4.

- Most frequently reported PTs (≥ 2) in subjects with ages of 6 months through 4 years (n=858):
- Following dose 1
  - Formulation 3 mcg (Maroon cap) (n=206): Wrong product administered (28), Pyrexia (19), Poor quality product administered (17), Overdose, Product administration error (14 each), Product preparation error (13), COVID-19 (6), Urticaria (5), Drug ineffective, Product administered at inappropriate site (4 each), Expired product administered, Rash, Vomiting (3 each), Cellulitis, Dyspnoea, Fatigue, Headache, Peripheral swelling, Pharyngeal erythema, Product packaging confusion, Suspected COVID-19, Vaccination site pain, and Vaccination site swelling (2 each).
  - Formulation other/unknown (n=104): Product administered to patient of inappropriate age (25), Overdose (24), Wrong product administered (8), Pyrexia (6), Off label use, Pain in extremity (3 each), Poor quality product administered, Product administration error, Product use issue, and Vomiting (2 each).
- Following dose 2
  - Formulation 3 mcg (Maroon cap) (n=184): Poor quality product administered (22), Wrong product administered (20), Inappropriate schedule of product administration, Product administration error (19 each), Pyrexia (11), Overdose, Product preparation error (8 each), Off label use (6), Interchange of vaccine products, Vomiting (5 each), Expired product administered, Product administered at inappropriate site, Rash (4 each), Constipation, Cough, Diarrhoea, Gastrooesophageal reflux disease, Product use issue, and Pruritus (2 each).
  - Formulation other/unknown (n=49): Overdose, Product administered to patient of inappropriate age (11 each), Wrong product administered (5), Expired product administered, Inappropriate schedule of product administration, and Seizure (2 each).
- Following dose 3
  - Formulation 3 mcg (Maroon cap) (n=125): Poor quality product administered, Product administration error (23 each), Wrong product administered (22), Inappropriate schedule of product administration, Interchange of vaccine products (9 each), Product preparation error (5), Off label use, Overdose (4 each), Fatigue, Pyrexia, and Underdose (2 each).
  - Formulation other/unknown (n=8): Poor quality product administered, and Product administration error (2 each).
- Following dose other/unknown
  - Formulation 3 mcg (Maroon cap) (n=102): Poor quality product administered (35), Product administration error (33), Incorrect dose administered, Product preparation error (7 each), Overdose (6), Pyrexia, Wrong product administered (3 each), and Expired product administered (2).
  - Formulation other/unknown (n=90): Overdose, Product administered to patient of inappropriate age (18 each), Poor quality product administered, Product administration error (11 each), Wrong product administered (6), Asthma, Cough, Expired product administered, Pyrexia, and Rhinorrhoea (2 each).

- Event outcome: fatal (9), resolved/resolving (128), not resolved (49), unknown (672).
  - Fatal cases (3):
    - Age: 1 year, 2 years, and 4 years (1 each).
    - MC cases (2), NMC cases (1).
    - Gender: males (3).

- Country/region of incidence: Japan, Taiwan, Province of China, and US (1 each).
- Fatal PTs (9): Arrhythmia, Cardio-respiratory arrest, Cyanosis, Death, Loss of consciousness, Muscle rigidity, Seizure, Sinus tachycardia, and Supraventricular tachycardia (1 each).
- Medical history (n=15): Blood calcium abnormal, Blood phosphorus abnormal, Cardiac failure, Cardiac hypertrophy, Congenital nephrotic syndrome, Gastrooesophageal reflux disease, Gene mutation, Hypertension, Hypertensive heart disease, Hyperuricaemia, Peritoneal dialysis, Respiratory disorder, Respiratory muscle weakness, Therapeutic aspiration, and Upper respiratory tract inflammation (1 each).

- The 3 fatal cases are summarised below:
  - The 1st case (NMC) reported only PT Death as the fatal AE. Neither cause of death nor information on autopsy was provided in this case involving a 2-year-old male subject "who died after being vaccinated (timing of vaccination and date of death was not reported.)". Limited information was provided, precluding any meaningful assessment.
  - The 2nd case (MC) originated from Japanese Pharmaceuticals and Medical Devices Agency (PMDA), in which the 1-year-old male subject received dose 3 (maroon cap) for COVID-19 immunisation on 16 February 2023. On the next day, he experienced minor pyrexia and productive cough. On 18 February 2023, the subject developed cardio-respiratory arrest and his body temperature decreased and died on the same day, although treatments included endotracheal intubation, gastric intubation, intraosseous needle placement, adrenaline intravenous injection, and Meylon (sodium bicarbonate) intravenous injection. In this case, the subject had severe underlying diseases (such as blood calcium abnormal, blood phosphorus abnormal, cardiac failure, cardiac hypertrophy, congenital nephrotic syndrome, gastrooesophageal reflux disease, gene mutation [Pierson syndrome], hypertension, hypertensive heart disease, hyperuricaemia, peritoneal dialysis, respiratory disorder, respiratory muscle weakness, therapeutic aspiration, and upper respiratory tract inflammation), making it difficult to determine the causal relationship between the vaccination and the fatal event (PT coded to Cardio-respiratory arrest).
  - The 3rd case (MC) originated from Taiwan Center for Disease Control, which involved a 4-year-old male subject, who experienced events with PTs coded to Arrhythmia, Loss of consciousness, Seizure, Sinus tachycardia, Supraventricular tachycardia, Muscle rigidity, and Cyanosis and died 11 days after the second dose of BNT162b2. The subject's medical history and concomitant medications were not reported. No autopsy was performed. Causality assessment from the reporter and BioNTech was "possible".

Rapporteur assessment comment:

During the interval period, post-marketing 396 cases were retrieved including 3 fatal cases of which 2 medically confirmed fatal cases: one case reported no medical history, concomitant medications, and no autopsy was performed, and one case reported severe underlying diseases. In the previous 4th PSUR there were reported 3 fatal cases of which 1 medically confirmed fatal case.

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

Paediatric subjects ≥5 years and ≤ 11 years of age

Clinical trial data

- Number of cases: 7 (original [4] and blinded therapy [3], originated from clinical studies C4591007, C4591007-OPENLABEL, and C4591024; 8.5% of 82 cases, the total CT dataset), compared to 34 cases (11.0%) retrieved in the PSUR#4. All events were assessed as unrelated to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 1225 (original [949], bivalent Omi BA.4/BA.5 [384]; 1.7% of 74,102 cases, the total PM dataset), compared to 4983 cases (1.8%) retrieved in the PSUR#4.
- Most frequently reported PTs (≥3% of cases): Poor quality product administered (318), Product administration error (189), Expired product administered (183), Overdose (150), Pyrexia (136), Wrong product administered (120), Product colour issue (99), Product administered to patient of inappropriate age (92), Product preparation error (82), Headache (60), Vaccination site swelling (59), Vomiting (55), Inappropriate schedule of product administration (48), and Cough (39).
- Relevant event outcome: resolved/resolving (603), resolved with sequelae (12), not resolved (207), fatal (3), unknown (1868).
    - Fatal cases (2):
        - Age: 9 years, and unknown (1 each).
        - MC cases (1), NMC cases (1).
        - Gender: females (2).
        - Country/region of incidence: Philippines, and Taiwan, Province of China (1 each).
        - Fatal PTs (3): Abdominal pain upper, Death, Pyrexia (1 each).
        - Medical history: not reported in 2 fatal cases.
    - The 2 fatal cases are summarised below:
        - The 1st NMC case recorded the subject's (unspecified age) death (PT coded to Death) as the only event, in which cause of death was unknown. This case provided limited information pertaining to dose and date of immunisation, medical history, concomitant medications, and date of the fatal outcome, which precluded a meaningful clinical assessment.
        - In the 2nd case, a 9-year-old female subject experienced pyrexia and upper abdominal pain 15 days after COVID-19 immunisation (unknown dose number). The subject's medical history and concomitant medications were not reported, and she died on an unknown date with the cause of death coded to the PTs Abdominal pain upper and Pyrexia.

Rapporteur assessment comment:

During the interval period, post-marketing 1,225 cases were retrieved including 2 fatal cases of which 1 medically confirmed fatal case reporting limited information. In the previous 4th PSUR there were reported 18 fatal cases of which 12 medically confirmed fatal cases (17 medically confirmed fatal cases in the 3rd PSUR, and 1 medically confirmed fatal case in the 2nd PSUR).

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

Paediatric subjects ≥12 years of age

Clinical trial data

- Number of cases: 5 (blinded therapy [5], originated from clinical studies C4591007, and C4591044; 6.1% of 82 cases, the total CT dataset), compared to 11 cases (3.6%) retrieved in the PSUR#4. All events were assessed as unrelated to blinded therapy.

Post-authorisation data

- Number of cases: 1287 (original [1062], bivalent Omi BA.1 [55], bivalent Omi BA.4/BA.5 [229], BNT162b2 Multivalent NOS [3]; 1.7% of 74,102 cases, the total PM dataset), compared to 7064 cases (2.5%) retrieved in the PSUR#4.
- Most frequently reported PTs (≥3%): Headache (182), Pyrexia (174), Poor quality product administered (124), Product administration error (115), Fatigue (102), Inappropriate schedule of product administration (77), Wrong product administered (76), Dizziness, Malaise (74 each), Nausea (70), Chest pain (60), Vomiting (59), COVID-19 (57), Myocarditis (55), Asthenia (51), Dyspnoea (45), Vaccination site pain (43), Abdominal pain, and Lymphadenopathy (38 each).
- Relevant event outcome: fatal (42), resolved/resolving (1224), not resolved (1038), resolved with sequelae (73), unknown (1481).
    - Fatal cases (13):
        - Age: 14 years, 15 years (3 each), 16 years, 17 years, unknown (2 each), and 12 years (1).
        - MC cases (9), NMC cases (4).
        - Gender: females, males (5 each), and unknown (3).
        - Country/region of incidence (> 2): Philippines (4), and Germany (3).
        - Fatal PTs (42): the most frequently (≥ 2) reported AEs included Cardiac arrest (4), Myocarditis, Pyrexia, Dyspnoea, Malaise, Pericarditis, Poisoning, and Vomiting (2 each).
        - Medical history (n=14): Becker's muscular dystrophy, Cerebral palsy, Cochlea implant, Hypoacusis, Intellectual disability, Language disorder, Mental disability, Myeloid leukaemia, Neuromyopathy, Orthostatic intolerance, Physical disability, Quadriparesis, Severe myoclonic epilepsy of infancy, and Wheelchair user (1 each).
    - The 13 fatal cases are summarised below:
        - In 4 MC cases, limited information was provided, precluding any meaningful assessment. The subjects' medical history/underlying conditions, concomitant medications, or date of death were not reported. Neither lab data nor information on autopsy was provided in these 4 cases.
        - In 2 NMC cases reported by a lawyer, both adolescents (unspecified ages) were reported to have sudden cardiac arrest within a week of BNT162b2 vaccination. Although it was not reported if autopsies were performed, the reporter stated that "pathologists recognized signs of poisoning and concluded that poisoning by the vaccine-induced spike protein was more likely to lead to death." Information on subject's medical history, concomitant medications and date of death was not provided.
        - In 1 MC case, a 17-year-old male subject received expired BNT162b2 for COVID-19 immunisation (PT coded to Expired product administered). The subject experienced fatal events (acute myocardial infarction, headache, pain, and vomiting) about 2 months after vaccination. The subject's medical history, concomitant medications, date of death and information on autopsy were not reported.
        - In 4 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

- One (1) MC case involved a 14-year-old male subject, who received BNT162b2 dose 1, 0.3 ml single for COVID-19 immunisation and neuromuscular disease (fatal PT coded to Off label use). Other fatal PTs were coded to Circulatory collapse, Pyrexia, Dyspnoea, Hypotonia, Hyperpyrexia, Chills, Pericarditis, and Myocarditis. The subject's death was possibly due to his severe underlying conditions, coded as Becker's muscular dystrophy, cerebral palsy, cochlea implant, COVID-19, hypoacusis, intellectual disability, language disorder, mental disability, neuromyopathy, physical disability, quadriparesis, and wheelchair user.
- One (1) NMC case involved a 15-year-old female subject who had underlying myeloid leukaemia, which could attribute to her fatal events (myocarditis, disease recurrence, and myeloid leukaemia).
- In 1 MC case, a 14-year-old female subject had severe underlying condition of Dravet syndrome and COVID-19 and was medicated with multiple antiepileptic drugs, which were confounding factors for the causality assessment between BNT162b2 vaccination and her fatal events (vaccination failure, COVID-19, hyperthermia, shock, COVID-19 pneumonia, and cardiac arrest).
- In 1 MC case, although the medical history was not reported, the 17-year-old female subject received multiple concomitant medications (such as amitriptyline, azathioprine, buprenorphine, colecalciferol, etanercept, paracetamol, piroxicam, prednisolone, and zoledronic acid), which were confounding factors for determination of the causal relationship between BNT162b2 vaccination and the fatal events (arrhythmogenic right ventricular dysplasia, Escherichia sepsis, and vomiting).

▪ In the remaining 2 cases, potential explanations other than vaccination for death are not evident in the reports however in the first case there is very limited information provided:

- In 1 NMC case, a 12-year-old female subject died of myocardial infarction 5 days after receiving BNT162b2 as dose 1, single for COVID-19 immunisation. The subject's medical history, concomitant medications, and information on autopsy were not reported.
- In 1 MC literature case reporting a 14-year-old female subject with following fatal PTs Myopericarditis, Cardiac failure, Arrhythmia, Arrhythmia supraventricular, Myocarditis, Pericarditis, and Sudden death, no confounding factors have been identified. Autopsy result showed inflammatory findings of pericardial tissue.

Rapporteur assessment comment:

During the interval period, post-marketing 1,287 cases were retrieved including 13 fatal cases of which 9 medically confirmed fatal cases: 1 literature case reporting vaccine-related myopericarditis that led to severe arrhythmias and progressive heart failure as the cause of death, 3 cases with underlying medical conditions, and 5 cases had limited information. In the previous 4th PSUR there were reported 28 fatal cases of which 21 medically confirmed fatal cases (45 medically confirmed fatal cases in the 3rd PSUR, and 40 medically confirmed fatal case in the 2nd PSUR).

No important new information could be identified regarding the use of Comirnaty in children/adolescents 12-17 years of age.

Analysis of confounders and risk factors

- Among the 2961 cases involving paediatric subjects, 763 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (355 cases) and/or underlying medical history (546 cases).

Literature

- During the reporting period, a literature article reporting important safety information about the use of bivalent vaccines and children aged 5-11 years was identified. Please refer to Section 11 Literature of the PSUR for further details.

Rapporteur assessment comment:

Please refer to section 1.2.5.5 'Literature' in this AR regarding the publication of Hause et al. reporting that no reports of myocarditis were recorded in VAERS by 01 January 2023 for the 861,251 children aged 5-11 years, who received a bivalent Pfizer-BioNTech booster in the US in the same period.

MAH's conclusion

Upon review, the most frequently reported AEs indicative of vaccination errors had a higher reporting proportion in paediatric groups <5 years and ≥5 Years and ≤11 Years of Ages compared to the ≥12 years of age; while the most frequent AEs indicative of reactogenicity type had a higher reporting proportion in paediatric group ≥12 years of age compared to groups of <5 years and ≥5 Years and ≤11 Years of Ages. Of the frequently reported AEs (≥2%) in the paediatric dataset, Pyrexia had a higher reporting proportion compared to the non-paediatric dataset (4.7% vs 2.6%). 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 CDS.

Rapporteur assessment comment:

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

Use in pregnant/lactating women

Search criteria: *Pregnancy cases are identified as cases where:*

- *Patient Pregnant Flag is "Yes";*
- *If there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly;*
- *If Delivery Notes are available;*
- *If any of the valid events on the case contains one of the following:"*
    - *SOC Pregnancy, puerperium and perinatal conditions, or*
    - *HLT Exposures associated with pregnancy, delivery and lactation; Lactation disorders, or PT Exposure via body fluid.*

Clinical trial data

- Number of pregnancy cases: 2 (2.4% of the total 82 cases from the CT dataset). Cases originated from clinical studies BNT162-17 and C4591007 (1 each) and study treatment was reported as BNT162b2 B.1.1.7, BNT162b2 B.1.617.2 (1) and blinded therapy (1).
- Country/region of incidence: [redacted] and [redacted] (1 each).
- Two (2) serious retrospective maternal cases reported event coded to the PT Abortion spontaneous (1 each), which occurred in the vaccinated pregnant females. In these 2 cases only the event of abortion spontaneous was reported and the trimester of exposure was unknown. Of these 2 cases, in 1 case the subject had a medical history of hypertension and was on concomitant medication ethinylestradiol, levonorgestrel which might have contributed to the reported event. In the remaining case there was limited information regarding the obstetric history which precluded meaningful causality assessment.

Post-authorisation data

- Number of **pregnancy cases**: 464 (original [397], bivalent Omi BA.1 [34], bivalent Omi BA.4/BA.5 [33]; 0.6% of 74,102 cases, the total PM dataset), compared to 988 cases (0.3%) retrieved in the PSUR#4. These 464 cases represent 422 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 41 pregnancies).
- Country/region of incidence (≥20): Sweden (152), UK (76), Germany (53), US (29), France (26), Norway (20).
- Of the 407 mother cases, 62 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 (47), Maternal exposure timing unspecified (13), Maternal exposure before pregnancy (2).
- There were 345 mother cases of which 169 were serious and 176 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 (204), Maternal exposure timing unspecified (21), Maternal exposure before pregnancy (10). Additional pregnancy related events reported in these cases (≥10) were coded to the PTs Abortion spontaneous (69), Heavy menstrual bleeding, Stillbirth (10 each). Other frequently reported (>20) clinical events coded to the PTs Vaccination site pain (67), Headache (53), Fatigue (48), Malaise (37). Pyrexia (31), Nausea (30), Vomiting (27), Chills (26), Myalgia (24), Arthralgia (22), COVID-19, Dizziness (21 each).
- Fifty-seven (57) baby/foetal cases, 51 serious and 6 non-serious. Cases are classified according to pregnancy outcome:
    - Pregnancy outcome: Live birth with congenital anomaly: 12 of these cases reported 30 congenital anomalies that coded to the PTs Cerebral palsy (3), Myoclonus, Hypospadias, Foot deformity (2 each), Abdominal hernia, Acrodermatitis enteropathica, Cerebral calcification, Congenital aortic stenosis, Congenital cystic kidney disease, Congenital hand malformation, Congenital hydronephrosis, Congenital musculoskeletal disorder of spine, Congenital ureterocele, Dextrocardia, Heart disease congenital, Intestinal obstruction, Kidney duplex, Kidney malformation, Multiple fractures, Nervous system disorder, Oesophageal atresia, Osteoporosis, Pulmonary aplasia, Single umbilical artery, VACTERL syndrome (1 each). Of these 12 cases, information regarding trimester of exposure was

available in 7 cases. Of these 7 cases, in 3 cases foetus was exposed during 1st trimester, in 3 cases foetus was exposed during 2nd trimester and in 1 case foetus was exposed during 3rd trimester. Of these 12 cases, in 1 case mother of the baby had a medical history of tobacco use which might have contributed to the reported event i.e., hypospadias and cerebral calcification. In the remaining 11 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: 14 cases reported spontaneous abortion. Of these 14 cases, information regarding trimester of exposure was provided in 2 cases. Of these 2 cases, in 1 case foetus was exposed during 1st trimester, in 1 case foetus was exposed during 2nd trimester. The clinical events in these 14 cases other than exposure related events were coded to PTs Congenital anomaly (5), Foetal growth restriction (4), Foetal cardiac disorder, Foetal chromosome abnormality (2 each), Brain malformation, Cerebellar hypoplasia, Double outlet right ventricle, Foetal cardiac arrest, Foetal death, Foetal disorder, Foetal malformation, Skeletal dysplasia (1 each). In these 14 cases, there was limited information regarding obstetric history or co suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Elective termination: 3 cases reported elective termination of pregnancy due to foetal defects. In all these 3 cases, foetus was exposed during 1st trimester. The events reported in these 3 cases other than exposure related events were coded to PTs Abortion induced, Congenital central nervous system anomaly, Exomphalos, Foetal cystic hygroma, Foetal death, Foetal heart rate abnormal (1 each). In these 3 cases, there was limited information regarding obstetric history or co suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Stillbirth: 1 case reported foetal death/ neonatal death. This case reported stillbirth with foetal defects. In this case foetus was exposed during 1st trimester. The events reported in this case other than exposure related events were coded to PTs Bronchopulmonary dysplasia, Congenital anomaly, Ecchymosis, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Joint contracture, Muscle contracture, Neonatal asphyxia, Polyhydramnios, Posthaemorrhagic hydrocephalus, Premature baby, Premature baby death, Umbilical cord short (1 each). In this case, there was limited information regarding obstetric history or co suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Live birth without congenital anomaly: 27 cases reported live birth babies without congenital anomaly. Of these 27 cases, information regarding trimester of exposure was available in 7 cases. Of these 7 cases, in 1 case, foetus was exposed during 1st trimester, in 1 case, foetus was exposed during 2nd trimester, and in 5 cases, foetus was exposed during 3rd trimester. The frequently reported events (≥2) in these 27 cases other than exposure related events were coded to PTs Premature baby (6), Foetal heart rate deceleration abnormality, Infantile apnoea, Jaundice neonatal (2 each). In these remaining 27 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Of the 464 cases, 356 cases provided pregnancy outcomes which are provided in Table 55 (not reproduced here. Pregnancy outcome was pending or not provided in the remaining 108 cases.

- Number of **lactation cases**: 119 (original [94], bivalent Omi BA.1 [19], bivalent Omi BA. 4/BA.5 [6]; 0.2% of 74,102 cases, the total PM dataset), compared to 302 cases (0.1%) retrieved in the PSUR#4.
- Breast feeding baby cases: 88, of which:
    - Sixty-eight (68) cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events.
    - Twenty (20) cases, 6 serious and 14 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk); the frequently reported clinical events (≥2) were coded to the PTs Pyrexia (6), Infantile vomiting (4), Insomnia, Restlessness, Pain, Infant irritability (3 each), Fatigue, Decreased appetite, Diarrhoea (2 each).
- Breast feeding mother cases: 31, of which:
    - Ten (10) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
    - Twenty-one (21) cases, 6 serious and 15 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>2) were coded to the PTs Pyrexia (6), Nausea, Myalgia (5 each), Pain in extremity (4), Paraesthesia, Chills, Fatigue, Vaccination site pain, Lymphadenopathy, Malaise (2 each).

Literature

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

MAH's conclusion

There were no safety signals regarding use in pregnant/lactating women that emerged from the review of these cases or the medical literature.

Rapporteur assessment comment:

Clinical trial data

During the interval period, 2 pregnancy cases (2.4% of the total CT dataset) were retrieved compared to 11 (3.6%) in the 4th PSUR.

Post-marketing data

During the interval period, 464 pregnancy cases (0.6% of the total PM dataset) compared to 988 cases (0.3%) retrieved in the 4th PSUR.

During the interval period, 119 lactation cases (0.2% of the total PM dataset) compared to 302 cases (0.1%) were retrieved in the 4th PSUR.

Regarding the 57 cases with pregnancy outcome: 12 (21%) of these cases reported live birth with congenital anomalies, 14 cases (25%) reported spontaneous abortion, 3 cases (5%) reported elective termination of pregnancy, 1 case (2%) reported foetal death/ neonatal death, and 27 cases (47%) reported live birth babies without congenital anomaly. Compared to the pregnancy outcomes in the previous interval period (n=125) these were 47 (38%), 10 (8%), 4 (3%), 9 (7%), and 55 (44%) respectively.

Literature

No new safety information.

Overall, based on provided data in the current PSUR, it is agreed that no new safety concerns were identified for use in pregnant/lactating women. The Comirnaty product information reflects that Comirnaty can be used during pregnancy and breastfeeding.

2.4. Characterisation of risks

2.4.1. Characterisation of important identified and potential risks

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

Please see Appendix 8 of the PSUR (not reproduced here) for the characterisation of the important identified and important potential risks of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 10.0 approved on 22 Jun 2023.

Rapporteur assessment comment:

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

2.4.2. Description of missing information

- Use in pregnancy and while breast feeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in patients with autoimmune or inflammatory disorders
- Interaction with other vaccines
- Long term safety data

Rapporteur assessment comment:

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

3. Benefit evaluation

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

Rapporteur assessment comment:

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

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

4. Benefit-risk balance

During the reporting period of the PSUR, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of safety concerns in both RMP and PSUR, as the available cumulative data (clinical trial and post-marketing) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance.

The risks have been evaluated in the context of the benefits of the vaccine. No additional changes to the Comirnaty risk minimisation measures are warranted.

Based on the PRAC Rapporteur review of the available safety and efficacy/effectiveness data from the current reporting period for the Comirnaty PSUR, the benefit-risk balance of Comirnaty Original (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran and riltozinameran), and Comirnaty Original/Omicron BA.4-5 (tozinameran and famtozinameran) remains unchanged.

The MAH should continue to review the safety of Comirnaty, including all reports of adverse events and should propose an update of the product information if an evaluation of the safety data identifies important new safety information, as applicable.

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

5. PRAC Rapporteur request for supplementary information

1. Regarding exposure in clinical trials, in the previous fourth PSUR the MAH reported that 8,958 participants received blinded therapy, and that in the current fifth PSUR only 2 participants received blinded therapy. The MAH should explain this discrepancy concerning the number of cumulative clinical trial participants receiving blinded therapy.

2. Regarding myocarditis, the MAH is requested to discuss the study of Yonker et al. (*Yonker LM, Swank Z, Bartsch YC, et al. Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis. Circulation. 2023;147:867–876. DOI: 10.1161/CIRCULATIONAHA.122.061025)* with a focus on the possibilities to mitigate individualized risk on myocarditis after Comirnaty exposure.
3. Regarding the AESI acute disseminated encephalomyelitis (ADEM), the MAH is requested to further discuss in detail the results of the O/E analyses concerning ADEM (narrow definition) with focus on the age group 25-49 years, and perform a cumulative review of (literature) cases reporting ADEM after Comirnaty exposure using ADEM Brighton Collaboration case definition and WHO-UMC causality assessment per case, and an updated cumulative O/E analysis, if applicable. The MAH should discuss whether ADEM should be added as an ADR in the Comirnaty PI.

6. MAH responses to Request for supplementary information

PRAC request 1: *Regarding exposure in clinical trials, in the previous fourth PSUR the MAH reported that 8,958 participants received blinded therapy, and that in the current fifth PSUR only 2 participants received blinded therapy. The MAH should explain this discrepancy concerning the number of cumulative clinical trial participants receiving blinded therapy.*

MAH response

The difference concerning the number of cumulative clinical trial participants receiving blinded therapy in the fourth PSUR (reporting period 19 Jun 2022 through 18 Dec 2022) and in the fifth PSUR (reporting period 19 Dec 2022 through 18 Jun 2023) is due to unblinding of the participants' study intervention for the CTs C4591007, C4591015, and C4591031 Substudies B, D and F.

The breakdown of the participants' post-unblinding study intervention is provided in Table 1.

Table 1. Breakdown of Post-Unblinding Study Intervention

	PSUR #4	PSUR #5 Post-Unblinding Study Intervention					
Protocol	**Blinded[a]**	**BNT162B2**	**BNT162b2/ BNT162b2 OMI**	**BNT162b2 OMI**	**BNT162b2/ Placebo**	**Placebo**	**Total**
C4591007	7003	4840	-	-	-	2163	7003
C4591015	346	173	-	-	-	173	346
C4591031 Substudy B	1485	-	-	-	1485[b]	-	1485
C4591031 Substudy D	2	1	-	1	-	-	2
C4591031 Substudy F	122	40	41	41	-	-	122
Total	**8958**	**5054**	**41**	**42**	**1485**	**2336**	**8958**

a. Blinded therapy did not include participants from protocol C4591001; this CT was inadvertently mentioned in the footnote listing protocols included under blinded therapy in Appendix 2.3 of PSUR #4.
b. Among these 1485 participants, 753 were randomised to Sequence 1 (BNT162b2 to placebo) and 732 were randomised to Sequence 2 (placebo to BNT162b2).

Rapporteur assessment comment:

The difference in the number of cumulative clinical trial participants receiving blinded therapy between the 4th and 5th PSUR is due to unblinding of the participants' study intervention for the studies C4591007, C4591015, and C4591031 sub-studies B, D and F.

Issue solved

PRAC request 2: *Regarding myocarditis, the MAH is requested to discuss the study of Yonker et al. (Yonker LM, Swank Z, Bartsch YC, et al. Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis. Circulation. 2023;147:867–876. DOI: 10.1161/CIRCULATIONAHA.122.061025) with a focus on the possibilities to mitigate individualized risk on myocarditis after Comirnaty exposure.*

MAH response

In the Yonker et al publication, the authors evaluated blood samples from 61 subjects who had received a COVID-19 mRNA vaccination. A subset of the subjects had developed myocarditis (n=16) and another subset (n=45) did not develop myocarditis (vaccinated control subjects). The authors evaluated blood and plasma samples from all subjects looking for differences between samples from subjects that experienced myocarditis versus vaccinated control subjects. Specifically, they examined the differences in the concentrations of SARS-CoV-2 antibodies, SARS-CoV-2 antigens (eg, full length spike protein), and cytokines, and performed haematology and T-cell profiling. Of all the analytical comparisons, the findings that correlated with statistical significance with myocarditis were increased circulating cytokines (eg, IL-8, IL-6, IL-10, IL-1 β, TNF α, IFN γ) and unbound, circulating full length spike protein. Elevations in circulating cytokines in patients with post-vaccine associated myocarditis have been previously described in the literature (Barmada et al, 2023).[1] However, a statistically significant correlation is not indicative of a causal relationship between circulating cytokines or unbound, circulating full length spike protein and vaccine-associated myocarditis, given that the mechanism behind myocarditis is not fully elucidated. As such, the interpretation of the MAH is that these findings are interesting and may be worth further investigation. However, at this time, the findings, which were obtained from patients with ongoing myocarditis, could only be used as potential indicators of post-vaccine associated myocarditis in addition to other more traditional parameters (such as clinical presentation, troponin, cardiac imaging, or endomyocardial biopsies), as opposed to causal agents. Therefore, the MAH considers that without causality between these findings and the occurrence of myocarditis, there is no intervention or individualised risk mitigation that can be implemented.

Rapporteur assessment comment:

MAH's conclusion is endorsed, that at this time, a statistically significant correlation is not a proof of a causal relationship between circulating cytokines or unbound, circulating full length spike protein and vaccine-associated myocarditis, because the mechanism behind myocarditis is not fully elucidated. Without causality between these findings and the occurrence of myocarditis, there is no risk mitigation that can be implemented.

Issue solved

PRAC request 3: *Regarding the AESI acute disseminated encephalomyelitis (ADEM), the MAH is requested to further discuss in detail the results of the O/E analyses concerning ADEM (narrow definition) with focus on the age group 25-49 years, and perform a cumulative review of (literature) cases reporting ADEM after Comirnaty exposure using ADEM Brighton Collaboration case definition and WHO-UMC causality assessment per case, and an updated cumulative O/E analysis, if applicable. The MAH should discuss whether ADEM should be added as an ADR in the Comirnaty PI.*

MAH response

Observed versus expected analysis

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the ADEM cases reported cumulatively through 15 May 2023 globally. These analyses were conducted to provide additional detail related to O/E results provided in the PSUR, specifically sensitivity analyses using a higher background

rate for ADEM as well as a refined case definition using the ADEM Brighton Collaboration case definition for certainty levels 1-3.

Methods

Observed cases were defined using the following PT: acute disseminated encephalomyelitis. In Table 2 and Table 3, O/E results using 21- and 42-day risk windows post Pfizer-BioNTech COVID-19 vaccines (any dose) are provided using low and high background rates, respectively, for calculation of the expected cases in the denominator and all observed cases with the specified PT in the numerator. Sensitivity analyses were repeated in Table 4 and Table 5 using low and high background rates, respectively, and only observed cases that met the ADEM Brighton Collaboration[2] certainty levels 1-3 in the numerator. The O/E results are reported globally overall for all ages, and then further stratified by age in the US and EEA countries because these regions made detailed vaccine administration data publicly available in a standardised, central online location.

The overall expected case counts of ADEM were estimated using a range of population -based background incidence rates from the vACCine covid-19 monitoring readinESS (ACCESS) project.[3] The conservative, low-range background rate source was Willame C et al (2023),[4] which presents pooled age- and sex-stratified results for selected AESIs according to the ACCESS recommendations. These rates represent the narrow ACCESS clinical definitions and are for the time periods 2017-2019. Sex-stratified rates in the supplementary materials of the manuscript were averaged to obtain the age-specific rates. This source reported a pooled incidence rate for ADEM of 0.21/100,000 person-years overall. Sensitivity analyses used higher-range ACCESS background rates reported by the Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) database, which provided an incidence rate of 0.51/100,000 person-years overall.[5]

The expected case counts of ADEM were estimated based on these background incidence rates, the estimated number of Pfizer-BioNTech vaccine doses through 15 May 2023, and the length of risk windows. COVID-19 vaccine administrations were limited to the Pfizer-BioNTech vaccine when available.[6,7,8] For countries where the Pfizer-BioNTech COVID-19 vaccine is authorised, but manufacturer stratified data were not available, the doses administered were assumed to be divided equally by the number of brands of vaccines authorised during that period. The estimate of administered doses may not reflect COVID-19 vaccine doses administered in countries that did not publicly report administration rates.

Results

Based on the selected background rates and the estimated number of exposure PY through 15 May 2023 after any dose of Pfizer-BioNTech COVID-19 vaccines, O/E ratios were well below 1 overall for all ages combined globally for both risk windows of 21- and 42-days using the low and high background rates (Table 2, Table 3, Table 4, Table 5). However, results varied by age-groups depending upon the background rate and Brighton Collaboration level of certainty used to define cases.

In Table 2, using the low background rate and all ADEM cases, O/E ratios were >1 for three age strata (18-24 years, 25-49 years, and 50-59 years) in the 21- day risk window. Only the result for 25-49 years was statistically significant. In the 42-day risk window, only the O/E ratio for 25-49 years of age was >1, but this finding was not statistically significant.

Table 2. Observed to Expected (O/E) Ratio for all Spontaneously Reported Cases of ADEM Through 15 May 2023, US and EEA, Low-Range Background Rate

Stratification	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY [4]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-day							
US/EEA							
<5 years	0	107,635	0.76	0.8	0.000	0.000	3.662
5-11 years	2	1,968,738	0.76	15.0	0.134	0.016	0.483
12-17 years	13	3,492,152	0.76	26.5	0.490	0.261	0.838
18-24 years	12	4,921,175	0.24	11.8	**1.016**	0.525	1.775
25-49 years	73	21,096,203	0.19	40.1	**1.821**	**1.428**	**2.290**
50-59 years	27	10,785,213	0.17	18.3	**1.473**	0.970	2.143
60-69 years	17	10,802,000	0.21	22.7	0.749	0.437	1.200
70+ years	19	15,030,672	0.16	24.0	0.790	0.476	1.234
Overall Global	163	147,014,176	0.21	308.7	0.528	0.450	0.616
42-day							
US/EEA							
<5 years	0	157,393	0.76	1.2	0.000	0.000	2.504
5-11 years	2	2,974,318	0.76	22.6	0.088	0.011	0.320
12-17 years	15	5,453,801	0.76	41.4	0.362	0.203	0.597
18-24 years	14	7,875,120	0.24	18.9	0.741	0.405	1.243
25-49 years	78	34,131,249	0.19	64.8	**1.203**	0.951	1.501
50-59 years	27	18,001,769	0.17	30.6	0.882	0.581	1.284
60-69 years	17	18,681,983	0.21	39.2	0.433	0.252	0.694
70+ years	22	25,968,815	0.16	41.6	0.529	0.332	0.802
Overall Global	175	242,065,797	0.21	508.3	0.344	0.295	0.399

CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States

Source: Willame C, 2023.[4] Background incidence rates by age calculated as follows: <5, 5-11, 12-17 years=0-19 years from source; 18-24 years=20-29 years from source, 24-49 years=Average of 20-29 years, 30-39 years, and 40-49 years from source; 50-59=50-59 years from source; 60-69=60-69 from source; 70+ years = Average of 70-79 years and 80+ years from source.

Table 3. Observed to Expected (O/E) Ratio for all Spontaneously Reported Cases of ADEM Through 15 May 2023, US and EEA, High-Range Background Rate

Stratification	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY [5]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-day							
US/EEA							
<5 years	0	107,635	1.42	1.5	0.000	0.000	1.960
5-11 years	2	1,968,738	1.42	28.0	0.072	0.009	0.258
12-17 years	13	3,492,152	1.42	49.6	0.262	0.140	0.448
18-24 years	12	4,921,175	0.84	41.3	0.290	0.150	0.507
25-49 years	73	21,096,203	0.30	63.3	**1.153**	0.904	1.450
50-59 years	27	10,785,213	0.26	28.0	0.963	0.635	1.401
60-69 years	17	10,802,000	0.22	23.8	0.715	0.417	1.145
70+ years	19	15,030,672	0.30	45.1	0.421	0.254	0.658
Overall Global	163	147,014,176	0.51	749.8	0.217	0.185	0.253
42-day							
US/EEA							
<5 years	0	157,393	1.42	2.2	0.000	0.000	1.340
5-11 years	2	2,974,318	1.42	42.2	0.047	0.006	0.171
12-17 years	15	5,453,801	1.42	77.4	0.194	0.108	0.319
18-24 years	14	7,875,120	0.84	66.2	0.212	0.116	0.355
25-49 years	78	34,131,249	0.30	102.4	0.762	0.602	0.951
50-59 years	27	18,001,769	0.26	46.8	0.577	0.380	0.839
60-69 years	17	18,681,983	0.22	41.1	0.414	0.241	0.662
70+ years	22	25,968,815	0.30	77.9	0.282	0.177	0.428
Overall Global	175	242,065,797	0.51	1234.5	0.142	0.122	0.164

CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States

Source: ACCESS FISABIO.[5] Background incidence rates by age calculated as follows: <5, 5-11, 12-17 years = 0-19 years from source; 18-24 years = 20-29 years from source, 24-49 years=Average of 20-29 years, 30-39 years, and 40-49 years from source; 50-59 = 50-59 years from source; 60-69 = 60-69 from source; 70+ years = Average of 70-79 years and 80+ years from source.

In Table 3 using the high background rate estimate and all ADEM cases, only the O/E ratio for the 25-49 years age strata was >1 in the 21-day risk window, but this finding was not statistically significant.

Table 4. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of ADEM Meeting Brighton Collaboration Levels 1-3 Through 15 May 2023, US and EEA, Low-Range Background Rate

Events	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21 Day							
US/EEA							
<5 years	0	107,635	0.76	0.8	0.000	0.000	3.662
5-11 years	2	1,968,738	0.76	15.0	0.134	0.016	0.483
12-17 years	3	3,492,152	0.76	26.5	0.113	0.023	0.330
18-24 years	7	4,921,175	0.24	11.8	0.593	0.238	1.221
25-49 years	42	21,096,203	0.19	40.1	1.048	0.755	1.416
50-59 years	12	10,785,213	0.17	18.3	0.654	0.338	1.143
60-69 years	6	10,802,000	0.21	22.7	0.265	0.097	0.576
70+ years	6	15,030,672	0.16	24.0	0.249	0.092	0.543
Overall Global	78	147,014,176	0.21	308.7	0.253	0.200	0.315
42 Day							
US/EEA							
<5 years	0	157,393	0.76	1.2	0.000	0.000	2.504
5-11 years	2	2,974,318	0.76	22.6	0.088	0.011	0.320
12-17 years	5	5,453,801	0.76	41.4	0.121	0.039	0.282
18-24 years	9	7,875,120	0.24	18.9	0.476	0.218	0.904
25-49 years	46	34,131,249	0.19	64.8	0.709	0.519	0.946
50-59 years	13	18,001,769	0.17	30.6	0.425	0.226	0.726
60-69 years	6	18,681,983	0.21	39.2	0.153	0.056	0.333
70+ years	8	25,968,815	0.16	41.6	0.193	0.083	0.379
Overall Global	89	242,065,797	0.21	508.3	0.175	0.141	0.215

CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States

Source: Willame C, 2023.[4] Background incidence rates by age calculated as follows: <5, 5-11, 12-17 years=0-19 years from source; 18-24 years = 20-29 years from source, 24-49 years=Average of 20-29 years, 30-39 years, and 40-49 years from source; 50-59 = 50-59 years from source; 60-69=60-69 from source; 70+ years = Average of 70-79 years and 80+ years from source.

Table 5. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of ADEM Meeting Brighton Collaboration Levels 1-3 Through 15 May 2023, High-Range Background Rate

Events	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21 Day							
US/EEA							
<5 years	0	107,635	1.42	1.5	0.000	0.000	1.960
5-11 years	2	1,968,738	1.42	28.0	0.072	0.009	0.258
12-17 years	3	3,492,152	1.42	49.6	0.060	0.012	0.177
18-24 years	7	4,921,175	0.84	41.3	0.169	0.068	0.349
25-49 years	42	21,096,203	0.30	63.3	0.664	0.478	0.897
50-59 years	12	10,785,213	0.26	28.0	0.428	0.221	0.748
60-69 years	6	10,802,000	0.22	23.8	0.252	0.093	0.550
70+ years	6	15,030,672	0.30	45.1	0.133	0.049	0.290
Overall Global	78	147,014,176	0.51	749.8	0.104	0.082	0.130
42 Day							
US/EEA							
<5 years	0	157,393	1.42	2.2	0.000	0.000	1.340
5-11 years	2	2,974,318	1.42	42.2	0.047	0.006	0.171
12-17 years	5	5,453,801	1.42	77.4	0.065	0.021	0.151
18-24 years	9	7,875,120	0.84	66.2	0.136	0.062	0.258
25 - 49 years	46	34,131,249	0.30	102.4	0.449	0.329	0.599
50 -59 years	13	18,001,769	0.26	46.8	0.278	0.148	0.475
60 - 69 years	6	18,681,983	0.22	41.1	0.146	0.054	0.318
70+ years	8	25,968,815	0.30	77.9	0.103	0.044	0.202
Overall Global	89	242,065,797	0.51	1234.5	0.072	0.058	0.089

CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United States

Source: ACCESS FISABIO.[5] Background incidence rates by age calculated as follows: <5, 5-11, 12-17 years=0-19 years from source; 18-24 years = 20-29 years from source, 24-49 years=Average of 20-29 years, 30-39 years, and 40-49 years from source; 50-59=50-59 years from source; 60-69=60-69 from source; 70+ years = Average of 70-79 years and 80+ years from source.

After including only ADEM cases meeting Brighton Collaboration certainty levels 1-3 in the numerator, the O/E ratio was >1 for ages 25-49 using the low background rate, but the result was not statistically significant (Table 4).

All O/E ratios were <1 using the high background rate and including only the cases meeting Brighton Collaboration certainty levels 1-3 in the numerator (Table 5).

These results suggest that the number of ADEM cases post-vaccination is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines when using a range of background rates from pre-2020 timeframe and including only cases meeting Brighton Collaboration certainty levels 1-3.

Rapporteur assessment comment:

The O/E analyses performed by the MAH were based on the selected (ACCESS) background rates and the estimated number of exposure through 15 May 2023.

The O/E ratio was (only) for the age group 25-49 above 1 and statistically significant (1.8 [95%CI 1.4;2.3]) using a 21-day risk window and low-range background rate of ADEM, indicating that there are more ADEM cases observed after vaccination in persons aged 25-49 years than expected.

When the MAH used only the Brighton Collaboration certainty levels 1-3 of the reported ADEM cases in the O/E analysis in persons aged 25-49 years, (the details of assignment of BC levels not provided by the MAH) the O/E ratio was 1 and not statistically significant (1.0 [95%CI 0.8;1.4]).

Limitations

There are several limitations to O/E analyses for signal detection. The observed case counts are likely to be underestimated due to the spontaneous reporting nature with passive safety surveillance. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous reporting systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition. Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association. Furthermore, some observed cases were missing age and/or TTO information. Missing values were imputed based on the known distribution of observed cases with these characteristics.

Regarding the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Also, country-specific dose volume data are dynamic and specific to the date of download from the websites, and subject to retrospective updates at the country level.[9] The expected count also assumes the background rates of the COVID-19 vaccinated population in the absence of vaccination is the same as those in the historical cohort. The background rates used in these analyses are derived from studies prior to the COVID-19 era and in individual countries. It is possible that the delivery of healthcare, population demographics, and the underlying health status of the populations used for the background rate estimates differ from those expected in the vaccinated population.

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

Rapporteur assessment comment:

The limitations of the O/E analyses are acknowledged.

Literature review

A cumulative search of literature was conducted through 14 Nov 2023 to identify articles describing BNT162b2 and the MedDRA preferred term (PT) Acute disseminated encephalomyelitis in the Medline, Biosis and Embase database. There were 5 relevant literature articles, and the associated case reports are summarised in the safety database review section of this review.

Sturkenboom et. al[10] conducted a retrospective cohort study including subjects from 01 Jan 2020 to 31 Oct 2021, in primary and/or secondary health care data from 4 European countries: Italy, Netherlands, UK, and Spain. The cohort comprised 25,720,158 subjects who had received first and second doses of Pfizer, AstraZeneca, Moderna or Janssen COVID-19 vaccines. Twenty-nine of the author-identified AESIs, including ADEM, were analysed. The incidence of ADEM was estimated as very rare with an incidence of 1.05 per 100,000 PY, and Poisson regression did not show an association between ADEM and any of the vaccine studied, including Comirnaty.

Nabizadeh et. al[11] conducted a comprehensive systematic review of ADEM following COVID-19 vaccination using 3 databases: PubMed, Scopus, and Web of Science. Studies that reported the occurrence of ADEM after COVID-19 vaccination were eligible for inclusion in the authors' publication as were observational studies, case reports, and case series that reported cases of ADEM with sufficient detail to confirm the clinical diagnosis. A total of 159 studies were retrieved from the databases after duplicate removal. Twenty studies with a total of 54 cases were included. Among included patients, 45 (85.1 %) developed ADEM after the first dose of the COVID-19 vaccine, and 7 (12.9 %) cases after the second dose. The median time interval between vaccination and neurological symptoms was 14 days (range from 12 hours to 63 days). Twelve (22.2 %) patients experienced symptoms of muscle weakness, 10 (18.5 %) had loss of consciousness, 9 (16.6 %) patients had urinary complaints, 9 (16.6 %) had visual impairments, and 5 (9.2 %) experienced a seizure. Four (13.8 %) patients died and 46 (85.1%) had clinical improvement; improvement in brain MRI was observed in 44 (81.4 %) patients. The authors concluded that it is not clear whether ADEM could be a potential complication of COVID-19 vaccination based on the current evidence.

Kim et. al[12] conducted a disproportionality analyses of CNS demyelinating disease following COVID-19 vaccination in the Vigibase compared with those cases for the entire database and for all other viral vaccines. The authors identified 220 cases of ADEM. The authors found a weak association between mRNA-based Covid vaccines and ADEM (IC025=0.78, ROR025=1.83) using a broad definition of ADEM and the entire ADR database (including AEs from all vaccine and all medications), however, the mRNA-based Covid vaccines did not have a signal of disproportionality for ADEM ((IC025=−1.45, ROR025=0.24) when using a broad definition and the AEs database for all other viral vaccines (excluding medication-related events and vaccine other than viral vaccines).

Li et. al[13] conducted a descriptive cohort study in public healthcare service settings in Hong Kong. This study included around 3.9 million Hong Kong residents, of which 1,122,793 received at least 1 dose of vaccine (BNT162b2: 579,998; CoronaVac: 542,795), and 721,588 completed 2 doses (BNT162b2: 388,881; CoronaVac: 332,707). ADEM was 1 of 16 pre-specified conditions studied. Within 28 days following vaccination the cumulative incidence for ADEM per 100,000 persons was 0 after BNT162b2 Dose 1 and 0.55 after BNT162b2 dose 2. The authors concluded that the age-standardised incidence rate was not significantly higher than the non-vaccinated individuals.

Frontera et.al[14] utilised publicly available data from the US VAERS collected between 01 Jan 2021 and 14 Jun 2021 to identify neurological events following mRNA or adenovirus vector COVID-19 vaccine

administration. All free text events that were reported within 42 days of COVID-19 vaccine administration were manually reviewed and grouped into 36 individual neurological diagnostic categories including ADEM. For the 3 authorised COVID-19 vaccines, 306,907,697 doses were administered during the study timeframe. The authors estimated the number of events of ADEM per 1,000,000 vaccine doses as 0.06 for BNT162b2. The authors also conducted an observed versus expected analysis for BNT162b2 using pre-COVID background incidence rates of ADEM in the US which was 0.97 (95% CI 0.46-1.78), indicating that the observed incidence of ADEM was not higher than expected.

Rapporteur assessment comment:

Through 14 Nov 2023, 5 relevant articles were retrieved by the MAH:

1. The study of Sturkenboom et al.[10] showed in 4 EU countries no association between ADEM and any of the vaccine studied, including Comirnaty.
2. The study of Nabizadeh et al.[11] concluded in the executed systematic review that it is not clear whether ADEM could be a potential complication of COVID-19 vaccination.
3. The study of Kim et al.[12] reported in Vigibase that the mRNA-based Covid vaccines did not have a signal of disproportionality for ADEM.
4. The study of Li et al.[13] showed in Hong Kong that for ADEM the age-standardised incidence rate in vaccinated persons was not significantly higher than the non-vaccinated persons.
5. The study of Frontera et al,[14] performed an O/E analysis in VAERS and indicated that the observed number of ADEM cases was not higher than expected.

Based on the information from the retrieved literature, no new important safety information concerning ADEM after Comirnaty exposure could be identified.

Cumulative review of ADEM cases

A cumulative review of ADEM cases within Pfizer's global safety database up to the DLP of the PSUR (18 Jun 2023) was performed. The database was searched for all BNT162b2; BNT162b2/BNT162b2 OMI BA.1; BNT162b2/BNT162b2 OMI BA.4-5 and BNT162b2 OMI cases reporting the MedDRA version 26.0 PT Acute disseminated encephalomyelitis (ADEM). The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

Rapporteur assessment comment:

The limitations of post-marketing AE reporting are acknowledged.

One hundred ninety-nine cases were cumulatively retrieved out of 1,839,454 total cases; all were serious and 8 were fatal. The large majority of cases (191) were reported for BNT162b2; 7 were reported for BNT162b2/BNT162b2 OMI BA.4-5 and 1 was reported for BNT162b2/BNT162b2 OMI BA.1. Fourteen of the reports were from literature articles and the remaining were spontaneously reported; none were from the Pfizer/BNT clinical studies. Countries reporting >5 cases were: Japan (84), Germany (35), UK (11), US and France (10), Italy (8), and Austria (6). The Brighton Collaboration case definition, guidelines and decision tree for ADEM were used in the review of cases to designate BC level of diagnostic certainty (Level 1 is highest level of diagnostic certainty) for each of the 199 cases (see Table 6).

Table 6. Brighton Criteria Classification of potential ADEM cases

BC Level	Number of Cases
1	13 (12 individuals)
2	78
3	26
4	44
5	38 (37 individuals)
TOTAL	**199 (197 individuals)**

Level 1 is the highest level of diagnostic certainty and Level 3 is the lowest level. Level 3 cases lack brain MRI information. Level 4 cases are those in which ADEM is reported but insufficient information is provided to meet the case definition. Level 5 cases are those that are not a case of ADEM based on the case details provided.

Per the BC decision tree, exclusion criteria for ADEM cases are as follows: other diagnosis confirmed, brain MRI findings inconsistent with ADEM, recurrence or relapse 3 months or longer after symptomatic nadir and proven acute infectious aetiology.

It should be acknowledged that BC criteria are most useful when applied to clinical study reports which, in comparison to spontaneous reports, generally are of a higher scientific quality and have a higher likelihood of responses to follow-up queries.

The remaining review is focused on the BC Level 1 and 2 reports because they have the highest level of diagnostic certainty. For these reports, the WHO-UMC causality assessment system was applied as requested. It should be noted that the WHO-UMC system was designed for application to AEs following exposure to medications, not vaccines. Dechallenge contributes to the WHO-UMC causality judgement, in particular for "certain" and "probable/likely" causality assessments. Due to the nature of vaccines, the concept of dechallenge is not a criterion that can be applied. This limits its use as a causality tool. The WHO Causality assessment of an adverse event following immunisation[15] notes that causality assessment of a case is meant to assist in determining the level of certainty of such an association. The framework states that a case with adequate information may ultimately be classified into 1 of 3 categories: consistent causal association to immunisation, indeterminate, or inconsistent causal association to immunisation.

Additionally, it is notable that ADEM is a rare disorder with an incompletely understood pathogenesis and no specific diagnostic tests. These features are apt to increase the likelihood of ADEM being attributed to vaccination and indeed, historically, many vaccines have had cases of ADEM reported following their administration. However, a large US Vaccine Safety Datalink study in 2016 16failed to show a statistically increased risk of ADEM in almost 64 million vaccine doses, to any vaccine except Tdap (and this was based on 2 cases).

Rapporteur assessment comment:

Through 18 Jun 2023, 199 cases reporting ADEM were retrieved in MAH's global safety database.

The majority (n=191, 96%) were reported for BNT162b2 original.

Thirteen cases (12 patients) were classified by the MAH as BC level 1, 78 as BC level 2, 26 as BC level 3, 44 as BC level 4 and 38 cases (37 patients) as BC level 5.

BC Level 1 reports

Reports qualify as Level 1 if they do not describe specific exclusion criteria and if they include brain histology describing diffuse or multifocal demyelination or if they include even 1 of BC-required CNS signs and symptoms, brain MRI with white matter lesions and no recurrences or relapses for 3 months or longer after a symptomatic nadir. There are 13 Level 1 cases describing 12 patients. The cases described 7 female and 5 male patients 13 Level 1 cases describing 12 patients. The cases described 7 female and 5 male patients, ranging in age from 25 to 73 years (mean 44.9); all were serious and none were fatal. Time from vaccination to onset of the event of interest ranged from 3 to 132 days (not specified in 1 case) and outcome was recovered/recovering/recovered with sequelae in 9, not recovered in 1 and unknown in 1 report.

Table 7 (not reproduced here) showed the ADEM cases considered BC level 1, including MAH's causality assessment.

Rapporteur assessment comment:

MAH's causality assessment of the 12 ADEM patients considered BC level 1 is accepted:

Table 7 ADEM cases BC level 1.pdf

In 6 patients (4 females and 1 male; 3 patients between 25-49 years old and 3 patients >49 years old) the ADEM was considered possible related to Comirnaty exposure, in 5 patients unlikely related, and 1 patient was unassessable. However, detailed case descriptions were not provided (only case summaries of the 12 patients considered ADEM BC level 1), which hampers assessor's causality assessment.

BC Level 2 reports

Reports qualify as Level 2 if they do not describe the specific exclusion criteria mentioned above and if they describe even 1 of the BC-required signs/symptoms, an MRI with white matter lesions and <3 months of follow-up to capture any recurrence or relapse. Because follow-up for level 2 reports is <3 months following the nadir of symptoms, there is an uncertainty whether or when a recurrence may occur (signifying the diagnosis is not ADEM); this makes it difficult to assess a causality higher than "possible" since the diagnostic certainty is questionable. There are 78 Level 2 cases.

Thirty-one of the 78 Level 2 reports were assessed as having an unlikely causality:

- Twenty-three of the 31 provided information supportive of an alternate explanation for the described neurological abnormalities (potential ADEM). These included infectious pathogens (eg, H. zoster, EBV, non-specific pre-occurring viral infection) malignancies (eg, CNS malignant lymphoma, Chronic lymphocytic leukemia, malignancy requiring previous whole brain radiation therapy) and medical histories of other brain disorders (eg, multiple sclerosis, cardioembolic

stroke, venous malformation, post-infectious rhombencephalitis, idiopathic myelitis, unspecified baseline motor and sensory aberrations).

- Eight of the 31 did not describe time to onset or provided a time to onset that was distal to vaccination (eg, 36 to 75 days).

Nine of the 78 Level 2 reports were assessed as having a conditional causality. These cases included a competing diagnosis to ADEM with more data needed for a proper assessment of the diagnosis. The most common other diagnoses noted were demyelinating disorders like transverse myelitis and multiple sclerosis.

Twelve of the 78 Level 2 reports were assessed as having an unassessable causality. Ten of them lacked sufficient information about medical history or the work-up (including MRI and disease course) that they could not be judged. Two of the 12 cases described neurological events that occurred after Dose 4 in patients who had had an interchange of different COVID-19 vaccines.

The remaining 26 Level 2 cases are described in Table 8 (not reproduced here). The cases described 15 female and 11 male patients, ranging in age from 6 to 83 years (mean 44.8); all were serious and none were fatal. Time from vaccination to onset of the event of interest ranged from 1 to 30 days and outcome was recovered/recovering/recovered with sequelae in 19, not recovered in 3 and unknown in 4 reports.

Rapporteur assessment comment:

Of the 78 BC level 2 ADEM cases, 31 cases were considered unlikely related to Comirnaty exposure and 21 cases unassessable. However, detailed case descriptions were not provided which hampers assessor's causality assessment.

MAH's causality assessment of the 26 remaining ADEM patients considered BC level 2 is accepted:

Table 8 ADEM cases BC level 2.pdf

In 24 patients (14 females and 10 males; 6 patients <25 years old, 7 patients between 25-49 years old, 11 patients >49 years old) the ADEM was considered possible related to Comirnaty exposure and in 2 patients unlikely related. However, detailed case descriptions were not provided (only case summaries of the 26 patients considered ADEM BC level 2), which hampers assessor's causality assessment.

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 EB05>2 report is a product specific Bayesian (Multi-Item Gamma Poisson Shrinker) computer-generated statistical data mining report, which provides data on product or AE combinations for which there is an emerging statistic of disproportionate reporting, using an EB05>2 as the metric or threshold and using a subtraction option to omit the most previously reviewed events from subsequent for more in-depth review.

On cumulative review of the EB05 report for ADEM, the EB05 scores were as follows:

Table 9. EB05 scores

PT	BNT162b2	BA.1	BA.4/5	XBB 1.5
ADEM	1.14	0.2	1.45	-

Summary: The EB05 is less than the EB05□2 threshold, thus indicating no emerging statistical signal for the selected PT.

Rapporteur assessment comment:

There was no signal for ADEM following MAH's routine signal detection activities.

MAH's discussion and conclusion

The results of the updated O/E analysis suggest that the number of ADEM cases post-vaccination is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines when using a range of background rates from pre-2020 timeframe and including only cases meeting Brighton Collaboration certainty levels 1-3.

The review of the available scientific literature showed that the incidence of ADEM after vaccination is very rare and a causal relationship with vaccination with BNT162b2 is not supported. One study[14] conducted an observed versus expected analysis for BNT162b2 using pre-COVID background incidence rates of ADEM in the US which was 0.97 (95% CI 0.46-1.78), indicating that the observed incidence of ADEM was not higher than expected in the absence of vaccination with BNT162b2.

The search of the safety database using the PT ADEM revealed a total of 199 cases out of >1.8 million COVID-19 vaccine AE reports in the global safety database. The majority were reported for BNT162b2 original, 13 cases (12 individuals) were classified as BC 1, 78 as BC 2, 26 as BC 3, 44 as BC 4 and 38 cases (37 individuals) as BC 5.

Six cases of BC 1 and 24 cases of BC 2 were classified as possibly related, mainly based on timing after immunisation. Given that ADEM is a diagnosis of exclusion, many cases assessed as possible do not provide full work-up details that would allow exclusion of all other possible causes of ADEM therefore the "possibly related" assessments are considered to be quite conservative and should be regarded in the context of the totality of the data on ADEM and Comirnaty. No cases were assessed to be probably nor certainly related to vaccination with BNT162b2.

Routine statistical reports did not show an emerging statistical signal for ADEM.

The totality of data reviewed does not provide enough evidence to support the conclusion of a causal relationship between vaccination with BNT162b2 and the occurrence of ADEM, therefore the MAH does not consider any Product Information nor RMP updates are necessary, and this topic will continue to be monitored with routine pharmacovigilance.

Rapporteur assessment comment:

<u>O/E analyses of ADEM through 15 May 2023</u>

The O/E ratio was only for the age group 25-49 above 1 and statistically significant (1.8 [95%CI 1.4;2.3]) using a 21-day risk window and low-range background rate of ADEM, indicating that there are more ADEM cases in persons aged 25-49 years observed after vaccination than expected. However, when using only the Brighton Collaboration certainty levels 1-3 of the reported ADEM cases in the O/E analyses, the O/E ratio for the age group 25-49 was 1 and not statistically significant (1.0 [95%CI 0.8;1.4]).

<u>Literature through 14 Nov 2023</u>

No new important safety information concerning ADEM after Comirnaty exposure could be identified from the retrieved 5 relevant articles.

<u>Cumulative review of ADEM cases through 18 Jun 2023</u>

199 cases reporting ADEM were retrieved in MAH's global safety database. Thirteen cases (12 patients) were classified by the MAH as BC level 1, 78 as BC level 2, 26 as BC level 3, 44 as BC level 4 and 38

cases (37 patients) as BC level 5.

Causality assessment was performed by the MAH for the ADEM cases considered BC level 1 (12 patients) or BC level 2 (78 patients):

BC Level 1 reports – in 6 patients (of which 3 patients 25-49 years old) the ADEM was considered possible related to Comirnaty exposure, in 5 patients unlikely related, and 1 patient was unassessable.

BC Level 2 reports – in 24 patients (of which 7 patients 25-49 years old) the ADEM was considered possibly related to Comirnaty exposure, in 33 patients unlikely related, and in 21 patients was unassessable.

Routine signal detection

There was no signal for ADEM following MAH's routine signal detection activities.

In conclusion, based on the data provided by the MAH there is no evidence for a causal relationship between Comirnaty exposure and ADEM. Cases reporting ADEM should continue to be monitored with routine pharmacovigilance.

Issue solved

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7. Comments from member states

MS1 and MS2

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

MS3

MS3 fully supports the PRAC rapporteur assessment report and conclusion, especially regarding the evaluation of HLH and the request to continue the monitoring.

Rapporteur assessment comment:
The endorsements of the Comirnaty PSUR assessment are appreciated.

PERIODIC SAFETY UPDATE REPORT #5
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (nucleoside modified) (BNT162b2)[1]

BNT162b2 Original[2] – BNT162b2 Bivalent (Original and Omicron BA.1) – BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)

ATC CODE: J07BN01

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD)[3]: 19 DECEMBER 2020

EUROPEAN UNION REFERENCE DATE (EURD): 19 DECEMBER 2020

INTERVAL COVERED BY THIS REPORT:

19 DECEMBER 2022 through 18 JUNE 2023

DATE OF THIS REPORT: 17 AUGUST 2023

SIGNATURE: [redacted] **Date: 17 AUGUST 2023**

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

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

[2] Monovalent including the following variant-adapted vaccines BNT162b2 (B.1.351), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7) and BNT162b2 (B.1.1.529).

[3] Earliest conditional approval date.

EXECUTIVE SUMMARY

This is the 5th Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (Coronavirus disease 2019 messenger ribonucleic acid) (nucleoside modified) COMIRNATY®, also referred to as BNT162b2 Original (tozinameran),[4] BNT162b2 (Original and Omicron BA.1) (tozinameran/riltozinameran) or BNT162b2 (Original and Omicron BA.4/BA.5) (tozinameran/famtozinameran),[5] covering the reporting interval 19 December 2022 through 18 June 2023.

COMIRNATY® approved presentations include:

Original (BNT162b2)

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

Bivalent (Original + Omicron)

Original +

- Tris/Sucrose BA.1 (15/15 micrograms/ dose) – for age 12 years and older [Grey cap];
- Tris/Sucrose (BA.4/BA.5 15/15 micrograms/ dose) – for age 12 years and older [Grey cap];[6]
- Tris/Sucrose (BA.4/BA.5 15/15 micrograms/ dose) – for age 12 years and older [Light grey cap];[7]
- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/ dose) – for age 5 years to <12 years [Orange cap];

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

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

[6] Multi-dose cap vials.

[7] Single-dose cap vials first approved in European Union (EU) after data lock point (DLP) on 22 June 2023.

- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/dose) – for age 5 years to <12 years [Dark blue cap];[8]
- Tris/Sucrose BA.4/BA.5 (5/5 micrograms/dose) – for age 5 years to <12 years [Light blue cap];[9]
- Tris/Sucrose BA.4/BA.5 (1.5/1.5 micrograms/dose) – for age 6 months to <5 years [Maroon cap].[10]

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

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

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

[8] Multi-dose cap vials, first approved in EU after DLP on 22 June 2023.

[9] Single-dose cap vials, first approved in European Union (EU) after data lock point (DLP) on 22 June 2023.

[10] First approved in EU after DLP on 22 June 2023.

Age group	**12 years and older**					**5 through 11 years**				**6 months through 4 years**	
Presentation	PBS sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose
Name	Comirnaty	Comirnaty	Comirnaty Original/ Omicron BA.1	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5[10]
Dose	30 mcg (with dilution)	30 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	10 mcg (with dilution)	5/5 mcg (with dilution)	5/5 mcg (no dilution)	5/5 mcg (no dilution)	3 mcg (with dilution)	1.5/1.5 mcg (with dilution)
Vial cap colour	Purple	Grey	Grey	Grey	Light Gray[7]	Orange	Orange	Dark blue[8]	Light blue[9]	Maroon	Maroon
Dose Volume	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL
Dose per vial	6 doses per vial (after dilution)	6 doses per vial	6 doses per vial	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)
Route of Administration	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM

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

Cumulatively, it is estimated that 69,372[11] participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with:

- 63,843 participants exposed to BNT162b2;
- 8851 participants exposed to clinical candidates developed as variant and variant-adapted vaccines based on BNT162b2 (BNT162b2 [B.1.351], BNT162b2 [B.1.1.7 + B.1.617.2], BNT162b2 [B.1.617.2], BNT162b2 [B.1.1.529], BNT162b2 [B.1.1.7], BNT162b2/ BNT162b2 Omi [1815], BNT162b2 original/ BNT162b2 Omi BA.1 [102], BNT162b2 original/ BNT162b2 Omi BA.2 [104], and BNT162b2 original/ BNT162b2 Omi BA.4/BA.5 [2965]);
- 633 participants exposed to other early development candidates (including BNT162a1 [30], BNT162b1 [411], BNT162b3 and BNT162c2 [96 participants each]).

There were 2 participants exposed to blinded therapy, 6352 to placebo, and 7 to seasonal inactivated influenza vaccine (SIIV)/placebo.

BNT162b2 is also being utilised in 3 other Pfizer clinical development programs: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026[12], 796 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine in the clinical study C5261001[13] and 757 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine in the clinical study C5481001.[14]

From the receipt of the first temporary authorisation for emergency supply on 01 December 2020[15] through 18 June 2023, approximately 4,615,732,025 doses of BNT162b2 (original and bivalent) were shipped from BioNTech and Pfizer worldwide. Considering the current status of the vaccination schedule and the availability of only partial data published on the European Centre for Disease Prevention and Control (ECDC) websites for doses of BNT162b2 vaccines (original and bivalent) administered in the EU- European economic area (EEA) countries, it is no longer applicable to estimate the number of doses administered from those shipped. Out of the cumulative number of shipped doses,

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

[12] 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.

[13] 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.

[14] A phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of combined vaccine candidates against infectious respiratory illnesses, including COVID-19 and RSV, in healthy individuals.

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

4,154,348,225 were original and bivalent adult[16] presentations (including PBS and Tris/Sucrose); 461,383,800 were original and bivalent paediatric[17] presentations; 686,454,460 were bivalent vaccines of which 21,075,900 were for paediatric presentations; 2,446,319,885 doses of BNT162b2 (original and bivalent) were shipped to rest of world (ROW).[18]

During the current reporting interval (19 December 2022 through 18 June 2023), approximately 257,566,530 doses of BNT162b2 original and bivalent vaccines were shipped worldwide. Out of the doses shipped during the reporting period, 29,554,970 were original and bivalent adult[16] presentations (including PBS and Tris/Sucrose); 57,416,700 were original and bivalent paediatric[17] presentations; 170,594,860 were bivalent vaccines of which 10,112,000 were for paediatric presentations; 183,755,610 doses of BNT162b2 (original and bivalent) were shipped to ROW.[19]

Additionally, as per data provided by contractual party (CP) in Hong Kong, Macau, and Taiwan, 32,269,283 doses of original BNT162b2 and bivalent Omi BA.4/BA.5 were administered cumulatively through the DLP, and 909,044 doses were administered from 19 December 2022 through the DLP.

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

Marketing Authorisation Holders of BNT162b2 original and BNT162b2 Bivalent Vaccines

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held		
	BNT162b2 original	BNT162b2 Bivalent (original and Omicron BA.1)	BNT162b2 Bivalent (original and Omicron BA.4/BA.5)
BioNTech	58	37	47
Pfizer	38	8	24[a]
Fosun Pharma	1	0	1
Local MoH	3	0	0
Local Government	3	1	1
Hemas (CP)	1	0	0
All	**104**	**46**	**73**

a. BNT162b2 Bivalent (original and Omicron BA.4/BA.5) presentation was approved in Colombia after DLP in July 2023.

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

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

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

[19] CP data are not included in the reported amount.

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

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

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 21.0 dated 25 May 2023, in effect at the end of the reporting period. Three (3) previous CDS versions (version 20.0 dated 22 February 2023, version 19.0 dated 22 December 2022 and version 18.0 dated 05 December 2022) were also in effect during the reporting period. No safety-related changes were made to CDS version 20.0.

Safety-related changes included updates of the following Sections: 4.2. Posology and method of administration (CDS version 21.0), 4.8. Undesirable effects (CDS versions 21.0 and 19.0), 5.1 Pharmacodynamic properties (CDS version 19.0), Appendix A and Appendix B (CDS versions 21.0 and 19.0).

During the reporting period, the following signals were evaluated:

Signals determined not to be risks: Myositis, Pemphigus and Pemphigoid.

Ongoing signals: Sensorineural Hearing Loss, Retinal Vascular Occlusion, and Menstrual Irregularities.

During the reporting period, one action was taken with respect to BNT162b2 for safety reasons. In Switzerland the approval for bivalent Omi BA.1 was not obtained for individuals 12 to less than 18 years because there was no clinical data available for that population. Because country-specific packaging was not available, Switzerland received EU packaging that displayed age on the carton as 12+ (as per EU MA). Therefore, an information Letter (in English) explaining the discrepancy between age on the carton and age approved by Swissmedic was provided with each shipment. In addition, the MAH provided electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

Requests addressed in this PSUR were received from the European Medicines Agency (EMA), WHO, and 3 Health Authorities (HA) (Health Canada, Medsafe [New Zealand Medicines and Medical Devices Safety Authority], and Therapeutic Goods Administration, Australia [TGA]). The Pharmacovigilance Risk Assessment Committee (PRAC) requests were received in Assessment Reports (ARs) of PSUR #4 and of signals. The WHO requests were received in the EUL Procedure. Topics covered in these requests are summarised in the table below.

Source	Request(s)
EMA PSUR#4 AR (19 June 2022 through 18 December 2022)	Report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases is below 99%.
	Continue to closely monitor multisystem inflammatory syndrome in children/adults (MIS-C/-A) and all new cases of MIS-C/-A including a WHO causality assessment should be reported in the future PSURs[a].
	For future PSURs in the section 'Evaluation of AESIs', the adverse events of special interests (AESIs) in subjects with Malnutrition; HIV infection, Tuberculosis should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs in the section 'Evaluation of Other Risks (not categorised as important)', the reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs in the section 'Evaluation of special situations', death (cases reporting fatal outcome) should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	The MAH should continue to report on the administered 1st, 2nd, 3rd,4th, etc. doses of Comirnaty as presented in future PSURs.
	The MAH should present a case level analysis for all cumulative positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a time to onset (TTO) of <2 days. The MAH should discuss whether these events should be added in section 4.8 of the Comirnaty Summary of Product Characteristics (SmPC) and Product Information Leaflet (PIL) accordingly.
Previous AR commitments applicable for "Future PSURs"	For future PSURs the evaluation of cardiovascular AESIs, haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity, should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs the evaluation of overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	For future PSURs the evaluation of the use in frail patients with co-morbidities, and/or interactions with other vaccines should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
	Concerning hearing loss, the MAH is requested in future reviews of cases reporting hearing loss to conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss, if applicable.
	The MAH is requested in future summary safety reports (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.
Further EMA Commitment	Any new data from literature on hemophagocytic lymphohistiocytosis (HLH) with COVID-19 vaccines, and more particularly on a new hypothesis of a possible involvement of Epstein-Barr Virus (EBV) reactivation.

Source	Request(s)
Signals' AR	The signal of Pemphigus and Pemphigoid (EMEA/H/C/005735/SDA/061 - EPITT 19859) is closed and in the next PSUR, the MAH should perform a review of all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to the vaccine, including data from clinical trials, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an observed versus expected (O/E) analysis and provide all case narratives within this review.
	MAH will continue closely monitor Idiopathic inflammatory myopathies (IIM) / autoimmune myositis, and IIM flares through routine pharmacovigilance, including (but not restricted to) any relevant new cases and scientific literature on possible pathogenic mechanisms, as appropriate. In addition, the MAH will explore the feasibility of using healthcare data from prior to and during the COVID-19 era to better understand the occurrence of myositis in a broad population. Specifically, the MAH is expected to increase their efforts, and provide proposals to obtain more recent/contemporaneous IIM background incidence rates, i.e. during the pandemic/immunisation campaigns.
WHO	Pregnancy outcome in clinical trials.
Health Canada	Provide the cumulative review for post-market cases, with a focus on reports following bivalent vaccination. An updated review of any new literature (e.g., prospective cohort studies) on the risk of heavy menstrual bleeding (HMB) following monovalent and/or bivalent Comirnaty COVID-19 vaccination.
	Presentation and discussion of interim reports of the studies C4591010, C4591021 and C4591022.
Medsafe	Adverse events reported in <5-year-old should be split by dose 1, 2 and 3.
	Differentiate between ADRs reported in <5-year-old following the 3 mcg maroon cap formulation vs given another product not approved for this age group.
	Include global usage data of the bivalent vaccines and present data, where available, on race and ethnicity, including Māori and Pacific peoples.
TGA	The TGA requests that Pfizer provide the TGA with an updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses in the next PSUR to enable further evaluation of this signal.

a. As outlined in PRAC's signal recommendation (EPITT 19732).

According to the European Union Risk Management Plan (EU-RMP) version 9.0 dated 04 November 2022 (EMEA/H/C/005735//II/0147) approved on 10 November 2022, in effect at the beginning of the reporting period, safety concerns for BNT162b2 are:

- Important identified risk: Myocarditis and Pericarditis.
- Important potential risk: Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD).[20]
- 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,

[20] The important potential risk of VAED/VAERD was removed from the list of safety concerns in RMP version 10.0 (procedures EMEA/H/C/005735/X/0176, EMEA/H/C/005735/II/0177, and EMEA/H/C/005735/X/0180). Additionally, the Rapporteur agreed to remove the important potential risk of VAED/VAERD from the list of safety concerns for the PSUR #5 reporting period [as per PSUR #4 PRAC AR (EMEA/H/C/PSUSA/00010898/202212)].

cardiovascular disorders); Use in patients with autoimmune or inflammatory disorders; Interaction with other vaccines; Long term safety data.

No new safety concerns were identified during the reporting period.

After the DLP,

- an updated CDS (version 22.0) was made effective on 24 July 2023; this updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5), several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.

- Signals:
  - A new signal (Mastitis/Breast swelling) was opened based upon an enquiry from the Australian regulatory authority (TGA). The signal is ongoing.
  - The ongoing signals (Menstrual irregularities and Sensorineural Hearing Loss) were closed as no risk on 26 July 2023 and on 19 July 2023, respectively.

- The EU-RMP versions (with version number agreed with EMA) and associated procedures were approved, as detailed in the table below.

Procedure #, Description	Procedure Submission Date	Submitted EU-RMP	Approval date
Reporting period			
EMEA/H/C/005735/X/0176 PI update regarding Original/Omicron BA.4/BA.5 in 6mo-4yo (primary series and booster including revised vaccination posology) EMEA/H/C/005735/II/0177 PI update regarding Original/Omicron BA.4/BA.5 in 5-11yo and 12yo+ (primary series including revised vaccination posology)	03 March 2023	RMP v9.1: 03 March 2023 (Gateway) Consolidated RMP v9.3 = X-0176 RMP v9.1 + X-0180 RMP v9.2: 14 June 2023 (Eudralink) Updated consolidated RMP v9.5 = consolidated RMP v9.3 + X-0180 RMP v9.4: 21 June 2023 (Eudralink) Upversioned RMP v10.0 (content-wise similar to updated consolidated RMP v9.5 = v9.3 + v9.4): 22 June 2023 (Eudralink)	Approved CHMP Opinion: 22 June 2023
EMEA/H/C/005735/X/0180 PI update regarding Original/Omicron BA.4/BA.5 in 5-11yo (RTU – blue caps)	14 April 2023	RMP v9.2: 14 April 2023 (Gateway) RMP v9.4: 19 June 2023 (Eudralink)	Approved CHMP Opinion: 22 June 2023

CHMP = Committee for Medicinal Products for Human Use; PI = Product Information; RTU = ready-to-use.

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

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APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADEM	acute disseminated encephalomyelitis
ADR	adverse drug reaction
AE	adverse event
AER	adverse event report
AESI	adverse event of special interest
AR	assessment report
ARDS	acute respiratory distress syndrome
ATC	anatomical therapeutic chemical
AV	Atrioventricular
BMI	body mass index
CANOMAD	Chronic Ataxic Neuropathy Ophthalmoplegia IgM paraprotein Cold Agglutinins Disialosyl antibodies
CDC	Centres for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMI	Charlson comorbidity index
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	coronavirus disease 2019
COVID-19 vaccine NRVV MVA	modified vaccinia virus Ankara COVID-19 vaccine
COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19)	Vaxzevria, AstraZeneca COVID-19 vaccine
COVID-19 vaccine NRVV AD26 (JNJ 78436735)	Jcovden, Janssen COVID-19 vaccine
COVID-19 vaccine prot. Subunit (NVX COV 2373)	Novavax COVID-19 vaccine
CP	contractual party
CPSA	Circulatory Support Smart Assist
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial
CVST	cerebral venous sinus thrombosis
D	dose
DLP	data lock point
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECDC	European Centre for Disease Prevention and Control

Abbreviation	Term
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEA	European economic area
EMA	European Medicines Agency
EPITT	European pharmacovigilance issues tracking tool
EU	European Union
EUA	emergency use authorisation
EUL	emergency use listing
EURD	European Union reference date
FDA	Food and Drug Administration
FFRNT	fluorescent focus reduction neutralization test
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
GVP	Good pharmacovigilance practices
HA	Health Authority
HCP	healthcare professional
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HLGT	high level group term
HLT	high level term
HMB	heavy menstrual bleeding
HPV	human papilloma virus
IBD	International Birth Date
IC	immunocompromised
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICH	International Council for Harmonisation; intracerebral haemorrhage
ICU	Intensive care unit
ID	Identifier
IFN	interferon
Ig	Immunoglobulin
IM	intramuscularly
IIM	idiopathic inflammatory myopathies
IMP	investigational medicinal product
INACT 4V	inactivated quadrivalent
INACT 3V	inactivated trivalent
IND	Investigational New Drug
IR	incident rate

Abbreviation	Term
IRR	incidence rate ratio
IVY	Investigating Respiratory Viruses in the Acutely Ill
JAMA	Journal of American Medical Association
JNJ	Johnson & Johnson
JST	Japan Standard Time
LLOQ	lower limit of quantitation
LMIC	low- and middle-income country
LNP	lipid nanoparticles
LOE	lack of efficacy
MA	marketing authorisation
MAA	marketing authorisation application
MAH	marketing authorisation holder
MC	medically confirmed
ME	medication error
MEA	additional pharmacovigilance activity in the risk-management plan
Medsafe	Medicines and Medical Devices Safety Authority
MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
MHRA	Medicines and Healthcare products Regulatory Agency
MIS	multisystem inflammatory syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MoH	ministry of health
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
NA or N/A	not applicable
NAAT	nucleic acid amplification test
NEC	not elsewhere classified
NIS	Non interventional study
NMC	non-medically confirmed
NOS	not otherwise specified
NT50	50% neutralising titer
O/E	observed versus expected
Omi	Omicron
OR	odds ratio
PAM	post-authorisation measure
PASS	post-authorisation safety study
PBRER	periodic benefit-risk evaluation report
PBS	phosphate buffered saline
PC	product complaint
PI	product information
PIL	Product Information Leaflet
PM	post-marketing

Abbreviation	Term
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product quality complaint
PRAC	Pharmacovigilance Risk Assessment Committee
preF	prefusion F
PSUR	periodic safety update report
PSUSA	periodic safety update report single assessment
PT	Preferred Term
PVP	pharmacovigilance plan
QPPV	qualified person for pharmacovigilance
RA	Regulatory Authority
RMP	risk management plan
ROW	rest of world
RNA	ribonucleic acid
RSI	reference safety information
RSV	respiratory syncytial virus
RT-PCR	reverse transcription-polymerase chain reaction
RTU	ready-to-use
RVE	relative vaccine efficacy
S	Spike
SAE	serious adverse event
SAG	surface antigen
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBSR	summary bimonthly safety report
SIIV	seasonal inactivated influenza vaccine
SIRS	systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SMSR	summary monthly safety report
SOC	system organ class
SPEAC	Safety Platform for Emergency vACcines
SSR	summary safety report
TGA	Therapeutic Goods Administration
TME	targeted medical event
Tris	Tromethamine
TTO	time to onset
UK	United Kingdom
US	United States
USG	United States Government
VACTERL	Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy

Abbreviation	Term
WHO	World Health Organization
WT	wild type

1. INTRODUCTION

This is the 5th PSUR for the COVID-19 mRNA vaccine (nucleoside modified), COMIRNATY®, also referred to as BNT162b2,[4] covering the reporting interval 19 December 2022 through 18 June 2023.

The format and content of this PSUR is in accordance with the Guideline on GVP Module VII—Periodic safety update report (EMA/816292/2011 [December 2013]), with ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, January 2013]),[21] and Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance v. 3.1 (EMA/PRAC/73244/2022 [01 September 2022]).

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

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

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

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

Age group	**12 years and older**					**5 through 11 years**				**6 months through 4 years**	
Presentation	PBS sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose	Tris/Sucrose
Name	Comirnaty	Comirnaty	Comirnaty Original/ Omicron BA.1	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty Original/ Omicron BA.4/BA.5	Comirnaty	Comirnaty Original/ Omicron BA.4/BA.5[10]
Dose	30 mcg (with dilution)	30 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	15/15 mcg (no dilution)	10 mcg (with dilution)	5/5 mcg (with dilution)	5/5 mcg (no dilution)	5/5 mcg (no dilution)	3 mcg (with dilution)	1.5/1.5 mcg (with dilution)
Vial cap colour	Purple	Grey	Grey	Grey	Light Gray[7]	Orange	Orange	Dark blue[8]	Light blue[9]	Maroon	Maroon
Dose Volume	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL	0.3 mL	0.3 mL	0.2 mL	0.2 mL
Dose per vial	6 doses per vial (after dilution)	6 doses per vial	6 doses per vial	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)	6 doses per vial	1 dose per vial	10 doses per vial (after dilution)	10 doses per vial (after dilution)
Route of Administration	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM	IM

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

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

Table 1. List of PSURs

PSUR Number	Reporting Period
1	19 December 2020 through 18 June 2021
2	19 June 2021 through 18 December 2021
3	19 December 2021 through 18 June 2022
4	19 June 2022 through 18 December 2022

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

2. WORLDWIDE MARKETING APPROVAL STATUS

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK[22] on 01 December 2020.

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020. In the European Union, conditional marketing authorisation was granted on 21 December 2020; this was switched to a standard marketing authorisation on 10 October 2022. Overall, BNT162b2 original received marketing authorisation approval in 104 countries/regions.

In 2022, to address the emergence of Omicron variants, bivalent formulations were developed. Bivalent BNT162b2 (original/Omicron BA.1) and bivalent BNT162b2 (original/Omicron BA.4/BA.5) received marketing authorisation approval in 46 and 73 countries/regions, respectively. The MAHs and the number of countries where the different MAHs hold the authorisation are presented in Table 2.

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.

Different dosages are available for use in different age groups.

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

BNT162b2 original formulations:

- PBS/Sucrose 30 µg formulation for individuals 12 years and older [Purple cap];
- Tris/Sucrose formulation:
  - at the dosage of 30 µg for individuals aged 12 years and older [Grey cap];
  - at the dosage of 10 µg for individuals aged 5 years to <12 years [Orange cap];
  - at the dosage of 3 µg for individuals aged 6 months to <5 years [Maroon cap].

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

- original/Omicron BA.1 at the dosage of 15/15 µg for individuals aged 12 years and older [Grey cap].

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

- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Grey cap];[6]
- original/Omicron BA.4/BA.5 at the dosage of 15/15 µg for individuals aged 12 years and older [Light grey cap];[7]
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Orange cap];
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Dark blue cap];[8]
- original/Omicron BA.4/BA.5 at the dosage of 5/5 µg for individuals aged 5 years to <12 years [Light blue cap];[9]
- original/Omicron BA.4/BA.5 at the dosage of 1.5/1.5 µg for individuals aged 6 months to <5 years [Maroon cap];[10]

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

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held		
	BNT162b2 Original	BNT162b2 Bivalent (Original and Omicron BA.1)	BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)
BioNTech	58	37	47
Pfizer	38	8	24[a]
Fosun Pharma	1	0	1
Local MoH	3	0	0
Local Government	3	1	1
Hemas (CP)	1	0	0
All	**104**	**46**	**73**

a. BNT162b2 Bivalent (original and Omicron BA.4/BA.5) presentation was approved in Colombia after DLP in July 2023.

In addition, WHO had approved the EUL of BNT162b2.

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

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, the following action was taken with respect to BNT162b2 for safety reasons. In Switzerland the approval for bivalent Omi BA.1 was not obtained for individuals 12 to less than 18 years because there was no clinical data available for that population. Because country-specific packaging was not available, Switzerland received EU packaging that displayed age on the carton as 12+ (as per EU MA). Therefore, an information Letter (in English) explaining the discrepancy between age on the carton and age approved by Swissmedic was provided with each shipment. In addition, the MAH provided electronic versions of the letter in German, French and Italian to the Federal Office of Public Health.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID-19 mRNA vaccine CDS version 21.0 dated 25 May 2023, in effect at the end of the reporting period and included in Appendix 1.

Three (3) previous CDS versions (version 20.0 dated 22 February 2023, version 19.0 dated 22 December 2022 and version 18.0 dated 05 December 2022) in effect during the reporting period, are included in Appendix 1.2, Appendix 1.3 and Appendix 1.4, respectively. No safety-related changes were made to CDS version 20.0.

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

- 4.2. Posology and method of administration (CDS version 21.0), to include Bivalent (Original/Omicron BA.4/BA.5) presentation, 15/15 micrograms/dose (grey cap) as primary series and booster for ages 6 months and above and to update dosing interval.

- 4.8. Undesirable effects (CDS versions 21.0 and 19.0), to include updated median follow-up time values and safety profiles for the age groups (12 and older, 5 through < 12 years, 2 to 4 years, 6 months through 23 months of age) after Bivalent use in clinical setting. Diarrhoea was added as adverse reaction (>10%) in Children 5 through <12 years of age – after 2 doses.

- 5.1 1 Pharmacodynamic properties (CDS version 19.0) to include efficacy information in participants 6 months through 4 years of age – after 3 doses.

- Appendix A and Appendix B (CDS versions 21.0 and 19.0) to include frequencies and frequency categories (Very Common, Common, Uncommon or Rare) for some ADRs in different age groups.

After the DLP, an updated CDS (version 22.0) was made effective on 24 July 2023. This updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5); several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.

5. ESTIMATED EXPOSURE AND USE PATTERNS

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

Response

Please refer to Section 5.2.1.2. *Health Authority Public Data – Cumulative Exposure* and to Section 5.2.2.2 *Health Authority Public Data – Interval Exposure*, where information about the total number of doses administered of BNT162b2 and bivalent vaccines, is provided cumulatively in Table 7 through Table 11 for the EU/EEA countries and in Table 12 and Table 13 for Japan; Table 19 through Table 22 display the incremental number of doses (reported as first, second, third, fourth, fifth, sixth and seventh, respectively) of BNT162b2 administered in the EU/EEA countries.

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 69,372[11] participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

BNT162b2: 63,843 participants of which:

- 35,274 had received BNT162b2;
- 26,489 had received BNT162b2 post-unblinding and had received placebo before;
- 959 had received BNT162b2/placebo;
- 2 had received BNT162b2/ SIIV[23];
- 1119 had received BNT162b2/ SIIV/placebo.

[23] Seasonal inactivated influenza vaccine.

Variant and variant-adapted vaccines based on BNT162b2: 8851 participants of which:

- 753 had received BNT162b2 (B.1.351)[24];
- 372 had received BNT162b2 (B.1.617.2);
- 768 had received BNT162b2 (B.1.1.7 + B.1.617.2);
- 20 had received BNT162b2 (B.1.1.7);
- 71 had received BNT162b2 (B.1.1.529)[25];
- 1881 had received BNT162b2 Omi;
- 1815 had received BNT162b2/ BNT162b2 Omi;
- 102 had received BNT162b2 original/ BNT162b2 Omi BA.1;
- 104 had received BNT162b2 original/ BNT162b2 Omi BA.2;
- 2965 had received BNT162b2 original/ BNT162b2 Omi I BA.4/BA.5.

Early development candidates: 633 participants of which:

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

Blinded therapy: 2 participants.

Placebo: 6352 participants.

SIIV/placebo: 7 participants.

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

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

B747: 372 participants received BNT162b2 as a study vaccine in the clinical study B7471026;[12]

C526: 796 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine in the clinical study C5261001.[13]

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

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

C548: 757 participants received BNT162b2 Bivalent (BNT162b2 original/Omi BA.4/BA.5) as a study vaccine in the clinical study C5481001.[14]

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

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1. Cumulative Exposure

5.2.1.1. MAH and Contractual Party Data – Cumulative Exposure

MAH Data

The number of doses cumulatively administered (as per public available data for the EU-EEA countries,[26] the US,[27] and Japan[28]) is either no longer updated or currently updated on a bi-weekly base. Considering the current status of the vaccination schedule and the availability of only partial data published on the ECDC websites for doses of BNT162b2 vaccines (original and bivalent) administered in the EU-EEA countries,[29] it is no longer applicable to estimate the number of doses administered from those shipped. Estimated administered doses were provided separately, as available on the public source data.

Approximately a total of 4,615,732,025[30] doses of BNT162b2 (original and bivalent) were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 June 2023. The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group based on data provided in the shipment tracker (Order Book)[31] through 18 June 2023 is showed in Table 3 through Table 5. Out of the cumulative number of shipped doses, 4,154,348,225 were original and bivalent adult[16] presentations (including PBS and Tris/Sucrose); 461,383,800 were original and bivalent paediatric[17] presentations; 686,454,460 were bivalent vaccines of which 21,075,900 were for paediatric presentations; 2,446,319,885 doses of BNT162b2 (original and bivalent) were shipped to ROW.[18]

[26] https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea, Accessed on 16 June 2023.

[27] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5, Last updated on 12 May 2023 and accessed on 14 July 2023.

[28] https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html, Accessed on 21 June 2023, 12:00 [JST].

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

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

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

Table 3. Cumulative Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses[a]	6-month – 4 years	5 – 11 years	≥12 years[b]	All
Europe	**30.9**	**4368000**	**69859200**	**1139387235**	**1213614435**
European Union (27)	22.4	3355200	57434400	820816440	881606040
European Economic Area Countries (3)	0.3	9600	452400	12007185	12469185
Switzerland	0.3	0	600000	11397330	11997330
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**	**501181315**	**587310415**
US	13.0	13669300	64199800	433517935	511387035
Canada	1.9	1710000	6550000	67663380	75923380
Central and South America	**15.6**	**24694800**	**86753900**	**502138755**	**613587455**
Asia	**29.9**	**13657200**	**135614200**	**1026803760**	**1176075160**
Japan	7.1	10017600	16016400	252909540	278943540
Other Countries	22.8	3639600	119597800	773894220	897131620
Oceania	**2.2**	**1195200**	**12203400**	**74875230**	**88273830**
Australia/New Zealand	2.2	1195200	12129600	73584360	86909160
Other Countries	0.0	0	73800	1290870	1364670
Africa	**6.4**	**0**	**5832900**	**244583370**	**250416270**
Total	**100**	**59294500**	**381013400**	**3488969665**	**3929277565**

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

Region/Country	≥12 years	All
Europe	**76181760**	**76181760**
European Union (27)	47076480	47076480
European Economic Area Countries (3)	1016640	1016640
Switzerland	3084480	3084480
UK	25004160	25004160
Other Countries	0	0
Commonwealth of Independent States	0	0
North America	**0**	**0**
US	0	0
Canada	0	0
Central and South America	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 5. Cumulative Estimated Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**38.4**	**0**	**1814400**	**212616720**	**214431120**
European Union (27)	34.9	0	1795200	192931920	194727120
European Economic Area Countries (3)	0.5	0	19200	2554560	2573760
Switzerland	0.0	0	0	48960	48960
UK	2.5	0	0	13999680	13999680
Other Countries	0.1	0	0	800640	800640
Commonwealth of Independent States	0.4	0	0	2280960	2280960
North America	**22.4**	**4066600**	**11893700**	**109343620**	**125303920**
US	19.8	4066600	11070100	95708860	110845560
Canada	2.6	0	823600	13634760	14458360
Central and South America	**11.9**	**0**	**114000**	**66293280**	**66407280**
Asia	**23.5**	**0**	**3187200**	**127897470**	**131084670**
Japan	18.0	0	2016000	98662590	100678590
Other Countries	5.4	0	1171200	29234880	30406080
Oceania	**3.4**	**0**	**0**	**18786240**	**18786240**
Australia/New Zealand	3.4	0	0	18766080	18766080
Other Countries	0.0	0	0	20160	20160
Africa	**0.5**	**0**	**0**	**2551680**	**2551680**
Total	**100**	**4066600**	**17009300**	**537489010**	**558564910**

CP Data

Cumulative CP (Fosun) data on the number of original BNT162b2 and bivalent doses administered in Hong Kong, Macau and Taiwan is provided in Table 6.

Table 6. Cumulative Administered Doses of BNT162b2 Original and BNT162b2 Bivalent Omi BA.4/BA.5 Vaccine – Contractual Party Data

Region **Country** ***-Vaccine Presentation***	**Number of Administered Doses**
Asia	**32269283**
Hong Kong[a]	11984703
- BNT162b2 (Original)	*11428078*
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	*556625*
Macau [b]	397380
Taiwan[c]	19887200
- BNT162b2 (Original)	*19887200*

a. Cumulatively through 20 June 2023, except for Bivalent data cumulatively through 23 June 2023.
b. For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. Cumulatively through 13 June 2023.

5.2.1.2. Health Authority Public Data – Cumulative Exposure

Estimated cumulative data about the number of COMIRNATY® doses administered are published for EU/EEA countries, and Japan in the respective Health Authorities' websites.[32]

Table 7 below displays the cumulative EU/EEA published data with number of doses administered for each age group and by vaccine type.

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

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

Table 7. EU/EEA – Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[g]	TOTAL
< 18 years	27055225	25854	65085[c]	25068[c]	27171232
0 – 4 years	15576[d]	NA[e]	NA[e]	NA[e]	15576
5 – 9 years	4143991[h]	NA[e]	2510[f]	0	4146501
10 – 14 years	4336133	830	9472[f]	7864	4354299
15 – 17 years	8230880	4099	9601	19266	8263846
18 – 24 years	30506062	136044	113494	97169	30852769
25 – 49 years	138812452	1016068	1374517	859745	142062782
50 – 59 years	67561353	1064487	1805745	961536	71393121
60 – 69 years	55528600	1592713	1352473	2687844	61161630
70 – 79 years	54055930	1992782	1155012	2733674	59937398
⩾ 80 years	40376375	1283438	1313886	2130269	45103968
Age Unknown	263332	43	160	0	263535
All	**497783992**	**7085524**	**15136438**	**9470237**	**529476191**

[32] The CDC COVID Data Tracker: Vaccinations in the US is no longer updated since 12 May 2023. US data related to the cumulative number of doses of original and bivalents vaccines are not included.

Table 7. EU/EEA – Cumulative Number of BNT162b2 Original and BNT162b2 Bivalent Omi Vaccines Administered Doses by Age Group

Age Group	BNT162b2 Original[a]	BNT162b2 Bivalent Omi BA.1[b]	BNT162b2 Bivalent Omi BA.4/BA.5[c]	BNT162b2 Bivalent Omi[g]	TOTAL

a. Cumulative period: from 2020 week 50 through 2023 week 24 (up to 17 June 2023).
b. Cumulative period: from 2022 week 35 through 2023 week 24.
c. Cumulative period: from 2022 week 37 through 2023 week 24.
d. BNT162b2 Original for 6 months through <5 years was approved in EU/EEA on 20 October 2022; correspondent data for BNT162b2 original evaluated from 2022 week 42 through 2023 week 24.
e. Not approved.
f. BNT162b2 Bivalent Omi BA.4/BA.5 for 5 through <12 years was approved in EU/EEA on 10 November 2022; correspondent data for evaluated BNT162b2 Bivalent Omi BA.4/BA.5 from 2022 week 45 through 2023 week 24.
g. Not specified if BA.1 or BA.4/BA.5.
h. Line extension 5-11 years old Tris/Sucrose Paediatrics approved on 03 December 2021 (week 48); cumulative period: from 2021 week 48 through 2023 week 24.
Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 18 June 2023. Some data are smaller than those available on 17 December 2022.

Table 8 through Table 11 provide the cumulative total number of administered Comirnaty doses for both BNT162b2 original and bivalent Omi in EU/EEA, by age group for each dose. Individual country data are provided in Appendix 5.1.

Table 8. EU/EEA – Cumulative Number of Original Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
< 18 years	12772444	11783695	2489188	8686	113	0	1099
18 – 24 years	12277974	11419732	6665254	138481	531	0	4090
25 – 49 years	54905456	52439365	30147700	1276743	5979	3	37206
50 – 59 years	25318917	24710183	16274987	1222779	7159	7	27321
60 – 69 years	17376228	17249116	17415639	3439785	16515	53	31264
70 – 79 years	17143899	17012880	15672261	4170325	28685	214	27666
≥80 years	12919083	12708906	10925297	3760840	48832	112	13305
Age Unknown	104661	83133	62067	12890	106	0	475
All	178554954	173436375	125261274	20178211	211936	389	140853

Cumulative period: from 2020 week 50 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 9. EU/EEA – Cumulative Number of Bivalent Omi BA.1 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	277	444	11888	12899	346	0	0	0
18 – 24 years	344	468	16385	115384	3427	0	0	36
25 – 49 years	1711	1793	69325	906348	36710	3	1	177
50 – 59 years	518	533	30814	983977	48567	10	0	68
60 – 69 years	593	437	39565	1416300	135597	83	0	138
70 – 79 years	583	432	32000	1714923	244339	186	0	319
≥80 years	582	530	20852	599519	661574	108	1	272
Age Unknown	2	3	4	27	3	0	0	4
All	4331	4193	208941	5736450	1130214	390	2	1003

Cumulative period: from 2022 week 35 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 10. EU/EEA – Cumulative Number of Bivalent Omi BA.4/BA.5 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
< 18 years	690	1056	29965	33048	314	12	0
18 – 24 years	1151	1802	37917	133976	2998	31	85
25 – 49 years	4350	5085	154606	1173416	35810	629	621
50 – 59 years	1128	1387	79326	1670423	52231	806	444
60 – 69 years	1228	1040	89603	2196799	193169	3551	870
70 – 79 years	985	913	61027	1734478	334360	41589	522
≥80 years	947	1101	32351	813106	441324	24854	203
Age Unknown	2	2	14	122	14	0	6
All	45417	57883	692205	11125391	3141346	71460	2736

Cumulative period: from 2022 week 37 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

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

Dose Number → Age Group ↓	D1	D2	D3	D4	D5
< 18 years	17	26	26347	1977	146
18 – 24 years	16	37	43894	52452	770
25 – 49 years	79	162	164716	682991	11797
50 – 59 years	14	31	70073	875905	15513
60 – 69 years	11	23	66471	2599021	22318
70 – 79 years	14	29	37364	2682644	13623
≥80 years	23	31	36474	2087695	6046
Age Unknown	0	0	0	0	0
All	157	313	418992	8980708	70067

Not specified if BA.1 or BA.4/BA.5. Being the Omi variant unknown, the same approach of BA.4/BA.5 has been taken.
Cumulative period from 2022 week 37 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 12 and Table 13 show the cumulative number of BNT162b2 original and bivalent vaccines doses administered in Japan. The number of bivalent administered doses alone is not available.

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

Population(s)	Number of Doses	
	1st Dose	2nd Dose
General population[a]	81813346	81362856
Elderly[c]	32183220	32108377
Child (5 to < 12 years)	1765076	1710809
Infant only (6 months – 4 years)	174484	161696
Medical workers[b]	6378205	5709228
All	**88191551**	**87072084**

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

Population(s)	Number of Doses	
	1st Dose	2nd Dose

a. Including elderly, children and infants.
b. Counting of vaccinations for medical workers (1st and 2nd dose) ended on 30 July 2021.
c. This reported value is smaller respect the one reported in PSUR #4. Administration data corrected between PSUR #4 and PSUR #5.

Source: Government's website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed on: 21 June 2023, 12:00 [JST].

Table 13. Japan - Cumulative Number of Original and Bivalent Omi Administered Doses (3rd through 6th)

Population(s)	Number of Doses			
	3rd Dose	4th Dose	5th Dose	6th Dose
General population[a]	**52736726**	**42862105**	**30130339**	**9129040**
Elderly	20758817	20392809	23915646	8285215
Child (5 to < 12 years)	711738	144388	7	N/A
Infant only (6 months – 4 years)	122430	N/A[b]	N/A[b]	N/A[b]

a. Including elderly, children and infants
b. Booster vaccination for subjects aged 6 months through less than 5 years is not approved in Japan.

Source: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html.
Accessed on: 21 June 2023, 12:00 [JST].

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

5.2.2. Interval Exposure

5.2.2.1. MAH and Contractual Party Data – Interval Exposure

Approximately 257,566,530 doses of BNT162b2 original and bivalent vaccines were shipped worldwide during the current reporting interval from 19 December 2022 through 18 June 2023. Out of the doses shipped during the reporting period, 29,554,970 were original adult[16] presentations (including PBS and Tris/Sucrose); 57,416,700 were original paediatric[17] presentations; 170,594,860 were bivalent vaccines of which 10,112,000 were for paediatric presentations; 183,755,610 doses of BNT162b2 (original and bivalent) were shipped to ROW.[18]

The worldwide estimated interval number of shipped doses BNT162b2 original, bivalent Omi BA.1, and bivalent Omi BA.4/BA.5 by region and countries and by age group, based on data provided in the shipment tracker (Order Book)[31] are displayed in Table 14 through Table 16.

Table 14. Interval Estimated Shipped Doses of BNT162b2 Original by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years[a]	All
Europe	**3.4**	**1104000**	**43200**	**1843200**	**2990400**
European Union (27)	0.1	96000	33600	0	129600
European Economic Area Countries (3)	0.0	4800	0	0	4800
Switzerland	0.0	0	0	0	0
UK	1.2	1003200	0	0	1003200
Other Countries	0.0	0	4800	2880	7680
Commonwealth of Independent States	2.1	0	4800	1840320	1845120
North America	**12.3**	**2580200**	**2752900**	**5348480**	**10681580**
US	12.3	2580200	2752900	5348480	10681580
Canada	0.0	0	0	0	0
Central and South America	**48.5**	**22852800**	**18948300**	**396000**	**42197100**
Asia	**9.0**	**2611200**	**3321600**	**1897920**	**7830720**
Japan	1.4	1214400	0	0	1214400
Other Countries	7.6	1396800	3321600	1897920	6616320
Oceania	**1.2**	**388800**	**158400**	**539640**	**1086840**
Australia/New Zealand	1.2	388800	153600	463680	1006080
Other Countries	0.1	0	4800	75960	80760
Africa	**25.5**	**0**	**2655300**	**19529730**	**22185030**
Total	**100**	**29537000**	**27879700**	**29554970**	**86971670**

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

Table 15. Interval Estimated Shipped Doses of BNT162b2 Bivalent Omi BA.1 by Region Worldwide and Age Group

Region/Country	≥12 years	All
Europe	**0**	**0**
European Union (27)	0	0
European Economic Area Countries (3)	0	0
Switzerland	0	0
UK	0	0
Other Countries	0	0
Commonwealth of Independent States	0	0
North America	**0**	**0**
US	0	0
Canada	0	0
Central and South America	**5760**	**5760**
Asia	**0**	**0**
Japan	0	0
Other Countries	0	0
Oceania	**0**	**0**
Australia/New Zealand	0	0
Other Countries	0	0
Africa	**0**	**0**
Total	**5670**	**5670**

Table 16. Interval Estimated Shipped Doses of BNT162b2 Omi Bivalent BA.4/BA.5 by Region Worldwide and Age Group

Region/Country	% of Total Doses	6-month – 4 years	5 – 11 years	≥12 years	All
Europe	**19.8**	**0**	**28800**	**33739200**	**33768000**
European Union (27)	10.2	0	14400	17352000	17366400
European Economic Area Countries (3)	0.0	0	14400	0	14400
Switzerland	0.0	0	0	48960	48960
UK	8.2	0	0	13999680	13999680
Other Countries	0.0	0	0	57600	57600
Commonwealth of Independent States	1.3	0	0	2280960	2280960
North America	**25.7**	**3092400**	**3694400**	**36976940**	**43763740**
US	24.8	3092400	3322400	35968940	42383740
Canada	0.8	0	372000	1008000	1380000
Central and South America	**36.9**	**0**	**114000**	**62837280**	**62951280**
Asia	**5.1**	**0**	**3182400**	**5585760**	**8768160**
Japan	1.2	0	2016000	0	2016000
Other Countries	4.0	0	1166400	5585760	6752160
Oceania	**11.0**	**0**	**0**	**18786240**	**18786240**
Australia/New Zealand	11.0	0	0	18766080	18766080
Other Countries	0.0	0	0	20160	20160
Africa	**1.5**	**0**	**0**	**2551680**	**2551680**
Total	**100**	**3092400**	**7019600**	**160477100**	**170589100**

CP Data

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

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

Region **Country** ***-Vaccine Presentation***	**Number of Administered Doses**
Asia	**909044**
Hong Kong[a]	512911
- BNT162b2 (Original), 30 µg	*64078*
- BNT162b2 (Original), 10 µg	*5900*
- BNT162b2 (Original), 3 µg	*9400*
- Bivalent (Original + BNT162b2 Omi BA.4/BA.5) 15/15 µg	*433533*
Macau [b]	67633
Taiwan[c]	328500
- BNT162b2 (Original), 30 µg	*52800*
- BNT162b2 (Original), 10 µg	*188900*
- BNT162b2 (Original), 3 µg	*86800*

a. 19 December 2022 through 20 June 2023.
b. For Macau no discrimination between administration data for BNT162b2 Original and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was possible.
c. 19 December 2022 through 13 June 2023.

5.2.2.2. Health Authority Public Data – Interval Exposure

Estimated interval data about the number of COMIRNATY® doses administered are published only for the EU/EEA countries.

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

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

Age Group	BNT162b2 Original	BNT162b2 Bivalent Omi BA.1	BNT162b2 Bivalent Omi BA.4/BA.5	BNT162b2 Bivalent Omi[a]	TOTAL
< 18 years	33417	1689	19974	17872	72952
0 – 4 years	12557	NA	NA	0	12557
5 – 9 years	24332	NA	1442	0	25774
10 – 14 years	13488	160	5166	5437	24251
15 – 17 years	8459	228	4987	12368	26042
18 – 24 years	34167	4323	56288	49221	143999
25 – 49 years	193716	28470	375046	360812	958044
50 – 59 years	97515	21557	276502	450303	845877
60 – 69 years	73753	44960	338320	508671	965704
70 – 79 years	50345	51616	436450	314054	852465
≥ 80 years	32411	51794	338984	130268	553457
Age Unknown	52019	2	56	0	52077
All	530237	202720	4260084	1813329	6806370

Interval period: 2022 week 51 through 2023 week 24.
a. Not specified if BA.1 or BA.4/BA.5.
Source: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed on: 18 June 2023.

Table 19 through Table 22 provide for the interval reporting period the total number of administered Comirnaty doses for both BNT162b2 original and bivalent Omi in EU/EEA, by age group for each dose. Individual country data are provided in Appendix 5.1.

Table 19. EU/EEA – Interval Number of Original Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	14644	14924	3110	643	46	0	0	50
18 – 24 years	5284	5146	8537	15118	72	0	0	10
25 – 49 years	13646	14240	34343	130649	786	1	0	51
50 – 59 years	2083	2478	8920	82960	1012	5	0	57
60 – 69 years	1516	1874	7652	60129	2474	28	0	80
70 – 79 years	1196	1386	5967	34230	7233	191	0	142
≥80 years	1402	1346	3374	17305	8833	89	0	62
Age Unknown	2975	2411	36160	10462	8	0	0	3
All	33280	34288	80100	352972	28881	314	0	402

Incremental period: from 2022 week 51 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 20. EU/EEA – Interval Number of Bivalent Omi BA.1 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	D7	Unknown
< 18 years	63	89	784	747	6	0	0	0
18 – 24 years	78	87	1080	3027	51	0	0	0
25 – 49 years	473	346	4378	22474	794	3	1	1
50 – 59 years	126	86	1707	18403	1229	5	0	1
60 – 69 years	123	65	2457	33562	8733	20	0	0
70 – 79 years	132	59	1735	34333	15302	54	0	1
≥80 years	109	79	1114	18928	31523	40	1	0
Age Unknown	0	0	0	1	1	0	0	0
All	1041	722	12471	130727	57632	122	2	3

Incremental period: from 2022 week 51 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 21. EU/EEA – Interval Number of Bivalent Omi BA.4/BA.5 Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5	D6	Unknown
< 18 years	427	513	10456	8358	208	12	0
18 – 24 years	518	718	13806	39970	1189	31	56
25 – 49 years	1574	1923	45305	309297	15928	629	390
50 – 59 years	375	446	15694	234089	24894	801	203
60 – 69 years	336	302	15136	234879	83931	3534	202
70 – 79 years	297	255	10798	208478	174966	41560	96
≥80 years	369	397	6290	122943	184124	24839	22
Age Unknown	2	0	5	40	7	0	2
All	23372	30599	205641	2302209	1625899	71394	970

Incremental period: from 2022 week 51 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

Table 22. EU/EEA – Interval Number of Bivalent Omi Administered Doses by Age Group

Dose Number → Age Group ↓	D1	D2	D3	D4	D5
< 18 years	13	20	17083	715	41
18 – 24 years	16	31	24511	24352	311
25 – 49 years	68	117	71171	285643	3813
50 – 59 years	8	11	30025	415253	5006
60 – 69 years	8	8	17734	484497	6424
70 – 79 years	6	7	5918	304805	3318
≥80 years	8	13	3207	125616	1424
Age Unknown	0	0	0	0	0
All	114	187	152566	1640166	20296

Not specified if BA.1 or BA.4/BA.5. Incremental period: from 2022 week 51 through 2023 week 24.
Source: Data on COVID-19 vaccination in the EU/EEA (europa.eu). Accessed on: 18 June 2023.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 26.0 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: BNT162-17[33], C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, C4591024, C4591030, C4591031, C4591044 and C4591048.

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

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

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

Response

The Appendix 2.2.6 displays, for the PM dataset, demographic interval data including ethnicity and race, when available.

Appendix 2.2 provides the overall (including original and bivalent vaccines) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. Appendix 2.2.1 through Appendix 2.2.4 provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [BNT162b2 original and BNT162b2 bivalent (Omi BA.1, Omi BA.4/BA.5, Omi)]. These tabulations include serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited

[33] Thirty-eight (38) clinical trial cases from BioNTech protocol BNT162-17 were entered in the global safety database as Pfizer sponsored study to allow appropriate reporting to the US FDA as IND Application safety reports, since Pfizer assumed responsibility of this reporting on sponsor's behalf. As such, the cumulative summaries of all SAEs from Pfizer sponsored trials in Appendix 2.1 and cumulative summaries of SAEs in Appendix 2.1.1 have been updated to reflect the more appropriate categorisation. No data was lost from previous reports.

sources. The cumulative data include all data up to 18 June 2023 and the interval data are from 19 December 2022 to 18 June 2023. This appendix is organised according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non-interventional sources.

Please note that adverse event totals presented for safety topic evaluations in Section 16 *Signal and Risk Evaluation*, may differ from Appendix 2.2 through Appendix 2.2.4 totals, due to the fact that Appendix 2.2 only displays the number of serious reactions from non-interventional studies and solicited sources as described above, whereas the safety topic evaluation includes all reported events. Cases from non-interventional studies and other non-interventional solicited sources must contain at least 1 serious related event to meet PSUR inclusion criteria and may also contain additional events that are considered unrelated, all of which would be evaluated.

The cumulative Summary tabulations (Appendix 2.2 through Appendix 2.2.4) and the data related to the current reporting period and included in the body of the PSUR, do not include (due to a technical issue) a set of 575 cases (all received in the current reporting period) reporting as only suspect BNT162b2 Multivalent NOS. A separate cumulative (= interval) Summary tabulation for these 575 cases is provided as Appendix 2.2.5.

Upon review of these 575 cases, there were 6 fatal cases, 31 cases reporting Drug ineffective, 3 cases of maternal exposure during pregnancy, 6 cases of myocarditis and pericarditis[34] (none of which with a fatal outcome), 1 case of MIS-C/A (SIRS), 8 cases involving paediatric subjects, and 104 cases indicative of other AESIs. Upon review, the safety profile of this subset of cases did not differ from the safety profile of the overall population; all these cases will be included in the next PSUR.

Appendix 2.2.6 displays, for the PM dataset, demographic interval data, including ethnicity and race when available.

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

Table 23 below summarizes the study treatments in the clinical studies by original vaccine or the Omicron-modified vaccine.

[34] Reported PTs: Myopericarditis (3), Myocarditis (2), Pericarditis (1).

Table 23. Clinical Trials during the Reporting Period: Study Treatments – Original and Bivalent Vaccines

Original	BNT162b2	C4591001, C4591007, C4591015, C4591024, C4591030, C4591031 Substudy A, Substudy B, and Substudy C, C4591036[a], BNT162-01[b], BNT162-14, BNT162-17
Other constructs	BNT162b1	C4591001, BNT162-01,
Variant and variant-adapted vaccines	BNT162b2 (B.1.351)	C4591001, BNT162-14[c]
	BNT162b2 (B.1.1.7) BNT162b2 (B.1.1.7 + B.1.617.2) BNT162b2 (B.1.617.2) BNT162b2 (B.1.1.529.1)	BNT162-17
	Original + Omi BA.1	C4591031 Substudy D, Substudy E, and Substudy F, C4591036[a], C4591044
	Original + Omi BA.2[d]	C4591044
	Original + Omi BA.4/BA.5	C4591036[a], C4591044, C4591048, BNT162-21[e]

a. Low-Interventional.
b. BNT162a1, BNT162b1, and BNT162c2 were also study vaccines in this trial.
c. BNT162b2 (B.1.351), which is also referred to as BNT162b2s01 and BNT162b2$_{SA}$.
d. BNT162b5.
e. BNT162b4 is also study treatment in this study.

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

7.1. Completed Clinical Trials

1. Safety Trials

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

2. Other Trials that reported new significant efficacy information

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

3. Remaining Trials

During the reporting interval, there was a single completed clinical trial (BNT162-01) with a final CSR (available upon request). No clinically important new information has emerged from this clinical trial; overall conclusions for the study are provided below.

Table 24. Summary of Results from Clinical Trials Completed During the Reporting Period – Remaining Trials

Protocol ID	Protocol Title	Conclusions
BNT162-01	A multi-site, phase I/II, 2-Part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults.	Based on the totality of the safety data, BNT162b1 and BNT162b2 were generally well tolerated and had acceptable safety profiles in healthy participants and BNT162b2 was generally well tolerated and had an acceptable safety profile in IC participants, at the dose levels tested. For BNT162b1, twice dosing at 60 µg was not considered acceptable due to dose-related increases in reactogenicity. Participants dosed with BNT162b1 and BNT162b2 showed a strong, dose-dependent functional antibody response which was independent of age. The induced immune response was found to be multi-epitopic by BNT162b2. The more favourable tolerability profile of BNT162b2 was the main driver for choosing dosing with two doses of 30 µg BNT162b2 for further study in the Phase II/III evaluation of efficacy.

7.2. Ongoing Clinical Trials

During the reporting period, there were 12 ongoing[35] sponsor-initiated clinical trials.

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

   There were 3 ongoing clinical trials.

   a) PASS:

   - ***Original Vaccine***
     - C4591015: *A phase 2/3, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older* is an ongoing PASS. No clinically important new information has emerged from this ongoing PASS.
     - C4591024[36]: *A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised*

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

[36] On 10 November 2022 in the final Assessment report for PAM-MEA-016.4, the CHMP granted permission to cease enrollment in Study C4591024 due to the futility reasons. The study started to recruit participants in October 2021, when all countries provided vaccine against COVID-19 after the authorization at first to the most vulnerable population, which includes the immunocompromised individuals, making difficult

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

- ***Original and Bivalent:***

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

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

- None.

2) Other Trials that reported new significant efficacy information

There were 7 ongoing clinical trials, of which 3 were with the BNT162b2 original vaccine (BNT162-14, C4591001 and C4591007) and 3 were with the bivalent vaccine (BNT162-21, C4591044 and C4591048); in the 7th clinical trial (C4591031) both original and bivalent vaccine were administered.

- ***Original vaccine***

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

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

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

- ***Original and Bivalent vaccines***

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

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the enrollment of vaccine naïve immunocompromised participants without a prior history of COVID-19 infection. Currently, enrolled participants should continue in the study and the results of the planned analyses such as safety and immunogenicity evaluations should be completed.

Study C4591031 consists of 6 substudies. Substudies A and B (both with original) were completed[37] and provided clinically important emerging efficacy and safety findings, while for the remaining 4 ongoing substudies (C [original] and D through F [bivalent vaccine]) no clinically significant safety and/or efficacy information has emerged.

Study C4591031 Substudy A was a Phase 3 randomized, placebo-controlled, observer-blind substudy aimed at evaluating the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who had completed a 2-dose primary series of BNT162b2 in Study C4591001 at least 6 months prior to randomization, were enrolled and randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization was stratified by age, such that approximately 60% of participants enrolled were ≥16 through 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 randomized to placebo were offered a dose of BNT162b2 30 µg.

Conclusions from the final study report for Substudy A:

- The cumulative incidence of confirmed COVID-19 cases showed that BNT162b2 30 µg provided strong protection against the Delta variant of SARS-CoV-2, with waning efficacy following the rise of the Omicron variant. Severe COVID-19 cases remained rare in the study population, despite increasing cases overall.

- The tolerability and safety profile of BNT162b2 30 µg in participants ≥16 years of age at up to 12 months after booster vaccination was acceptable and consistent with results previously reported from the clinical trial experience with BNT162b2 2-dose primary vaccination.

Substudy B of C4591031 was a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third or fourth) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age that received 2 or 3 prior doses of BNT162b2 (30-µg doses), with their last dose at least 4 months (120 days) prior to randomization, were enrolled. Participants were randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at their first vaccination visit and then crossed over to the alternative, four weeks later and were stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Serum samples were tested for troponin before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration. The percentages of participants with elevated serum troponin I levels in participants aged 12 to 30 years who had received 2 or

[37] Final CSRs were issued for Substudy A (27 February 2023) and Substudy B (24 May 2023) of Study C4591031 during the reporting interval.

3 prior doses of BNT162b2 (30-µg doses) showed no significant difference between BNT162b2 30 µg and placebo.

- A total of 9 and 7 participants (0.7% and 0.5%) had elevated troponin I results at the 1-month visit (28-35 days) after BNT162b2 and placebo vaccination, respectively.

- The percentages of elevated troponin I results were similar between the two vaccine groups (after BNT162b2 or after placebo) across age group, sex, race, and ethnicity subgroups. In both vaccine groups, the percentages of elevated troponin I results were generally higher in younger age groups (12-17 years) and males.

- At the 4-day visit (2-5 days) after BNT162b2 or placebo, the difference in percentage of elevated troponin I results between the 2 groups was -0.5% (95% CI: -1.1%, 0.2%), which was not statistically significant. Similarly, 1 month (28-35 days) after BNT162b2 or placebo, the difference of 0.2% (95% CI: -0.3%, 0.7%) in the elevated troponin I results between the 2 groups was also not statistically significant.

➢ ***Bivalent vaccine***

♦ BNT162-21: *An exploratory Phase I, randomized, observer-blind, active controlled dose escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults*. This trial uses BNT162b4 as IMP in combination with BNT162b2 Bivalent and BNT162b2 Bivalent as investigational and active comparator.

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

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

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

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

3) Remaining Trials

There were 2 ongoing clinical trials:

- ***Original vaccine***
  - BNT162-17: *A phase II trial to evaluate the safety and immunogenicity of SARS-CoV-2, monovalent and multivalent RNA-based vaccines in healthy subjects.*
  - C4591030: *A phase 3, randomized, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.*

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

7.3. Long-term Follow-up

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

7.4. Other Therapeutic Use of Medicinal Product

BNT162b2 was also administered as study vaccine in other Pfizer-sponsored clinical development programs (C526 and C548[38]).

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

7.5. New Safety Data Related to Fixed Combination Therapies

BNT162b2 is not used in fixed or multi-vaccine combination with other vaccines.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

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

Response

Please refer to Appendix 5.9. through Appendix 5.11. for the interim reports of studies C4591010, C4591021 and C4591022 submitted in the reporting period.

During the reporting period, there were 15 ongoing sponsor-initiated non-interventional studies, and one non-interventional study (C4591006) was completed.

[38] No clinical trial exposure is available from this program.

8.1. Completed Non-Interventional Studies

1. Safety studies

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

2. Other studies

During the reporting period, the study C4591006[39] was completed. No new safety information emerged from this non-interventional study; the summary of results from this study is provided in Table 25.

Table 25. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions
C4591006	General Investigation of COMIRNATY Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post-Approval Stage).	Through the follow-up period after the primary series vaccination, no new safety concerns or risks were identified.

8.2. Ongoing Non-Interventional Studies

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

   - PASS[40]: Non-interventional studies C4591008,[41] C4591009,[42] C4591010,[43] C4591012,[44] C4591021,[42] C4591022, [42] C4591038,[42] and C4591055[45] are PASS. No

[39] Study C4591006 was a commitment to the Japanese regulatory. The full CSR in Japanese was finalised in April 2023. The expectation period for English abstract CSR finalisation is August 2023.

[40] During the reporting period, interim CSRs were issued for the studies C4591008 (31 December 2022), C4591009 (24 October 2022), C4591010 (01 March 2023), C4591012 (24 June 2022), C4591021 (20 September 2022, 31 Mar 2023), and C4591022 (31 January 2023).

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

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

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

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

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

clinically important information has emerged from PASS. Summary of the interim reports of the NIS C4591010, C4591021 and C4591022 submitted during the reporting period are available in Appendix 5.9, Appendix 5.10 and Appendix 5.11, respectively.

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

2. Other Studies

There were 7 ongoing non-interventional studies:

- C4591014,[46] *Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- C4591025,[47] *A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.*
- C4591034, *Patient-Reported Health-Related Quality of Life Associated With COVID-19: A Prospective Survey Study on Symptomatic Adults Confirmed With RT-PCR From Outpatient Settings in the US.*
- C4591042, *Patient characteristics, healthcare resource utilization and costs among patients with COVID-19 in England.*
- C4591050[48], *Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance.*
- C4591053, *The impact of Pfizer-BioNTech (BNT162b2) vaccination on the long-term effects of COVID among adults in England diagnosed with COVID prior to Omicron dominance.*
- C4591061, *Investigating uptake and subsequent health outcomes associated with Pfizer-BioNTech bivalent COVID-19/Influenza vaccine concomitant administration using a claims-based real-world data source in the US.*

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

[46] PAM-MEA-013.

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

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

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

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

9.2. Medication Errors

Analysis of the safety database

Cases potentially indicative of medication errors[49] that occurred in the reporting period are summarised below.

Of the 11,805 cases, 443 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 282 cases [50];
- 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 161 cases.

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

[49] Medication errors search criteria: MedDRA (version 26.0): *HLTs (All paths):* Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product prescribing errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR *PTs:* Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Contraindication to vaccination; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

[50] Among the 443 cases, 61 cases involved children 6 months to 4 years and 98 cases involved children 5 through 11 years.

Post-Authorisation Data

- From the global safety database, 11,362 cases reporting 32,838 events (15.3% of 74,102 cases, the total PM dataset for the reporting period) indicative of potential medication errors were retrieved compared to 56,865 relevant cases (20.1%) analysed in the PSUR #4.

- The 11,362 relevant medication error cases originated (≥2% of cases) from the following countries: US (4906), Germany (1249), Sweden (1029), Japan (939), UK (938), Norway (517), Finland (360), France (279), Canada (225).

- The most frequently reported (≥2%) medication error PTs included Poor quality product administered (4731), Inappropriate schedule of product administration (4116), Product administration error (3562), Wrong product administered (1359), Product temperature excursion issue (1058), Expired product administered (464), Incorrect route of product administration (338).

- Clusters of medication errors were reported in one instance. The medication error cases (>200) were identified and coded to the PTs Poor quality product administered and Product administration error. No cases demonstrated harm and none had co-reported events: in 350 cases, it was reported that the provider administered BNT162b2 beyond the use date.

9.2.1. Medication Errors Categorisation

Among the medication error cases (11,362 cases), compared to 56,865 medication errors in the PSUR #4, 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)]: 360 cases (3.2%) compared to 1670 cases (2.9%) in the PSUR #4.
- Medication errors without harm [i.e., not resulting in adverse reaction(s)]: 10,995 cases (96.8%) compared to 55,167 (97.0%) in the PSUR #4.
- Potential medication errors: 6 cases (0.1%) compared to 39 cases (0.1%) in the PSUR #4.
- Intercepted medication errors: 1 case (0.001%) compared to 3 cases (0.01%) in the PSUR #4.

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

Cases are clustered in monovalent (original) or bivalent according to the vaccine formulation administered as last suspect dose.

9.2.2. Medication Errors in Subjects aged 6 Months through <5 Years[51]

- Number of relevant cases: 249.
- Country/region of incidence: US (233), Australia (7), Brazil, Japan (3 each), Canada (2), Germany (1).
- Number of relevant events: 396.
- Relevant event seriousness: non-serious (396).
- Relevant medication errors PTs most frequently reported (>10): Poor quality product administered (112), Product administration error (103), Wrong product administered (78), Product preparation error (33), Inappropriate schedule of product administration (25), Expired product administered (11).

Table 26 describes for each ME category the top 3 medication errors by vaccine presentation (monovalent versus bivalents) in individuals aged 6 months through <5 years.

Table 26. 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	**Monovalent**	Product administered at inappropriate site	0	1	1
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
Medication Errors without harm	**Monovalent**	Product administration error	0	40	40
		Inappropriate schedule of product administration	0	13	13
		Poor quality product administered, Product administered at inappropriate site	0	7	7
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	Wrong product administered	3	61	64
		Product administration error	0	37	37
		Poor quality product administered	0	12	12
Potential Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
Intercepted Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0

[51] Cases where the age was reported as "Infant" (3 cases) were evaluated in this age group.

9.2.3. Medication Errors in Subjects aged 5 through <12 Years[52]

- Number of cases: 716.
- Country/region of incidence (≥2%): US (413), Japan (122), Brazil (108), Canada (23).
- Number of relevant events: 1019.
- Relevant event seriousness: non-serious (1019).
- Relevant medication errors PTs most frequently reported (>10): Poor quality product administered (313), Product administration error (185), Expired product administered (181), Wrong product administered (118), Product preparation error (80), Inappropriate schedule of product administration (43), Product preparation issue (15), Product temperature excursion issue (14), Product label issue (13), Product label confusion (11).

Table 27 describes for each ME category the top 3 medication errors that occurred by vaccine presentation (monovalent versus bivalents) in individuals aged 5 through <12 years.

Table 27. 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	**Monovalent**	Expired product administered	0	1	1
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
Medication Errors without harm	**Monovalent**	Expired product administered	0	146	146
		Poor quality product administered	0	112	112
		Product administration error	0	47	47
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	Product administration error	0	104	104
		Wrong product administered	2	100	102
		Product preparation error	0	20	20
Potential Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
Intercepted Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0

[52] Cases where the age was reported as "Child" (235 cases) were evaluated in this age group.

9.2.4. Medication Errors in Subjects aged 12 Years and Older[53]

- Number of cases: 6525.
- Country/region of incidence (≥2%): US (1305), Germany (1202), Sweden (1025), UK (761), Norway (513), Finland (352), Japan (316), France (234), Canada (159).
- Number of relevant events: 7906.
- Relevant event seriousness: non-serious (7769), serious (137).
- Relevant medication errors PTs most frequently reported (>10): Inappropriate schedule of product administration (3932), Poor quality product administered (1112), Wrong product administered (901), Product administration error (879), Incorrect route of product administration (298), Product temperature excursion issue (242), Incorrect dose administered (107), Expired product administered (89), Medication error (64), Underdose (63), Product administered at inappropriate site (60), Vaccination error (56), Product preparation error (21), Wrong technique in product usage process (18), Product label issue (11).

Table 28 below describes for each ME category the top 3 medication errors occurred by vaccine presentation (monovalent versus bivalents) in individuals aged 12 years and older age group.

Table 28. 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	**Monovalent**	Inappropriate schedule of product administration	0	164	164
		Incorrect route of product administration	0	8	8
		Product administered at inappropriate site	0	7	7
	Bivalent Omi BA.1	Wrong product administered	4	14	18
		Inappropriate schedule of product administration	0	1	1
		Medication error	0	1	1
	Bivalent Omi BA.4/BA.5	Wrong product administered	1	3	4
		Product administered at inappropriate site	0	1	1
Medication Errors without harm	**Monovalent**	Inappropriate schedule of product administration	0	3028	3028
		Incorrect route of product administration	0	193	193
		Product administration error	0	81	81

[53] Cases where the age was reported as: "Adolescent" (4 cases), "Adult (174 cases) or "Elderly" (157 cases) were evaluated in this age group.

Table 28. Medication Error Categories: Top 3 Medication Errors in Subjects aged 12 Years and Older by Vaccine Presentations

ME Categories	Type of Vaccines	Medication error PTs	Intended	Administered	Total
Medication Errors without harm *Cont'd*	**Bivalent Omi BA.1**	Wrong product administered	36	220	256
		Product administration error	0	51	51
		Incorrect dose administered	0	16	16
	Bivalent Omi BA.4/BA.5	Product administration error	0	608	608
		Wrong product administered	4	367	371
		Product temperature excursion issue	0	179	179
Potential Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0
Intercepted Error	**Monovalent**	-	0	0	0
	Bivalent Omi BA.1	-	0	0	0
	Bivalent Omi BA.4/BA.5	-	0	0	0

9.2.5. Medication Errors in Subjects with Unknown Age

- Number of cases: 3872.
- Country/region of incidence (≥2%): US (2955), Japan (498), UK (174).
- Number of relevant events: 7243.
- Relevant event seriousness: non-serious (7234), serious (9).
- Relevant medication errors PTs most frequently reported (>115, >2%): Poor quality product administered (3194), Product administration error (2395), Product temperature excursion issue (799), Wrong product administered (262), Expired product administered (183), Inappropriate schedule of product administration (116).

Table 29 below describes for each ME category the top 3 medication errors occurred by vaccine presentation (monovalent versus bivalents) when the vaccine presentation is unknown age.

Table 29. 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	**Monovalent**	Inappropriate schedule of product administration	2
	Bivalent Omi BA.1	Wrong product administered	1
	Bivalent Omi BA.4/BA.5	-	0
Medication Errors without harm	**Monovalent**	Product administration error	743
		Product temperature excursion issue	172
		Inappropriate schedule of product administration	98
	Bivalent Omi BA.1	Product administration error	41
		Wrong product administered	39
		Expired product administered	28
	Bivalent Omi BA.4/BA.5	Product administration error	1358
		Product temperature excursion issue	396
		Poor quality product administered	387
Potential Error	**Monovalent**	Circumstance or information capable of leading to medication error	3
	Bivalent Omi BA.1	-	0
	Bivalent Omi BA.4/BA.5	Circumstance or information capable of leading to medication error	3
Intercepted Error	**Monovalent**	Intercepted product dispensing error	1
	Bivalent Omi BA.1	-	0
	Bivalent Omi BA.4/BA.5	-	0

Conclusion

Overall, among the 11,362 relevant medication error PM cases, 360 cases (0.5% of the total interval cases, 3.2% of total relevant medication error cases) were considered harmful because they were accompanied by clinically relevant co-reported events.

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

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

10. NON-CLINICAL DATA

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

11. LITERATURE

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

Response

Please refer to the content of this Section.

Nonclinical (Published)

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

Clinical (Published)

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

However, during the current reporting period, the literature article "Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023" (Hause et al.) reported important safety information about the use of bivalent vaccines and young children.

Hause et al state that no reports of myocarditis were recorded in VAERS by 01 January 2023 for the 861,251 children aged 5-11 years, who received a bivalent Pfizer-BioNTech booster in the US in the same period.

The article reference and the abstract are reported in Table 30. Full publication is available upon request.

Table 30. Relevant Literature

Article Reference	Abstract
Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among children aged 5-11 years - United States, October 12-January 1, 2023	On October 12, 2022, the Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) for bivalent (mRNA encoding the spike protein from the SARS-CoV-2 ancestral strain and BA.4/BA.5 Omicron variants) formulations of Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines for use as a single booster dose ≥2 months after completion of primary series or monovalent booster vaccination for children aged 5-11 years (Pfizer-BioNTech) and 6-17 years (Moderna); on December 8, 2022, FDA amended the EUAs to include children aged ≥6 months. The Advisory Committee on Immunization Practices (ACIP) recommends that all persons aged ≥6 months receive an age-appropriate bivalent mRNA booster dose. The safety of bivalent mRNA booster doses among persons aged ≥12 years has previously been described. To characterize the safety of bivalent mRNA booster doses among children aged 5-11 years after receipt of bivalent Pfizer-BioNTech and Moderna booster doses, CDC reviewed adverse events and

Table 30. Relevant Literature

Article Reference	Abstract
	health impacts reported to v-safe, a voluntary, smartphone-based U.S. safety surveillance system established by CDC to monitor adverse events after COVID-19 vaccination, and to the Vaccine Adverse Event Reporting System (VAERS), a U.S. passive vaccine safety surveillance system co-managed by CDC and FDA. During October 12-January 1, 2023, a total of 861,251 children aged 5-11 years received a bivalent Pfizer-BioNTech booster, and 92,108 children aged 6-11 years received a bivalent Moderna booster. Among 3,259 children aged 5-11 years registered in v-safe who received a bivalent booster dose, local (68.7%) and systemic reactions (49.5%) were commonly reported in the week after vaccination. Approximately 99.8% of reports to VAERS for children aged 5-11 years after bivalent booster vaccination were nonserious. There were no reports of myocarditis or death after bivalent booster vaccination. Eighty-four percent of VAERS reports were related to vaccination errors, 90.5% of which did not list an adverse health event. Local and systemic reactions reported after receipt of a bivalent booster dose are consistent with those reported after a monovalent booster dose; serious adverse events are rare. Vaccine providers should provide this information when counseling parents or guardians about bivalent booster vaccination. Preliminary safety findings from the first 11 weeks of bivalent booster vaccination among children aged 5-11 years are reassuring. Compared with the low risk of serious health effects after mRNA COVID-19 vaccination, the health effects of SARS-CoV-2 infection include death and serious long-term sequalae. ACIP recommends that all persons aged ≥ 6 months receive an age-appropriate bivalent mRNA booster dose ≥2 months after completion of a COVID-19 primary series or receipt of a monovalent booster dose.

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.

12. OTHER PERIODIC REPORTS

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

The list of periodic reports prepared and submitted by the MAH during the reporting period is provided in Table 31.

Table 31. List of Periodic Reports submitted in the Reporting Period

Periodic Report Type	No.	Reporting Period
Abbreviated SMSR[a]	12	16 December 2022 through 15 January 2023
	13	16 January 2023 through 15 February 2023
	14	16 February 2023 through 15 March 2023
	15	16 March 2023 through 15 April 2023
	16	16 April 2023 through 15 May 2023
	17	16 May 2023 through 15 June 2023

a. Submitted to non-EEA countries.

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

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

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

14. LATE-BREAKING INFORMATION

After the DLP,

- An updated CDS (version 22.0) was made effective on 24 July 2023; this updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5), several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.
- Signals:
    - A new signal (Mastitis/Breast swelling) was opened based upon an enquiry from the Australian regulatory authority (TGA). The signal is ongoing.
    - The ongoing signals (Menstrual irregularities and Sensorineural Hearing Loss) were closed as no risk on 26 July 2023 and on 19 July 2023, respectively.
- The CHMP approved on 22 June 2023, the EU-RMP versions 9.1 through 9.5, up-versioned to version 10.0 of the EURMP in the context of the procedures EMEA/H/C/005735/X/0176 (Original/Omicron BA.4/BA.5 in 6 month - 4 year primary series and booster including revised vaccination posology), EMEA/H/C/005735/II/0177(Original/Omicron BA.4/BA.5 in 5-11 years and 12+ years primary series including revised vaccination posology) and EMEA/H/C/005735/X/0180 (Original/Omicron BA.4/BA.5 in 5-11 years (RTU – blue caps).

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

Signal Overview

New signals for BNT162b2 during the reporting interval are presented below in Table 32 along with the ongoing signals and signals closed during the reporting interval.

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

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

Table 32. Overview of Signals (at DLP 18 June 2023)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Sensorineural Hearing Loss	New and ongoing	Enquiry from a competent authority (TGA, Australia)	Not applicable	
Retinal Vascular Occlusion	New and ongoing	Medical Literature	Not applicable	
Menstrual Irregularities	New and ongoing	This expanded focus topic (menstrual irregularities) is undergoing internal review following closure of the PRAC signal for Amenorrhea and Heavy Menstrual Bleeding	Not applicable	
Pemphigus and Pemphigoid[a]	Closed	Enquiry from a competent authority (EMA PRAC)	No Risk	EPITT No. 19859
Myositis	New and closed	Enquiry from a competent authority (EMA PRAC)	No Risk	EPITT No. 19883

a. Pemphigus and Pemphigoid is discussed in the subsection Other Safety Topic not Considered Signals as per PRAC indication [Signal procedure assessment report (EMEA/H/C/005735/SDA/061 - EPITT 19859)].
* Reflects the MAH position in the MAH signal log. This may differ from the position of the competent authority.

Other Safety Topics Not Considered Signals

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

- Whether the AE is new for the product;
- Seriousness, severity, increased frequency or medical significance of the data;
- High or rapidly increasing statistical disproportionality score;
- Potential public health impact;

- Factors suggestive of a relationship to the drug when considering disease knowledge, biological plausibility, mechanism of action of the drug or the drug class, alternative aetiologies based on clinical and scientific experience, and temporal clustering of events.

The safety topics monitored or reviewed are the following:

- Multisystem Inflammatory Syndrome (Appendix 5.2)
- Dyspnoea; Palpitations, Tachycardia/Heart Rate Increase (Appendix 5.3)
- Hemophagocytic lymphohistiocytosis (Appendix 5.5)
- Pemphigus and Pemphigoid (Appendix 5.6).

Product Lots and AE Reports

The most frequently reported lot numbers in PM case reports[54] (≥350 cases) are listed in Table 33 below.

Table 33. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases
EW6126	759
FC2336	694
GE3043	519
FE7053	491
FE2083	481
FC8889	437
FG3716	436
GD6800	432
EM0477	416
GD6797	393
FD0932	390
FD4555	383
FN3731	358
FA7812	353

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium). Among the cases reported in the table, only one case involving lot number EW6126 included a PT indicative of product quality issue (Product after taste), not associated to any AE.

The AEs most frequently reported (≥ 6%) with these lot numbers included Fatigue (733), Headache (725), Interchange of vaccine products (550), Heavy menstrual bleeding (547), Pain in extremity (492), Pyrexia (488), Lymphadenopathy (425), Arthralgia (414), and Menstruation irregular (397). These AEs do not differ from those reported in the overall incremental dataset.

[54] The inclusion of product lot numbers in this table does not imply product quality defects or issues.

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

Overall, the most frequently (≥ 65 occurrences) reported product issues regardless of lot number included the following PTs: Product temperature excursion issue (1058), Product colour issue (99), and Product label issue (65).

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

- Cases reporting PT Product colour issue described a colourless appearance for the vaccine. The PQC investigation results were pending in these cases.

- Cases reporting the PT Product label issue described vaccine administration after the beyond-use date, bivalent given as primary dose and second dose, bivalent given instead of monovalent, incorrect route of administration (subcutaneous)/bivalent diluted by mistake and injected, monovalent given as 1st and 2nd dose, monovalent given instead of bivalent, and no expiration date.

- The number of product issues did not show a trend that would require a change to the RSI. Vaccine administration and details on product storage are adequately described in the RSI. The expiry date is printed on every package. The monovalent and bivalent primary series/booster doses are adequately described on the product packaging/labelling. The product quality investigations performed for the cases that reported PT Product colour issue were pending.

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

AE/PC alerts are reviewed and evaluated to establish whether there is an association between the reported adverse event and the product quality defect or complaint. Upon safety evaluation, alerts are closed or undergo evaluation and escalation as per standard procedures.

Conclusion

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

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 34 summarises the important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU-RMP version 9.0 adopted on 10 November 2022 (Procedure number EMEA/H/C/005735/II/0147).

Table 34. Ongoing Safety Concerns at the Beginning of the Reporting Period (EU-RMP version 9.0)

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

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

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

1. Version 9.1 submitted on 03 March 2023:

- To support the extension of the indication to paediatric individuals aged 6 months to 4 years to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty original/Omicron BA.4-5 (3 micrograms) for primary series and as a 4th dose booster.

- To support the variation of the indication to paediatric individuals aged 5 to 11 years to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty Original/Omicron BA.4/BA.5 (10 micrograms) for primary series.

- To support the variation of the indication to individuals 12 years of age and older to receive bivalent Omicron BA.4/BA.5 modified vaccine (Comirnaty Original/Omicron BA.4-5 (30 micrograms) for primary series.

2. Version 9.2 submitted on 14 April 2023:

- To support the extension of the 10 mcg dose presentations for ages 5-11 years: the BA.4-5 (5/5 mcg) Dark Blue (multi-dose) and Light Blue (single dose) cap vials.

3. Version 9.3 submitted on 14 June 2023 to consolidate Version 9.1 and Version 9.2. and to propose:

- Inclusion of all pre-agreed PAM-MEA milestone changes: implementation of PAM-MEA-011.8 final outcome and PAM-MEA-011.9 preliminary AR outcome (i.e. study C4591010 deletion from the RMP).

- Removal of the important potential risk VAED/VAERD as result of the preliminary AR PSUR #04 (PSUSA/00010898/202212).

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

4. Version 9.4 submitted on 19 June 2023 to update the milestone for study C4591007 following the EMA approval of Justification milestone extension (EMEA/H/C/005735/X/0176).

5. Version 9.5 submitted on 21 June 2023:

– To consolidate the EU-RMP version by merging RMP versions 9.3 and 9.4.

– Updates RMP PART I according to the simplified posology implemented in the SmPC.

All these versions were approved on 22 June 2023 under RMP version 10.0.

16.2. Signal Evaluation

Please refer to Table 32 for signals that were ongoing and closed during the reporting interval.

16.2.1. Evaluation of Closed Signals

Table 35 provides the summary evaluations of the signals closed during the reporting period. Routine signal detection continues.

Table 35. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Signals Determined not to be risks	
Myositis	Following receipt of an EMA PRAC adopted recommendation (EMA/PRAC/3178/2023) for this signal on 12 January 2023, myositis and vaccination with BNT162b2 (original and bivalent) was evaluated by the MAH. Evaluation consisted of the review of non-clinical data that showed common occurrence of injection site reactions but no microscopic evidence of any inflammatory process in muscle sites beyond the injection site on necroscopy (e.g., gastrocnemius, tongue, heart). The clinical study database for 4 completed and 7 ongoing Pfizer-run clinical studies was searched for relevant reports per the MedDRA search strategy for myositis. Three cases were retrieved, all assessed by the investigators as not related: One report of dermatomyositis in the pivotal study of >44,000 participants (C4591001) occurring on day 44 after dose 3 of BNT162b2; 1 report of worsening dermatomyositis in a study of immunocompromised participants (C4591024) in a 6-year-old with a history of juvenile dermatomyositis occurring 76 days after dose 2 of BNT162b2; also in C4591024, 1 report of myositis in a 4 year-old with a history of renal transplantation occurring 74 days after dose 3 of BNT162b2. The literature search retrieved 10 articles (1 was a pre-print) that were mostly retrospective cohort studies in patients with inflammatory myopathies who were surveyed or otherwise assessed for flares following vaccination. Some studies reported new cases of myositis and flares of underlying disease in a minority of patients, but most authors acknowledged that it was not possible to assume a causal association based on their results. Indeed, the potential mechanisms for as association hypothesized by the

Table 35. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Myositis *Cont'd*	authors were not uniform. The MAH's safety database disproportionality analysis was unremarkable and a review of the 1017 cases retrieved were of variable quality. There were 16 cases (15 individuals) without alternative aetiologies that had temporality with vaccination. The O/E ratios in some age groups and risk windows were greater than 1 suggesting that the number of reported cases may be higher than expected compared to unvaccinated persons, however, the risk windows for myositis following Comirnaty vaccines are unclear, and the caveats of the O/E analyses, including the use of several risk windows, one background rate, the unknown degree of underreporting, the small number of observations in some age stratifications and the possibility of the numerator including patients with a medical history of IIM (that was not reported in the case), need to be weighed in consideration. Overall, in the context of the >4 billion doses of BNT162b2 original and bivalent shipped since Dec 2020, the totality of the data did not allow a causal link to be concluded. In the 2nd adopted PRAC recommendation (12 May 2023), the PRAC agreed that a causal association between Comirnaty and myositis could not be concluded, and no update to the product information and/or the risk management plan was warranted. Refer to Appendix 5 for the response to the PRAC's request included in the signal AR (PAM-SDA-063, EPITT: 19883) to explore the feasibility of using healthcare data prior to and during the COVID-19 pandemic to better understand the occurrence of myositis in a broad population and provide proposals to obtain more recent background incidence rates (during the pandemic/immunization campaigns).
Pemphigus and Pemphigoid	Following receipt of an EMA PRAC adopted recommendation (EMA/PRAC/868335/2022) for this signal on 01 December 2022, pemphigus/pemphigoid was evaluated by the MAH. On 14 Apr 2023, the PRAC concluded that the current evidence was insufficient to establish a causal relationship between Comirnaty and pemphigus or pemphigoid. They requested that within PSUR 5 the MAH perform a review of new emerging data on pemphigus and pemphigoid; this can be found in Appendix 5.6. The outcome of this updated review does not change the MAH previous assessment which concluded that there is insufficient evidence for a causal association between Comirnaty and pemphigus/pemphigoid.

16.2.2. Signal Evaluation Plan for Ongoing Signals

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

Table 36. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Menstrual irregularities[a]	Following closure of the EMA PRAC signal Heavy menstrual bleeding and Amenorrhea, the MAH determined that the broader concept of menstrual irregularities (not limited to HMB and Amenorrhea) should be evaluated. (Appendix 5.7).
Sensorineural hearing loss[a]	Following receipt of a request by TGA (Australia) for an "updated signal analysis" on this topic in the next PSUR, the MAH re-opened this signal and provides and full evaluation in Appendix 5.4.
Retinal vascular occlusion	Prompted by a literature article entitled *Risk assessment of retinal vascular occlusion after COVID-19 vaccination* by Li Jing-Xing et al.[1] the MAH has undertaken an evaluation of this signal; the evaluation is ongoing.

a. Closed after DLP as no risk.

16.3. Evaluation of Risks and New Information

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

16.3.1. Evaluation of Important Identified Risks

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 1014 potentially relevant cases of Myocarditis and Pericarditis: 711 cases reported myocarditis and 379 cases reported pericarditis (in 76 of these 1014 cases, both myocarditis and pericarditis were reported).

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

Literature Data

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

Risk Assessment of New Information

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

This risk is communicated in the BNT162b2 CDS, in:

- Section 4.4, *Special warnings and precautions for use - General recommendations*, which includes information on appropriate action to be taken, as follows: "Very rare

cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild, and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients".[55]

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

- Appendices A and B.

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

16.3.1.1.1. Important Identified Risks – Myocarditis

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

Overall – All Ages

Clinical Trial Data

- Number of cases: none, no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 711 (original [622], bivalent Omi BA.1 [50], bivalent Omi BA.4/BA.5 [49]; 1.0% of 74,102 cases of the total PM dataset), compared to 1287 cases (0.5%) retrieved in the PSUR #4.
- Country/region of incidence (≥10): Germany (209), UK (101), US (57), Japan (46), Australia (43), Canada (34), Austria (33), France (31), Sweden (26), Italy (25), Spain (16), Republic of South Korea (10). The remaining 80 cases were distributed among 35 countries.
- MC cases (385), NMC cases (326).
- Subjects' gender: female (249), male (427) and unknown (35).

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

- Subjects' age in years: n = 625, range: 5 – 92, mean: 41.0, median: 39.0.
- Medical history (n = 293); the most frequently (≥10) reported medical conditions included Hypertension (49), Asthma (29), Hypothyroidism (21), Seasonal allergy (19), Obesity (17), Tobacco user (15), Non-tobacco user (13), Myocarditis (11), and Hypersensitivity (10).
- COVID-19 Medical history (n = 39): COVID-19 (33), Suspected COVID-19 (5), Coronavirus infection, Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (1 each).
- Co-suspect medications (≥2): elasomeran (7), COVID-19 vaccine prot. subunit (NVX COV 2373) (3), COVID-19 vaccine, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), and influenza vaccine inact split 4V (2 each).
- Number of relevant events: 725.
- Relevant event seriousness: serious (725).
- Reported relevant PTs: Myocarditis (595), Myopericarditis (116), Carditis (5), Eosinophilic myocarditis (4), Chronic myocarditis (3), Giant cell myocarditis (2).
- Relevant event outcome: fatal (35), resolved/resolving (220), resolved with sequelae (43), not resolved (170), unknown (257).
- Risk factors: Of the 711 cases reporting events indicative of myocarditis, 385 cases (54.1%) were medically confirmed. Of the 711 cases, in 160 cases (22.5% of the cases reporting myocarditis related events) the events were confounded by subject' s relevant medical history such as cardiac disorders, neoplasms, COVID-19, immune disorders, embolic disorders etc and/or relevant co-suspect medications. Of the total 711 cases, in 216 cases (30.4%) the cases were confounded by co-reported events indicative of an alternate aetiology, such as neoplasms, ischaemic cardiomyopathy/coronary artery disease, infections, or the long time to onset of the myocarditis event post-vaccination (>21 days) did not match a suspected vaccine induced event. Of the 711 cases, in 557 cases (78.3%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

Age-stratified data[56]

Subjects aged 6 months through <5 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

[56] Cases where the age was reported only as:
- "Adolescent" (4 cases) were evaluated in the overall and in the 16-17 years age groups,
- "Adult" (16 cases) were evaluated in the overall and in the Age Unknown age group; and
- "Elderly" (2 cases) were evaluated in the overall and in the ⩾ 40 years age groups.

Post-Authorisation Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Subjects aged 5 through <12 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 2 (original [2]; 0.003% of 74,102 cases of the total PM dataset, 0.2% of the 968 subjects aged 5-11 years), compared to 18 cases (0.01 %) retrieved in the PSUR #4.
- Country/region of incidence: [redacted] and [redacted] (1 each).
- Subjects' age in years: 5 and 8.
- Medical history (n = 2): Cough and Vena cava thrombosis (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs: Chest pain, Fibrin D dimer increased, Inappropriate schedule of product administration, Methylene tetrahydrofolate reductase gene mutation (1 each).

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

Table 37. Myocarditis in Subjects aged 5 through <12 Years (N = 2)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	1	1	0
Relevant PT[a]	Myocarditis	1	1	0
Hospitalisation required/prolonged	Yes	0	1	0
	No	1	0	0
Relevant suspect dose	Dose 2	1	1	0
Vaccine Presentation	Monovalent (original)	1	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=2	1-5 days	1	0	0
	Unknown	0	1	0
Event Outcome	Resolved	1	0	0
	Unknown	0	1	0
Duration of event[b]	Unavailable	1	0	0

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

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 26 (original [26]; 0.04% of 74,102 cases of the total PM dataset, 3.2% of the 815 subjects aged 12-15 years), compared to 88 cases (0.03%) retrieved in the PSUR #4.
- Country/region of incidence: Japan (5), Australia, Germany (3 each), Canada, Italy, Republic of South Korea, Taiwan, Province of China (2 each), France, Hungary, Poland, Sweden, Thailand, Turkey, US (1 each).
- Subjects' age in years: n = 26, range: 12 – 15, mean: 14.0, median: 14.0.
- Medical history (n = 16); the most frequently (≥2) reported medical conditions included Asthma (4), Premature baby (3), and Myocarditis (2).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain, Pyrexia (8 each), Dyspnoea, Pericarditis, Tachycardia (3 each), Asthenia, Fatigue, Headache, Myalgia, Palpitations, and Pericardial effusion (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 38 below.

Table 38. Myocarditis in Subjects aged 12 – 15 Years (N = 26)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	3	17	1
	No	5	0	0
Relevant PT[a]	Myocarditis	8	14	1
	Myopericarditis	1	3	0
Hospitalisation required/prolonged	Yes	5	10	1
	No	4	7	0
Relevant suspect dose	Dose 1	1	3	0
	Dose 2	4	12	1
	Dose 3	1	1	0
	Dose 4	1	0	0
	Dose Unknown	1	1	0
Vaccine Presentation	Monovalent (original)	8	17	1

Table 38. Myocarditis in Subjects aged 12 – 15 Years (N = 26)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=27	≤ 24 hours	0	1	0
	1-5 days	1	2	0
	6-13 days	2	0	0
	14-21 days	0	1	0
	>365 days	0	1	0
	Unknown	6	12	1
Event Outcome	Fatal	3	1	0
	Not resolved	1	1	0
	Resolved	0	6	1
	Resolved with sequelae	1	0	0
	Resolving	1	4	0
	Unknown	3	5	0
Duration of event[b] n=1, median=N/A	Up to 3 days	0	1	0
	Unavailable	1	5	1

a. All serious occurrences. One case reported more than 1 relevant event.
b. For those cases where the event resolved/resolved with sequelae.

Fatal cases (3):

A 14-year-old male subject, dose 1 (monovalent [original]), medically confirmed, Germany:

- Medical history: Becker's muscular dystrophy, COVID-19, Cerebral palsy, Cochlea implant, Hypoacusis, Intellectual disability, Language disorder, Mental disability, Neuromyopathy, Physical disability, Quadriparesis and Wheelchair user.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Off label use, Circulatory collapse, Pyrexia, Dyspnoea, Hypotonia, Hyperpyrexia, Chills, Pericarditis and Myocarditis.
- Time to onset (myocarditis): not reported.
- Causes of death: In addition to the above events that had a fatal outcome, the autopsy reported Arnold-Chiari malformation, Marfanoid habitus, Myocarditis and Pericarditis.
- Comment: The subject with Becker's muscular dystrophy received the 1st dose of BNT162b2 for COVID-19 immunisation and neuromyopathy (off label use) and had the above reported events that had a fatal outcome the next day of receiving the vaccine. There is no information regarding the circumstances around the time of death. In this case, the subject's co-morbidities preclude an individual contributory role of the vaccine towards the fatal outcome.

A 14-year-old female subject, dose 3 (monovalent [original]), medically confirmed, Japan:

- Medical history: Orthostatic intolerance.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myopericarditis, Myocarditis, Pericarditis, Cardiac failure, Arrhythmia, Arrhythmia supraventricular, and Sudden death.

- Time to onset (myocarditis): 2 days.
- Causes of death: In addition to the above events that had a fatal outcome, the autopsy reported Myocarditis, Pericarditis, Pulmonary congestion, and Pulmonary oedema.
- Comment: The subject with a medical history of orthostatic intolerance received 3rd dose of BNT162b2 and 2 days later was found dead. In this case, a COVID-19 antigen quantification test performed using a nasopharyngeal swab taken before autopsy yielded negative results. Based on the available information, a vaccine-related multiple-organ inflammation (myopericarditis) was diagnosed based on the presence of erythrocyte-laden macrophages as well as congestive oedema of the lungs on histology suggested signs of heart failure from the previous day. Although the extent of inflammation was relatively narrow, reporter commented that the presence of foci centered on the atria and breathlessness are the findings that raise the suspicion of heart failure several hours before death and led to the diagnosis that the cause of death was vaccine-related myopericarditis, which led to severe arrhythmias and progressive heart failure.

A 15-year-old female subject, dose 2 (monovalent [original]), non-medically confirmed, Italy:

- Medical history: Myeloid leukaemia.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): 2 days.
- Causes of death: Myocarditis. It was not reported if an autopsy was performed.
- Comment: The subject with a medical history of myeloid leukaemia in the year 2020 underwent transplant (on an unknown date). She received the 1st dose of BNT162b2 in September 2021 and the 2nd dose of BNT162b2 in January 2022. On an unspecified day in January 2022, she developed myocarditis and underwent an unspecified surgery for myocarditis and was noted with the recurrence of myeloid leukaemia. It was only reported that subject died on 22 February 2022.

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 38 (original [38]; 0.05% of 74,102 cases of the total PM dataset, 8.5% of the 446 subjects aged 16-17 years), compared to 79 cases (0.03%) retrieved in the PSUR #4.

- Country/region of incidence: US (11), Republic of South Korea (7), Germany (5), Japan (4), Canada, Italy, Spain, UK (2 each), Australia, France and Slovakia (1 each).
- Subjects' age in years: n = 34, range: 16 – 17, mean: 16.5, median: 16.5.
- Medical history (n = 13); the most frequently (≥2) reported medical conditions included Asthma (3), and Hospitalisation (2).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect medications: meningococcal vaccine (1).
- Most frequently co-reported PTs (≥2): Pyrexia (5), Chest pain (4), Dyspnoea, Fatigue, Palpitations, Tachycardia (3 each), Chest discomfort, COVID-19, Dizziness, and Ejection fraction decreased (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 39 below.

Table 39. Myocarditis in Subjects aged 16 – 17 Years (N = 38)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	31	2
	No	3	0	0
Relevant PT[a]	Myocarditis	5	26	1
	Myopericarditis	0	5	1
Hospitalisation required/prolonged	Yes	3	22	2
	No	2	9	0
Relevant suspect dose	Dose 1	5	4	0
	Dose 2	0	15	0
	Dose 3	0	6	0
	Dose 4	0	1	0
	Dose Unknown	0	5	2
Vaccine Presentation	Monovalent (original)	5	31	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=38	≤24 hours	0	2	0
	1-5 days	1	5	1
	6-13 days	0	1	0
	22-31 days	1	0	0
	32-60 days	0	1	0
	61-180 days	1	0	0
	Unknown	2	22	1
Event Outcome	Not resolved	2	3	0
	Resolved	0	15	0
	Resolving	1	4	1
	Unknown	2	9	1
Duration of event[b] n=2, median= 16 days	11-26 days	0	2	0
	Unavailable	0	13	0

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

Subjects aged 18 – 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 89 (original [80], bivalent Omi BA.1 [5], bivalent Omi BA.4/BA.5 [4]; 0.12% of 74,102 cases of the total PM dataset, 2.3% of the 3944 subjects aged 18-24 years), compared to 199 cases (0.07%) retrieved in the PSUR #4.
- Country/region of incidence (≥3): Germany (26), Austria (10), US (8), UK (6), Italy, Japan (5 each), Australia, France (4 each), Hong Kong, Spain, Sweden (3 each). The remaining 12 cases were distributed among 10 countries.
- Subjects' age in years: n = 89, range: 18 – 24, mean: 20.8, median: 21.0.
- Medical history (n = 30): the most frequently (≥2) reported medical conditions included Asthma (5), Epilepsy, Myocarditis, Tobacco user (3 each), and Hypersensitivity (2).
- COVID-19 Medical history (n = 5): COVID-19 (5).
- Co-suspect medications: davesomeran, elasomeran (1 each).
- Most frequently co-reported PTs (≥5): Chest pain (13), Dyspnoea (11), Fatigue, Palpitations, Pericarditis (10 each), Headache, Pyrexia (9 each), Interchange of vaccine products (7), Dizziness, Tachycardia (6 each), and Exercise tolerance decreased (5).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 40 below.

Table 40. Myocarditis in Subjects aged 18 – 24 Years (N = 89)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	7	36	1
	No	13	32	0
Relevant PT[a]	Myocarditis	18	54	1
	Myopericarditis	3	15	1
Hospitalisation required/prolonged	Yes	15	37	2
	No	6	32	0
Relevant suspect dose	Dose 1	3	9	0
	Dose 2	7	22	0
	Dose 3	6	19	0
	Dose 4	2	2	1
	Dose Unknown	2	16	0
Vaccine Presentation	Monovalent (original)	18	62	0
	Bivalent Omi BA.1	1	3	1
	Bivalent Omi BA.4/BA.5	1	3	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n= 93[b]	≤24 hours	3	10	0
	1-5 days	5	15	0
	6-13 days	1	1	0
	14-21 days	1	4	0
	22-31 days	2	1	0
	32-60 days	0	3	0
	61-180 days	1	3	0
	181-365 days	1	3	0
	>365 days	1	2	0
	Unknown	7	27	2
Event Outcome	Fatal	1	2	0
	Not resolved	11	8	0
	Resolved	2	23	0
	Resolved with sequelae	4	3	0
	Resolving	2	9	1
	Unknown	1	24	1
Duration of event[c] n= 10, median= 90 days	Up to 3 days	0	1	0
	4-6 days	1	0	0
	7-10 days	0	1	0
	11-26 days	0	1	0
	27-57 days	0	1	0
	58-180 days	1	1	0
	181-365 days	0	2	0
	>365 days	0	1	0
	Unavailable	5	18	0

a. All serious occurrences. Three cases reported more than 1 relevant event.
b. One case (AER no. [redacted]) reported 2 occurrences of the same event (PT: Myopericarditis) with different onset dates. However, the event outcome was counted once as both events resolved with sequelae.
c. For those cases where the event resolved/resolved with sequelae.

Fatal cases (3):

A 22-year-old male subject, dose 3 (bivalent Omi BA.4/BA.5), medically confirmed, Japan:

- Medical history: none
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myocarditis, Cardio-respiratory arrest, Ventricular fibrillation, Cardiogenic shock.
- Time to onset (myocarditis): 3 days.
- Causes of death: As mentioned above, the events coded to the PTs Myocarditis, Cardio-respiratory arrest, Ventricular fibrillation, Cardiogenic shock had a fatal outcome. An autopsy was performed, and the cause of death was being evaluated at the time of reporting.
- Comment: Limited information: Three (3) days after receiving the 3rd dose of novel coronavirus vaccine, the subject experienced suspected myocarditis and was admitted to a medical emergency center. When the subject was brought in, the ventricular fibrillation was persisting and ECMO was started. The subject was in cardiogenic shock state and underwent insertion of Impella CPSA. Despite intensive treatment, he showed no improvement and expired 7 days post the vaccination. There is no information in the case regarding how or why myocarditis was suspected and if confirmed. Limited information provided regarding the subject's medical history limits a meaningful causality assessment in this case.

A 24-year-old male subject, dose 2 (monovalent [original]), non-medically confirmed, US:

- Medical history: none
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myocarditis, Cardiac failure.
- Time to onset (myocarditis): 40 days.
- Causes of death: As mentioned above, the events coded to the PTs Myocarditis, and Cardiac failure. An autopsy report from the coroner's office showed COVID-19 vaccine-related myocarditis.
- Comment: The subject received the first dose on 27 August 2021 and was noted with blood in his urine. However, he received the second dose on 17 September 2021, and he also developed flu-like symptoms that did not resolve. He was visited to the emergency department and was treated with amoxicillin/clavulanate, Mucinex and Nyquil. However, he was visited again to the emergency department with several symptoms, but none were related to cardiac events according to the report. His cough worsened, was found with a sinus infection and also developed photosensitivity. Despite intensive treatment, he died on 27 October 2021. In this case, based on the available information, a contributory role

of the infection cannot be ruled out and it is notable that although detailed history of the infectious condition is available for the subject, there is no detail provided regarding the myocarditis diagnosis.

A 21-year-old female subject, dose 2 (monovalent [original], Moderna), non-medically confirmed, Australia:

- Medical history: Antiphospholipid syndrome, Appendicectomy, Coagulopathy
- Co-suspect medications: davesomeran, elasomeran.
- Concomitant medications: none.
- PTs with fatal outcome: Interchange of vaccine products, Cardiac failure, Myocardial infarction, and Myocarditis.
- Time to onset (myocarditis): Not reported.
- Causes of death: As mentioned above, the events coded to the PTs Cardiac failure, Myocardial infarction, and Myocarditis. It is unknown if an autopsy was performed.
- Comment: The subject with a relevant medical history of coagulopathy received the first and the second doses of BNT162b2 in September and October 2021 followed by Moderna vaccine for the third dose (booster) on 18 February 2022. On the next day, the subject developed events coded to the PTs Syncope, Fall and Head injury. She also had events coded to the PTs Malaise, Fatigue, Illness, Abdominal pain upper, Vomiting and Pyrexia. She was hospitalized and diagnosed with heart failure. On 05 March 2022, she was drifting in and out of consciousness (PT: Altered state of consciousness). Despite treatment on 27 March 2022, she died. Her medical certificate stated that she died of myocardial infarction and that she had subacute myocarditis. In this case, due to presence of myocardial infarction that is an ischemic condition, criteria for myocarditis are not met.

Subjects aged 25 – 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 61 (original [57], bivalent Omi BA.1, bivalent Omi BA.4/BA.5 [3 each]; 0.08% of 74,102 cases of the total PM dataset, 1.3% of the 4622 subjects aged 25-29 years), compared to 108 cases (0.04%) retrieved in the PSUR #4.
- Country/region of incidence (≥2): Germany (17), UK (7), Australia (6), Austria (5), Italy (4), Spain, Sweden, US (3 each), Canada, France, and Iceland (2 each). The remaining 7 cases were distributed among 7 countries.
- Subjects' age in years: n = 61, range: 25 – 29, mean: 26.7, median: 27.0.

- Medical history (n = 20); the most frequently (≥2) reported medical conditions included Tobacco user (3), Hypothyroidism, Lactose intolerance, Mite allergy, Myopericarditis, Obesity, and Seasonal allergy (2 each).
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications: COVID-19 vaccine prot. subunit (NVX COV 2373) (3).
- Most frequently co-reported PTs (≥5): Chest pain (14), Fatigue (11), Dyspnoea (9), Interchange of vaccine products, Palpitations, Pyrexia, Tachycardia (7 each), Hypoaesthesia, and Pain in extremity (5 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 41 below.

Table 41. Myocarditis in Subjects aged 25 – 29 Years (N = 61)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	9	24	0
	No	8	20	0
Relevant PTs[a]	Myocarditis	11	34	0
	Myopericarditis	6	10	0
Hospitalisation required/prolonged	Yes	6	20	0
	No	11	24	0
Relevant suspect dose	Dose 1	6	9	0
	Dose 2	4	17	0
	Dose 3	2	11	0
	Dose 4	1	1	0
	Dose Unknown	4	6	0
Vaccine Presentation	Monovalent (original)	15	40	0
	Bivalent Omi BA.1	1	2	0
	Bivalent Omi BA.4/BA.5	1	2	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n= 61	≤ 24 hours	2	2	0
	1-5 days	1	4	0
	6-13 days	1	2	0
	14-21 days	1	1	0
	22-31 days	0	1	0
	32-60 days	2	2	0
	61-180 days	1	3	0
	181-365 days	0	2	0
	>365 days	0	1	0
	Unknown	9	26	0
Event Outcome	Not resolved	6	8	0
	Resolved	4	12	0
	Resolved with sequelae	1	4	0
	Resolving	2	4	0
	Unknown	4	16	0
Duration of event[b] n=3, median= 22 days	11-26 days	0	2	0
	58-180 days	0	1	0
	Unavailable	5	13	0

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

Subjects aged 30 – 39 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 112 (original [103], bivalent Omi BA.1 [8], bivalent Omi BA.4/BA.5 [4]; 0.2% of 74,102 cases of the total PM dataset, 1.1% of the 10,413 subjects aged 30-39), compared to 162 cases (0.06%) retrieved in the PSUR #4.
- Country/region of incidence (≥3): Germany (42), UK (18), Sweden (11), Australia (8), Austria (6), Japan (4), France, and Italy (3 each). The remaining 17 cases were distributed among 12 countries.
- Subjects' age in years: n = 112, range: 30 – 39, mean: 34.8, median: 35.0.
- Medical history (n = 39); the most frequently (≥2) reported medical conditions included Hypothyroidism, Seasonal allergy (8 each), Non-tobacco user (5), Asthma, Drug hypersensitivity, Tobacco user (4 each), Dermatitis contact, Hypersensitivity, Hypertension, and Mite allergy (2 each).
- COVID-19 Medical history (n = 10): COVID-19 (7), Suspected COVID-19 (3), Post-acute COVID-19 syndrome and SARS-CoV-2 test positive (1 each).
- Co-suspect medications: elasomeran (2), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine inact split 4V, and teriflunomide (1 each).
- Most frequently co-reported PTs (≥5): Fatigue (29), Chest pain (28), Dyspnoea (26), Palpitations (20), Tachycardia (14), Pyrexia (13), Headache, Inappropriate schedule of product administration (12 each), Arrhythmia, Malaise (10 each), Dizziness, Pericarditis, Syncope (9 each), Cardiac failure (8), Asthenia, Interchange of vaccine products (7 each), Arthralgia, Pain (6 each), Chronic fatigue syndrome, Disturbance in attention, Dyspnoea exertional, and Pain in extremity (5 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 42 below.

Table 42. Myocarditis in Subjects aged 30 – 39 Years (N = 112)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	18	37	0
	No	27	29	1
Relevant PT[a]	Myocarditis	38	53	1
	Myopericarditis	6	14	0
	Carditis	1	1	0
	Eosinophilic myocarditis	0	1	0
	Giant cell myocarditis	1	0	0
Hospitalisation required/prolonged	Yes	17	41	0
	No	29	28	1
Relevant suspect dose	Dose 1	9	18	0
	Dose 2	20	21	0
	Dose 3	7	16	0
	Dose 4	4	2	0
	Dose Unknown	5	9	1
Vaccine Presentation	Monovalent (original)	38	63	0
	Bivalent Omi BA.1	4	2	1
	Bivalent Omi BA.4/BA.5	3	1	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=116	≤24 hours	2	2	0
	1-5 days	7	6	0
	6-13 days	4	2	0
	14-21 days	1	3	0
	22-31 days	2	1	0
	32-60 days	2	1	0
	61-180 days	4	10	0
	181-365 days	0	7	0
	>365 days	0	5	0
	Unknown	24	32	1
Event Outcome	Fatal	0	1	0
	Not resolved	18	16	0
	Resolved	4	11	0
	Resolved with sequelae	5	6	0
	Resolving	6	11	1
	Unknown	13	24	0
Duration of event[b] n=4, median=456 days	58-180 days	0	1	0
	>365 days	2	1	0
	Unavailable	7	15	0

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

Fatal case (1):

A 32-year-old male subject, dose 4 (bivalent Omi BA.1), medically confirmed, Sweden:

- Medical history: Epilepsy.
- Co-suspect medications: none.
- Concomitant medications: lacosamide and levetiracetam.

- PTs with fatal outcome: Acute cardiac event, Myocarditis, Cardiovascular insufficiency.
- Time to onset (myocarditis): 27 days.
- Causes of death: Clinical autopsy showed lymphocytic myocarditis in the AV-node/ bundle of His which was believed to have triggered an acute cardiac event; widespread acute aspiration in the lungs; brain with oedema and chronic contusion. Autopsy reported cardiovascular insufficiency and myocarditis.
- Comment: Limited information reported – the subject who received 3 doses of Comirnaty received the bivalent Omi BA.1 as the 4th dose and developed the above events that had a fatal outcome. Due to limited information and a long latency from the vaccination, an individual role of vaccine in inducing myocarditis is unassessable.

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 303 (original [243], bivalent Omi BA.1 [30], bivalent Omi BA.4/BA.5 [35]; 0.4% of 74,102 cases of the total PM dataset, 0.7% of the 42,521 subjects ≥ 40 years), compared to 480 cases (0.2%) retrieved in the PSUR #4.
- Country/region of incidence (≥5): Germany (106), UK (55), Japan (24), US (15), Australia, Austria, France (12 each), Canada (11), Italy (9), Sweden (7), and Spain (5). The remaining 35 cases were distributed among 22 countries.
- Subjects' age in years: n = 301, range: 40 – 92, mean: 57.5, median: 55.0.
- Medical history (n = 160); the most frequently (≥5) reported medical conditions included Hypertension (44), Asthma, Obesity (12 each), Hypothyroidism (11), Diabetes mellitus, Type 2 diabetes mellitus (9 each), Atrial fibrillation (8), Hypercholesterolaemia (7), Depression, Myopericarditis, Seasonal allergy, Tobacco abuse (6 each), Appendicectomy, Cardiac disorder, Chronic obstructive pulmonary disease, Fibromyalgia, Hypersensitivity, Migraine, Myocarditis, and Non-tobacco user (5 each).
- COVID-19 Medical history (n = 13): COVID-19 (10), Suspected COVID-19 (2), Coronavirus infection (1).
- Co-suspect medications (≥2): elasomeran (3), COVID-19 vaccine (2).
- Most frequently co-reported PTs (≥10): Fatigue (76), Chest pain (69), Dyspnoea (68), Palpitations (45), Pericarditis (39), Pyrexia (34), Interchange of vaccine products, Tachycardia (32 each), Dizziness (30), Headache (26), Arrhythmia (23), Asthenia (22), Cardiac failure, Myalgia (20 each), Malaise (17), Angina pectoris (16), Chest discomfort, Dyspnoea exertional (15 each), Arthralgia, Condition aggravated, Disturbance in attention, General physical health deterioration, Pain (14 each), Off label use, Pain in extremity (13 each), Hypertension, Pericardial effusion (12 each), Memory impairment, Myocardial infarction, Paraesthesia, Sleep disorder (11 each), Blood pressure increased,

Cardiomyopathy, Inappropriate schedule of product administration, Pneumonia, and Somnolence (10 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 43 below.

Table 43. Myocarditis in Subjects aged ≥40 Years (N = 303)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	66	88	1
	No	64	78	6
Relevant PTs[a]	Myocarditis	111	138	7
	Myopericarditis	18	23	0
	Chronic myocarditis	1	2	0
	Eosinophilic myocarditis	0	3	0
	Carditis	0	1	0
	Giant cell myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	46	85	4
	No	84	83	3
Relevant suspect dose	Dose 1	22	30	1
	Dose 2	37	34	1
	Dose 3	31	48	1
	Dose 4	15	24	0
	Dose 5	9	9	0
	Dose 6	2	1	0
	Dose Unknown	14	20	4
Vaccine Presentation	Monovalent (original)	96	136	6
	Bivalent Omi BA.1	17	12	1
	Bivalent Omi BA.4/BA.5	17	18	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=305	≤24 hours	11	9	0
	1-5 days	21	25	1
	6-13 days	8	6	1
	14-21 days	7	6	1
	22-31 days	2	6	0
	32-60 days	3	7	0
	61-180 days	9	13	0
	181-365 days	4	6	0
	>365 days	3	1	0
	Unknown	62	89	4
Event Outcome	Fatal	7	16	0
	Not resolved	44	45	2
	Resolved	18	20	1
	Resolved with sequelae	9	9	0
	Resolving	11	30	0
	Unknown	41	48	4
Duration of event[b] n=13, median=58 days	Up to 3 days	2	1	0
	7-10 days	1	0	0
	11-26 days	1	0	0
	27-57 days	1	0	0
	58-180 days	4	0	0
	181-365 days	0	2	0

Table 43. Myocarditis in Subjects aged ≥40 Years (N = 303)

	>365 days	0	1	0
	Unavailable	18	25	1

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

Fatal cases (23):

Of these 23 cases, there were 18 medically confirmed cases and 5 non-medically confirmed cases.

- Non-medically confirmed cases (5):

Of these 5 non medically confirmed cases, all the cases were elderly subjects where the age ranged from 71 to 90. In these 5 cases, the subject's medical history such as coronary artery disease, chronic kidney disease, arteriosclerosis, cardiac disorder, Parkinson's disease or long latency period (such as 84 days, 111 days, 585 days) precluded a meaningful causality assessment.

- Medically confirmed cases (18):

Of the 18 medically confirmed cases, there were 10 elderly and 8 adult subjects. Of these 10 elderly cases, where the subjects' age ranged from 71 to 87 years, in 2 cases, the latency of the myocarditis events was ≤24 hours, where in both the cases, subjects' medical history such as hypertension, diabetes mellitus, autoimmune thyroiditis, cerebral infarction, obesity, thrombophlebitis, precluded an individual contributory role of the BNT162b2 vaccine towards the fatal events. In the remaining 8 elderly cases, the subjects' elderly age, or the medical history such as hypertension, arterial occlusive disease, chronic obstructive pulmonary disease, metastases, Type 2 diabetes mellitus, or long latency periods (such as ranging from 56 to 80 days) or limited information on the above details precluded an individual contributory role of the BNT162B2 vaccine towards the fatal events.

In the remaining 8 cases, the subjects' age ranged from 41 to 64 years. In these 8 cases, 1 case reported co-suspect medication – elasomeran (Moderna), where an individual contribution of the suspect vaccine towards the fatal event cannot be established. In 1 case, the latency was reported as 172 days which limits a meaningful causality assessment towards an individual contributory role of the BNT162b2 vaccine. In 4 cases, there was limited information regarding the subjects' medical history and/or other therapy details such as onset date, therapy date, latency, clinical course of the event, concomitant medications which limits a meaningful causality assessment. The 2 cases which reported a latency of ≤24 hours are described below:

A 46-year-old male subject, dose 1 (monovalent [original]), medically confirmed, Germany:

- Medical history: Essential hypertension, Intervertebral disc protrusion, Withdrawal syndrome (verbatim: *withdrawal from opiates*).
- Co-suspect medications: none.

- Concomitant medications: none.
- PTs with fatal outcome: Myopericarditis.
- Time to onset (myocarditis): ≤1 day.
- Causes of death: Arrhythmia and Myopericarditis.
- Comment: In this case, the subject with a BMI of 31, underwent inpatient opiate withdrawal after a herniated disc within 2 weeks prior to receiving the BNT162b2 (COVID-19 immunisation vaccine). After receiving the BNT162b2 vaccine, the subject died within 12 hours. There was limited information regarding the clinical course of the event and the concomitant medications, which limited a meaningful causality assessment.

A 43-year-old female subject, dose 3 (monovalent [original]), medically confirmed, Singapore:

- Medical history: none.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Myocarditis, Pericarditis, and Cardiac arrest.
- Time to onset (myocarditis): ≤1 day.
- Causes of death: Myocarditis, Pericarditis, and Cardiac arrest.
- Comment: In this case, the subject received the first and second dose of BNT162b2 in June 2021 and received the third dose on 09 December 2021. The next day, the subject was hospitalized with atypical chest pain and intrathoracic mass but was found normal and discharged. However, she was re-hospitalized as she felt unwell again. She was awaiting further tests to evaluate pulmonary embolism, pericarditis and myocarditis but developed cardiac arrest on 12 December 2021, was resuscitated and admitted to ICU. The subject had poor prognosis of neurological condition post the cardiac arrest, was extubated and died on 13 December 2021. Relevant investigations for this subject included normal troponin at admission that increased post-cardiac arrest, normal ECG with sinus rhythm, normal CRP. Limited information regarding the diagnostic certainty of myocarditis is provided, and in view of the cardiac arrest that occurred, the fatal outcome appears more likely related to the preceding cardiac arrest and brain dysfunction.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 80 (original [73], bivalent Omi BA.1 [4], bivalent Omi BA.4/BA.5 [3]; 0.1% of 74,102 cases of the total PM dataset, 0.8% of the 9954 subjects with unknown age), compared to 153 cases (0.05%) retrieved in the PSUR #4.

- Country/region of incidence (≥2): US (17), UK (13), Canada (12), Germany (10), Australia (9), France (8), Japan (3), Singapore (2). The remaining 6 cases were distributed among 6 countries.
- Medical history (n = 13); the most frequently (≥2) reported medical conditions included Hypertension (3), Gastrooesophageal reflux disease (2).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: elasomeran (2).
- Most frequently co-reported PTs (≥5) included Chest pain (19), Dyspnoea (12), Palpitations (11), Pericarditis, Pyrexia (10 each), Fatigue (9), Headache (7), and Chest discomfort (5).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 44 below.

Table 44. Myocarditis in Subjects of Unknown Age (N = 80)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	6	21	13
	No	17	13	10
Relevant PT[a]	Myocarditis	20	29	23
	Myopericarditis	5	5	0
	Carditis	0	2	0
Hospitalisation required/prolonged	Yes	5	3	2
	No	20	33	21
Relevant suspect dose	Dose 1	4	5	2
	Dose 2	6	5	2
	Dose 3	2	5	0
	Dose 4	2	0	0
	Dose 5	0	1	1
	Dose Unknown	9	18	18
Vaccine Presentation	Monovalent (original)	19	32	22
	Bivalent Omi BA.1	3	0	1
	Bivalent Omi BA.4/BA.5	1	2	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=84	≤24 hours	0	1	0
	1-5 days	5	6	0
	6-13 days	1	0	0
	14-21 days	1	0	0
	22-31 days	0	1	0
	32-60 days	0	1	0
	Unknown	18	27	23
Event Outcome	Fatal	0	2	2
	Not resolved	1	3	1
	Resolved	7	7	0
	Resolved with sequelae	0	1	0
	Unknown	17	23	20
Duration of event[b] n=1, median=N/A	Up to 3 days	1	0	0
	Unavailable	6	8	0

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

Fatal cases (4):

Of the 4 cases reporting a fatal outcome, in 1 case, the subject who received BNT162b2 (original) for COVID-19 immunisation had an underlying medical condition of congestive heart failure which confounded the fatal event of carditis (PT: Carditis). In this case, there was limited information regarding the therapy details such as therapy date, onset date of the events, latency details, concomitant medications, treatment provided, clinical course details of the events and/or autopsy details.

In the remaining 3 cases (BNT162b2 [original] 2 cases; bivalent Omi BA.4/BA.5 1 case), there was too limited information regarding the therapy details such as therapy date, onset date of the events, latency details, age, gender, medical history, concomitant medications,

treatment provided, clinical course details of the events and/or autopsy details, which precluded a meaningful causality assessment. Of note: of these 3 cases, 1 case reported a medical history of malignant neoplasm.

16.3.1.1.2. Important Identified Risks – Pericarditis

Search criteria - PTs: Autoimmune pericarditis; Immune-mediated pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Overall – All Ages

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 379 (original [322], bivalent Omi BA.1 [36], bivalent Omi BA.4/BA.5 [28]; 0.5% of 74,102 cases of the total PM dataset), compared to 796 cases (0.3%) retrieved in the PSUR #4.
- Country/region of incidence (≥16): UK (80), Germany (56), Australia (53), Canada (38), France (24), Italy, US (18 each), Sweden (16). The remaining 76 cases were distributed among 21 countries.
- MC cases (195), NMC cases (184).
- Subjects' gender: female (190), male (179) and unknown (10).
- Subjects' age in years: n = 336, range: 5 – 88, mean: 43.7, median: 42.5.
- Medical history (n = 155); the most frequently (≥10) reported relevant medical history included Hypertension (26), Pericarditis, Seasonal allergy (13 each), Type 2 diabetes mellitus (10).
- COVID-19 Medical history (n = 37): COVID-19 (26), Suspected COVID-19 (9), Post-acute COVID-19 syndrome (3), SARS-CoV-2 test positive (2), Coronavirus infection, and COVID-19 pneumonia (1 each).
- Co-suspect medications (n = 15); relevant co-suspect medications included COVID-19 vaccine, elasomeran (3 each), COVID-19 vaccine prot subunit (NVX COV 2373), influenza vaccine inact split 4V (2 each), diphtheria vaccine toxoid, pertussis vaccine acellular 5-component, polio vaccine inact 3V (VERO), tetanus vaccine toxoid, influenza vaccine, influenza vaccine inact SAG 4V, loxoprofen sodium dihydrate, and rituximab (1 each).
- Number of relevant events: 381.
- Relevant event seriousness: serious (381).
- Reported relevant PTs: Pericarditis (376), Pericarditis constrictive (3), Pleuropericarditis (2).

- Relevant event outcome: fatal (6), resolved/resolving (120), resolved with sequelae (17), not resolved (106), unknown (132).

Cumulatively, there were 11,114 cases of pericarditis which constitute 0.6% of the overall PM dataset (1,839,454). During the current reporting period, there were 379 cases that reported pericarditis which constitute 0.5% of 74,102 cases of the total PM dataset, and majority (93.9%) of these cases were spontaneously reported. Of these 379 cases, the majority of the cases (271 cases; 71.5%) were reported from adult population with the ages ranging from 18 to 64 years of age. Of these 379 cases where the female subjects (190 cases; 50.1%) and the male subjects (179 cases; 47.2%) were reported similar in proportion. In the majority (315 cases; 83.1%) of the cases, the event of pericarditis was reported after the original booster dose and relatively less after the bivalent booster doses (original + Omi BA.1 or original + Omi BA.4/BA.5) (16.9%).

Of the 379 cases reporting events indicative of pericarditis, 195 cases (51.5%) were medically confirmed. Of the 379 cases, in 109 cases (28.8% 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 379 cases, in 113 cases (29.8%) 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 379 cases, in 294 cases (77.6%) limited information was available on subject's age, latency of events, and/or medical history confounding causality assessment.

Based on the review of these cases reporting pericarditis events, there was no new significant safety information identified during the current reporting period. Hence, no label update is warranted based on the analysis of these cases.

Age-stratified data[57]

Subjects aged 6 months through <5 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: none; compared to no cases retrieved in the PSUR #4.

[57] 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" (1 case) was evaluated in the overall and in the 16-17 years age groups,
- "Adult" (13 cases) were evaluated in the overall and in the Age Unknown group; and
- "Elderly" (6 cases) in the overall and in the ≥ 40 years age groups.

Subjects aged 5 through <12 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 3 (original [3]; 0.004% of 74,102 cases of the total PM dataset, 0.3% of the 968 subjects aged 5-11 years), compared to 6 cases (0.002%) retrieved in the PSUR #4.
- Country/region of incidence: Canada (2), Australia (1).
- Subjects' age in year: n = 2, range: 5 – 11, mean: 8.0, median: 8.0.
- Medical history: Atrial septal defect, atrial septal defect repair, headache, intracardiac thrombus, migraine, pericarditis, peripheral artery thrombosis (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain, Palpitations (2 each).

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

Table 45. Pericarditis in Subjects Aged 5 through <12 Years (N = 3)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	0	3	0
	No	0	0	0
Relevant PT[a]	Pericarditis	0	3	0
Hospitalisation required/prolonged	Yes	0	1	0
	No	0	2	0
Relevant suspect dose	Dose 1	0	1	0
	Dose 2	0	1	0
	Dose 3	0	1	0
Vaccine Presentation	Monovalent (original)	0	3	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	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	0	1	0
Event Outcome	Resolved	0	1	0
	Not Resolving	0	1	0
	Unknown	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.

Subjects aged 12 – 15 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 10 (original [10]; 0.01% of 74,102 cases of the total PM dataset, 1.2% of the 815 subjects aged 12-15 years), compared to 15 cases (0.005%) retrieved in the PSUR #4.
- Country/region of incidence: Japan (4), Germany (2), Australia, Canada, Romania, UK (1 each).
- Subjects' age in years: n = 10, range: 12.0 – 15.0, mean: 13.8, median: 14.0.
- Medical history (n = 4): Becker's muscular dystrophy, Cerebral palsy, Cochlea implant, Hypoacusis, Intellectual disability, Language disorder, Mental disability, Myopericarditis, Neuromyopathy, Oropharyngeal pain, Orthostatic intolerance, Physical disability, Quadriparesis, Wheelchair user (1 each).
- COVID-19 Medical history: COVID-19 (3), Coronavirus infection (1).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Myocarditis (3), Encephalitis autoimmune, Pericardial effusion, Pyrexia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 46.

Table 46. Pericarditis in Subjects Aged 12-15 Years (N = 10)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	4	3	0
	No	0	3	0
Relevant PT[a]	Pericarditis	4	6	0
Hospitalisation required/prolonged	Yes	1	2	0
	No	3	4	0
Relevant suspect dose	Dose 1	1	1	0
	Dose 2	0	3	0
	Dose 3	2	0	0
	Unknown	1	2	0
Vaccine Presentation	Monovalent (original)	4	6	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	0

Table 46. Pericarditis in Subjects Aged 12-15 Years (N = 10)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=10	1-5 days	2	2	0
	6-13 days	0	1	0
	22-31	1	0	0
	Unknown	1	3	0
Event Outcome	Not resolved	0	1	0
	Resolved	2	1	0
	Resolved with sequelae	0	1	0
	Resolving	1	0	0
	Fatal	1	1	0
	Unknown	0	2	0
Duration of event[b] n=1, median: N/A	7-10 days	1	0	0

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

Fatal cases (2):

The 2 cases reporting fatal Pericarditis and Myocarditis are discussed in Section 16.3.1.1.1 *Important Identified Risks – Myocarditis in Subjects aged 12 – 15 Years*.

Subjects aged 16 – 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 5 (original [5]; 0.007% of 74,102 cases of the total PM dataset, 1.1% of the 446 subjects aged 16-17 years), compared to 11 cases (0.003%) retrieved in the PSUR #4.
- Country/region of incidence: UK (2), Brazil, Canada, Taiwan, province of China (1 each).
- Subjects' age in years: n = 4, range: 16 – 17, mean: 16.3, median: 16.0.
- Medical history: None
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥2): Chest pain, Dyspnoea, Palpitations, Pyrexia (3 each), Fatigue (2).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 47.

Table 47. Pericarditis in Subjects Aged 16-17 Years (N = 5)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	1	1	0
	No	2	1	0
Relevant PT[a]	Pericarditis	3	2	0
Hospitalisation required/prolonged	Yes	2	1	0
	No	1	1	0
Relevant suspect dose	Dose 1	1	0	0
	Dose 2	0	0	0
	Dose 3	2	1	0
	Unknown	0	1	0
Vaccine Presentation	Monovalent (original)	3	2	0
	Bivalent Omi BA.1	0	0	0
	Bivalent Omi BA.4/BA.5	0	0	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=5	1-5 days	0	1	0
	6-13 days	1	0	0
	Unknown	2	1	0
Event Outcome	Resolved	1	0	0
	Not Resolved	0	1	0
	Resolving	0	1	0
	Unknown	2	0	0
Duration of event[b] n=0, median: N/A	None	1	0	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 #4.

Post-Authorisation Data

- Number of cases: 38 (original [33]; bivalent Omi BA.1 [3]; bivalent Omi BA.4/5 [2]; 0.05% of 74,102 cases of the total PM dataset, 1.0% of the 3944 subjects aged 18-24 years), compared to 67 cases (0.02%) retrieved in the PSUR #4.
- Country/region of incidence: Germany (7), Australia (6), UK (5), Italy (4), France, Norway (3 each), Austria, Sweden (2 each), Denmark, Iceland, Israel, Japan, Netherlands, US (1 each).
- Subjects' age in years: n = 38, range: 18 – 24, mean: 21.1, median: 21.0.
- Medical history (n = 11): Epilepsy, Hypersensitivity, Seasonal allergy (2 each), Allergy to animal, Allergy to chemicals, Allergy to plants, Autism spectrum disorder, Chest pain, Dyspnoea, Fall, Familial risk factor, Immunodeficiency, Infectious mononucleosis,

Intellectual disability, Lipoma, Lung abscess, Meningitis, Migraine, Mite allergy, Non-tobacco user, Petit mal epilepsy, Pneumonia staphylococcal, Social alcohol drinker, Speech disorder developmental, Subarachnoid haemorrhage, Syncope, Tobacco user, Tonic convulsion, Tourette's disorder (1 each).

- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications (n = 1): COVID-19 vaccine (1).
- Most frequently co-reported PTs (≥3): Chest pain (13), Myocarditis (10), Dyspnoea, Fatigue (9 each), Pyrexia (8), Tachycardia (7), Angina pectoris (6), Arthralgia, Pericardial effusion (5 each), Chest discomfort, Headache, Myalgia, Palpitations, Somnolence (4 each), Asthenia, Dizziness, Dyspnoea exertional, Exercise tolerance decreased, Fibrin D dimer increased, Interchange of vaccine products, Malaise, Memory impairment, Mobility decreased, Nausea, Pain (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 48.

Table 48. Pericarditis in Subjects aged 18-24 years (N = 38)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	9	8	1
	No	7	13	0
Relevant PT[a]	Pericarditis	16	21	1
Hospitalisation required/prolonged	Yes	3	3	1
	No	13	18	0
Relevant suspect dose	Dose 1	5	6	0
	Dose 2	4	6	0
	Dose 3	4	3	0
	Dose 4	0	2	1
	Unknown	3	4	0
Vaccine Presentation	Monovalent (original)	14	19	0
	Bivalent Omi BA.1	0	2	1
	Bivalent Omi BA.4/BA.5	2	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=38	≤ 24 hours	3	0	0
	1-5 days	3	5	0
	6-13 days	2	1	0
	14-21 days	0	1	0
	22-31 days	1	0	0
	32-60 days	0	0	0
	61-180 days	0	1	0
	181-365 days	2	0	0
	>365 days	1	0	0
	Unknown	4	13	1
Event Outcome	Fatal	0	1	0
	Not resolved	5	2	0
	Resolved	2	1	0
	Resolved with sequelae	1	1	1
	Resolving	5	1	0
	Unknown	3	15	0

Table 48. Pericarditis in Subjects aged 18-24 years (N = 38)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Duration of event[b] n=1, median: N/A	>365 days	1	0	0
	None	2	2	1

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

Fatal case (1):

A 22-year-old male subject, dose 2 (monovalent [original]), medically confirmed, Israel:

- Medical history: Chest pain, Dyspnoea, Non-tobacco user.
- Co-suspect medications: none.
- Concomitant medications: none.
- PTs with fatal outcome: Mesothelioma, Pericarditis.
- Time to onset (pericarditis): not reported.
- Causes of death: As mentioned above, the events coded to the PTs Mesothelioma, Pericarditis had a fatal outcome.
- Comment: Limited information provided regarding the patient's, concomitant medications, co-suspect medications, and latency limits 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 #4.

Post-Authorisation Data

- Number of cases: 32 (original [32]; bivalent Omi BA.1 [2]; 0.04% of 74,102 cases of the total PM dataset, 0.7% of the 4622 subjects aged 25-29 years), compared to 79 cases (0.03%) retrieved in the PSUR #4.
- Country/region of incidence: Australia (10), Germany (9), UK (6), Italy (3), Canada (2), Saudi Arabia, Spain (1 each).
- Subjects' age in years: n = 32, range: 25 – 29, mean: 26.8, median: 26.5.
- Medical history (n = 10): the medical conditions reported more than once included Seasonal allergy (4), Allergy to animal (3), Asthma, Atrial fibrillation, Drug hypersensitivity, Mite allergy, Syncope (2 each).
- COVID-19 Medical history (n = 1): Suspected COVID-19 (1).

- Co-suspect medications (n = 3): COVID-19 vaccine prot. subunit (NVX COV2373) (2), elasomeran (1).
- Most frequently co-reported PTs (≥3): Chest pain (19), Dyspnoea, Fatigue (12 each), Palpitations (11), Tachycardia (10), Headache (8), Dizziness (6), Chest discomfort, Pain in extremity, Pericardial effusion (5 each), Performance status decreased (4), COVID-19, Drug ineffective, Interchange of vaccine products, Malaise, Myocarditis, Postural orthostatic tachycardia syndrome, Syncope (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 49

Table 49. Pericarditis in Subjects Aged 25-29 Years (N = 32)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	6	13	0
	No	5	7	1
Relevant PT[a]	Pericarditis	11	20	1
Hospitalisation required/prolonged	Yes	0	8	0
	No	11	12	1
Relevant suspect dose	Dose 1	8	5	0
	Dose 2	0	9	1
	Dose 3	3	4	0
	Dose 4	0	0	0
	Unknown	0	2	0
Vaccine Presentation	Monovalent (original)	11	18	1
	Bivalent Omi BA.1	0	2	0
	Bivalent Omi BA.4/BA.5	0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=32	≤ 24 hours	2	1	0
	1-5 days	1	2	0
	6-13 days	1	2	0
	14-21 days	0	2	0
	32-60 days	2	0	0
	61-180 days	1	1	0
	181-365 days	1	0	0
	>365 days	0	1	0
	Unknown	3	11	1
Event Outcome	Not resolved	7	7	0
	Resolved	1	5	0
	Resolved with sequelae	1	2	0
	Resolving	1	1	0
	Unknown	1	5	1
Duration of event[b] n=4, median: 174.5	27-57 days	0	1	0
	58-180 days	1	0	0
	181-365 days	0	2	0
	None	1	4	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 #4.

Post-Authorisation Data

- Number of cases: 67 (original [63], bivalent Omi BA.1, bivalent Omi BA.4/BA.5 [2 each]; 0.09% of 74,102 cases of the total PM dataset, 0.6% of the 10,413 subjects aged 30-39), compared to 133 cases (0.05%) retrieved in the PSUR #4.
- Country/region of incidence (≥3): Australia (13), UK (11), France (10), Germany (8), Italy (5), Canada, Ireland, US (3 each).
- Subjects' age in years: n = 67, range: 30 – 39, mean: 34.6, median: 35.0.
- Medical history (n = 27): the medical conditions reported more than once included the PTs Pericarditis (4), Seasonal allergy (3), Anxiety, Immunodeficiency, Mite allergy, Post traumatic stress disorder, Ventricular extrasystoles (2 each).
- COVID-19 Medical history (n = 9): COVID-19 (6), Suspected COVID-19 (4), COVID-19 pneumonia, Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (n = 2): COVID-19 vaccine, elasomeran (1 each).

  Most frequently co-reported PTs (≥5): Fatigue (24), Chest pain (22), Dyspnoea, Palpitations (18 each), Tachycardia (11), Myocarditis (9), Nausea (8), Myalgia, Pericardial effusion (6 each), Anxiety, Chest discomfort, Headache, Inappropriate schedule of product administration, Interchange of vaccine products, Pain, Syncope (5 each).

  Pericarditis relevant data in this subgroup of subjects are summarised in below Table 50.

Table 50. Pericarditis in Subjects Aged 30-39 Years (N = 67)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	25	16	0
	No	12	14	0
Relevant PT[a]	Pericarditis	37	30	0
Hospitalisation required/prolonged	Yes	9	12	0
	No	28	18	0
Relevant suspect dose	Dose 1	17	7	0
	Dose 2	9	13	0
	Dose 3	5	5	0
	Dose 4	2	1	0
	Unknown	4	4	0
Vaccine Presentation	Monovalent (original)	35	28	0
	Bivalent Omi BA.1	2	0	0
	Bivalent Omi BA.4/BA.5	0	2	0

Table 50. Pericarditis in Subjects Aged 30-39 Years (N = 67)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=67	≤ 24 hours	3	2	0
	1-5 days	7	6	0
	6-13 days	3	1	0
	14-21 days	4	3	0
	22-31 days	1	1	0
	32-60 days	2	2	0
	61-180 days	1	2	0
	181-365 days	1	2	0
	>365 days	0	1	0
	Unknown	15	10	0
Event Outcome	Not resolved	14	8	0
	Resolved	3	5	0
	Resolved with sequelae	3	3	0
	Resolving	3	3	0
	Unknown	14	11	0
Duration of event[b] n=2, median: 51 days	27-57 days	0	1	0
	58-180 days	0	1	0
	None	6	6	0

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

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 189 (original [146], bivalent Omi BA.1, bivalent Omi BA.4/BA.5 [24 each]; 0.26 % of 74,102 cases of the total PM dataset, 0.4% of the 42,521 subjects ≥ 40 years), compared to 381 cases (0.1%) retrieved in the PSUR #4.
- Country/region of incidence (≥3): UK (47), Germany (29), Australia (18), Canada (15), Sweden (13), US (12), France (9), Italy (6), Austria (5), Denmark, Iceland, Netherlands, Spain (4 each), Japan (3).
- Subjects' age in years: n = 183, range: 40 – 88, mean: 57.4, median: 55.0.
- Medical history (n = 87): the medical conditions reported more than 3 times included PTs Hypertension (24), Type 2 diabetes mellitus (10), Hypothyroidism, Pericarditis (8 each), Atrial fibrillation, Clinical trial participant, Gout, Rheumatoid arthritis (4 each).
- COVID-19 Medical history (n = 17): COVID-19 (11), Suspected COVID-19 (4), Post-acute COVID-19 syndrome, SARS-COV-2 test positive (2 each)

- Co-suspect medications (n= 9): influenza vaccine inact split 4V (2), COVID-19 vaccine, diphtheria vaccine toxoid, pertussis vaccine acellular 5-component, polio vaccine inact 3V (vero), tetanus vaccine toxoid, elasomeran, influenza vaccine, influenza vaccine inact SAG 4V, loxoprofen sodium dihydrate, rituximab (1 each).
- Most frequently co-reported PTs (≥10): Chest pain (68), Fatigue (55), Dyspnoea (54), Palpitations (38), Myocarditis (35), Pericardial effusion (34), Pyrexia (24), Tachycardia (21), Interchange of vaccine products (20), Dizziness (18), Headache (17), Malaise (14), Asthenia (12), Chest discomfort, Pain (11 each), Arrhythmia, Pain in extremity (10 each).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 51 below.

Table 51. Pericarditis in Subjects aged ≥ 40 years (N = 189)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	44	41	1
	No	54	46	3
Relevant PT[a]	Pericarditis	98	85	4
	Pericarditis constrictive	0	2	0
	Pleuropericarditis	0	2	0
Hospitalisation required/prolonged	Yes	36	51	1
	No	62	38	3
Relevant suspect dose	Dose 1	18	18	2
	Dose 2	33	14	1
	Dose 3	22	21	0
	Dose 4	11	21	1
	Dose 5	2	2	0
	Dose 6	2	0	0
	Unknown	10	11	0
Vaccine Presentation	Monovalent (original)	79	60	2
	Bivalent Omi BA.1	9	13	2
	Bivalent Omi BA.4/BA.5	10	14	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=191	≤ 24 hours	5	2	0
	1-5 days	19	10	0
	6-13 days	9	9	0
	14-21 days	3	10	1
	22-31 days	3	6	0
	32-60 days	8	3	0
	61-180 days	8	5	0
	181-365 days	2	4	0
	>365 days	4	0	0
	Unknown	37	40	3
Event Outcome	Fatal	1	2	0
	Not resolved	34	18	2
	Resolved	18	22	0
	Resolved with sequelae	2	2	0
	Resolving	16	18	0
	Unknown	27	27	2

Table 51. Pericarditis in Subjects aged ≥ 40 years (N = 189)

		Female No. of Events	Male No. of Events	Unknown No. of Events
Duration of event[b] n= 12, median: 20 days	Up to 3 days	0	2	0
	11-26 days	4	2	0
	27-57 days	1	2	0
	181-365 days	0	1	0
	unknown	15	17	0

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

Fatal cases (3)

- Cases medically confirmed (2):

A 43-year-old female subject, dose 3 (monovalent [original]), medically confirmed, Singapore: This case reporting fatal Pericarditis and Myocarditis is discussed in Section 16.3.1.1.1 *Important Identified Risks – Myocarditis in Subjects aged >40 Years sectio*n.

A 75-year-old male subject, dose 4 (monovalent [original]), medically confirmed, Japan:

- Medical history: Benign prostatic hyperplasia, Chronic obstructive pulmonary disease, Chronic respiratory failure, Emphysema, Hypokalaemia, Respiratory failure.
- Co-suspect medications: none.
- Concomitant medications: budesonide, formoterol fumarate, glycopyrronium bromide, esomeprazole magnesium, potassium gluconate, prednisolone, silodosin
- PTs with fatal outcome: Chronic respiratory failure, Hypotension, Hypoxia, Shock, Pericarditis, Pneumonia, Pyrexia, Blood pressure decreased, Condition aggravated, Sepsis.
- Time to onset (pericarditis): not reported.
- Causes of death: Chronic respiratory failure, Hypotension, Hypoxia, Shock, Pericarditis, Pneumonia, Pyrexia, Blood pressure decreased, Condition aggravated, Sepsis, Disease progression.
- Comment: In this case, the multiple comorbidities, concomitant medications could have contributed to the fatal outcome.

Case of non-medically confirmed (1):

Of the reported non medically confirmed 84-year-old male case from [redacted] with no medical history, concomitant medications, and long latency period (111 days) precluded a meaningful causality assessment in the case.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 35 (original [30], bivalent Omi BA.1 [5]; 0.05% of 74,102 cases of the total PM dataset, 0.4% of the 9954 subjects with unknown age), compared to 104 (0.04%) cases retrieved in the PSUR #4.
- Country/region of incidence: Canada (14), UK (8), Australia (4), Belgium, France, US (2 each), Brazil, Germany, Israel (1 each).
- Medical history (n = 15): the medical conditions reported more than once included PTs Anxiety, Asthma exercise induced, Gastrooesophageal reflux disease, Syncope (2 each).
- COVID-19 Medical history (n = 2): COVID-19 (2).
- Co-suspect medications: none.
- Most frequently co-reported PTs (≥3): Chest pain (15), Palpitations (13), Fatigue (12), Dyspnoea (11), Pyrexia (10), Myocarditis (8), Chest discomfort, Malaise, Tachycardia (6 each), Headache (5), Costochondritis, Dizziness, Pericardial effusion (4 each), Nausea, Vomiting (3 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 52.

Table 52. Pericarditis in Subjects with Unknown Age (N = 35)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	12	6	1
	No	9	4	3
Relevant PTs[a]	Pericarditis	21	9	4
	Pericarditis constrictive	0	1	0
Hospitalisation required/prolonged	Yes	3	3	2
	No	18	7	2
Relevant suspect dose	Dose 1	6	4	0
	Dose 2	5	2	2
	Dose 3	2	1	0
	Dose 4	3	0	0
	Dose 5	0	0	1
	Unknown	5	3	1

Table 52. Pericarditis in Subjects with Unknown Age (N = 35)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Vaccine Presentation	Monovalent (original)	18	9	3
	Bivalent Omi BA.1	3	1	1
	Bivalent Omi BA.4/BA.5	0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=35	≤ 24 hours	2	0	0
	1-5 days	2	3	0
	6-13 days	1	0	0
	14-21 days	1	0	0
	22-31 days	0	1	0
	Unknown	15	6	4
Event Outcome	Not resolved	5	1	0
	Resolved	5	1	0
	Resolving	0	2	0
	Unknown	11	6	4
Duration of event[b] n=0, median: N/A	Unknown	5	1	0

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

O/E Analysis

O/E analysis was performed for Myocarditis/Pericarditis (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

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

In the PSUR #4, the MAH, based on the review of clinical trial data, cumulative PM data, individual review of cases, and real-world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of VAED/VAERD from the list of the safety concerns. In the AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the PRAC agreed to remove VAED/VAERD from the list of safety concerns in both RMP and PSUR.

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

In the PRAC AR of the PSUR #3 (EMEA/H/C/PSUSA/00010898/202206), the PRAC requested that *For future PSURs in the section 'Evaluation of AESIs', the cardiovascular AESIs, haematological AESIs, dermatological AESIs, facial paralysis, hepatic AESIs, musculoskeletal AESIs, other AESIs, respiratory AESIs, vasculitic events, local adverse reactions, and/or severe reactogenicity should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Upon review of the incremental data of cases evaluated for all the above mentioned topics, no new safety issues/signals or reporting pattern changes were detected. These topics have been removed from the text of the PSUR.

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *The MAH should continue to closely monitor MIS-C/-A as outlined in PRAC's signal recommendation (EPITT 19732) and all new cases of MIS-C/-A including a WHO causality assessment should be reported in the future PSURs.*

Response

Please refer to (Appendix 5.2) for the review of the cases received in the reporting interval.

As part of the approval letter for the emergency use of Tozinameran – COVID-19 mRNA vaccine (nucleoside modified) – COMIRNATY®, the WHO requested the MAH *to provide additional data on vaccine immunogenicity, effectiveness and safety on population groups represented in Low- and Middle-Income Countries (LMICs) including individuals with conditions such as malnutrition and populations with existing co-morbidities such as tuberculosis, human immunodeficiency virus (HIV) infection and other high prevalent infectious diseases.*

In the PRAC AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition; HIV infection should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Please refer to Section 16.3.3.1.

There were no other risks that were classified as listed adverse events in which the previous PSUR or PSUR assessment report recommended/requested continued monitoring in future PSURs and/or risks not categorized as important in which new information has become available during the reporting interval that allows further characterisation of a previously recognized risk.

16.3.3.1. Adverse Events of Special Interest (AESIs)

The company's AESI list takes into consideration the lists of AESIs from several expert groups and regulatory authorities including but not limited to the following: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

Overlapping terms among multiple categories were assigned to one category only based on their most clinical relevance.

Please refer to Appendix 5.8 for the observed versus expected analysis for the AESIs.

16.3.3.1.1. Anaphylactic AESIs

Search criteria – PTs: Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock.

Clinical Trial Data

- Number of cases: none, compared to 1 case (0.32%) retrieved in the PSUR #4.

Post-Authorisation Data

- Number of cases: 188 (original [101], bivalent Omi BA.1 [24], bivalent Omi BA.4/BA.5 [63]; 0.25% of 74,102 cases, the total PM dataset), compared to 421 cases (0.15%) retrieved in the PSUR #4.
- MC cases (137), NMC cases (51).
- Country/region of incidence (≥ 10): Japan (74), Germany (29), UK (26), US (12); the remaining 47 cases were distributed among 22 countries.
- Subjects' gender: female (142), male (39) and unknown (7).
- Subjects' age in years: n = 168, range: 5 – 102 years, mean: 49.8, median: 49.0.
- Medical history (n = 109); the most frequently (≥ 4) reported medical conditions included Hypertension (18), Asthma (17), Drug hypersensitivity, Food allergy (14 each), Hypersensitivity (12), Urticaria (9), Diabetes mellitus, Rhinitis allergic (8 each), Dermatitis contact, Gastrooesophageal reflux disease, Seasonal allergy, Type 2 diabetes mellitus (6 each), Anaphylactic reaction, Atrial fibrillation, Cough, Steroid therapy (5 each), Contrast media allergy, Immunodeficiency, Insomnia, and Rheumatoid arthritis (4 each).
- COVID-19 Medical history (n = 11): COVID-19 (8), Coronavirus infection, SARS-CoV-2 test positive, and Suspected COVID-19 (1 each).
- Co-suspect medications (n = 10): relevant co-suspect medications (≥2) included macrogol (3), and influenza vaccine inact split 4V (2).
- Number of relevant events: 196.
- Relevant event seriousness: serious (196).
- Reported relevant PTs: Anaphylactic reaction (146), Anaphylactic shock (43), Anaphylactoid reaction (7).

- Time to event onset[58]: n = 134, range: <24 hours to 70 days, median: 0 days. Immunologic (IgE-mediated) hypersensitivity reactions such as anaphylaxis and non-immunologic (anaphylactoid) reactions generally occur shortly after exposure to exposure, however, for completeness, those events with inconsistent time to onset and/or duration reported are included.

  - <24 hours: 119 events (4 of which had a fatal outcome);
  - 1 day: 11 events;
  - 2-7 days: 1 event;
  - 8-14 days: 1 event;
  - 15-30 days: 0 events;
  - 31-70 days: 2 events;

- Duration of relevant events[59]: n = 55, range: <24 hours to 182 days, median: 0 days.

  - <24 hours: 33 events;
  - 1 day: 16 events;
  - 2-7 days: 4 events;
  - 8-30 days: 0 events;
  - 31-180 days: 1 event;
  - 181-182 days: 1 event.

- Relevant event outcome: fatal (4), resolved/resolving (109), resolved with sequelae (7), not resolved (16), unknown (60).

In 4 cases (reporting 4 relevant events with fatal outcomes), the reported causes of death were Anaphylactic reaction (3), Dyspnoea (2), Anaphylactic shock, Blood pressure decreased, Cardiac failure acute, Cerebrovascular accident, Depressed level of consciousness, Respiratory rate decreased, Shock (1 each). All cases involved elderly subjects (Age range: 77 to 102 years). Medical history was provided in 3 cases and included PTs under the SOC Cardiac disorders (4 events), Metabolism and nutrition disorders, Nervous system disorders (3 events each), Gastrointestinal disorders, Social circumstances, Surgical and medical procedures, Vascular disorders (2 events each), Endocrine disorders, Psychiatric disorders, Renal and urinary disorders (1 event each).

Of the 115 cases reporting medical history and/or co-suspect medications, 54 cases reported relevant medical history/risk factors (e.g., Allergy to animal/arthropod sting/chemicals/fermented products/metals/plants/vaccine, Anaphylactic reaction, anaphylactic shock, Autoimmune disorders, Contrast media allergy, Food allergy,

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

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

Hypersensitivity, Multiple allergy, Seasonal allergy) and/or co-suspect which may have contributed to the anaphylaxis related events.

Analysis by age group

CT: there are no case reporting anaphylaxis in the CT dataset.

PM: Paediatric[60] (12 – 6 children, 6 adolescents), Adults[61] (109), Elderly[62] (49) and Unknown (18).

– No significant difference was observed in the reporting proportion of anaphylaxis relevant PTs between adult and elderly populations. Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis Original versus Bivalent Vaccines

The majority of the anaphylaxis cases were reported after administration of the original vaccine (52%) rather than the bivalent Omi BA.4/BA.5 vaccine (35.7%); the PT most frequently reported was Anaphylactic reaction (70% versus 86%). Few cases of anaphylaxis were reported after the administration of bivalent Omi BA.1, therefore a meaningful comparison of the PTs reported with the other 2 vaccines was not possible.

O/E Analysis

O/E analysis was performed for Anaphylaxis (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.2. COVID-19 AESIs

This AESI with the MedDRA search criteria - SMQ COVID-19 (Narrow and Broad) OR PTs Ageusia; Anosmia[63] was foreseen as a way to monitor for possible cases of VAED/VAERD. Because, as agreed by EMA, VAED/VAERD has been removed as a safety concern (Important potential risk) after >2.5 years of surveillance, COVID-19 will no longer be

[60] Aged less than 17 years.

[61] Aged at least 18 years and less than 65 years.

[62] Aged at least 65 years.

[63] Due to MedDRA upgrade to version 26.0: 3 PTs (Asymptomatic COVID-19, Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease) have been removed.

considered an AESI for discussion in the PSUR, however, discussion of lack of efficacy cases will continue as per PSUR requirements.

Cases reporting long COVID (PT: Post-acute COVID-19 syndrome) are reviewed in this section. Please refer also to Section 18.1 *Benefit-Risk Context – Medical Need and Important Alternatives (Complications of COVID-19 and Post-acute COVID).*

Clinical Trial Data

- Number of cases: 2 (original [2]; 2.4% of 82 cases, the total CT dataset), compared to 4 cases (1.3%) retrieved in the PSUR #4.
- Country/region of incidence: US (2).
- Subjects' gender: female (2).
- Subjects' age in years: n = 2, range: 2 - 79, mean: 40.5, median: 40.5.
- Medical history (n = 2): the reported relevant medical conditions included the PTs Blood cholesterol increased, Dermatitis atopic, Drug hypersensitivity, Gastrooesophageal reflux disease, Hypertension, Malignant melanoma, Osteoarthritis, Pulmonary embolism, Pulmonary thrombosis, Scarlet fever, Skin neoplasm excision (1 each).
- COVID-19 Medical history: none.
- Co-suspect medications: none.
- Reported relevant PTs: COVID-19 (2). None of the events were related to BNT162b2.
- Relevant event outcome: not resolved (1), resolved (1).

Post-Authorisation Data

Number of relevant cases: 7738 (original [5398], bivalent Omi BA.1 [309], bivalent Omi BA.4/BA.5 [2031], BNT162b2 multivalent NOS [45]; 10.4% of 74,102 cases, the total PM dataset), compared to 57,462 cases (20.3%) retrieved in the PSUR #4.

- MC cases (2211), NMC cases (5527).
- Country/region of incidence (≥ 10): US (2800), UK (1394), Germany (744), France (477), Japan (387), Netherlands (216), Spain (206), Australia (177), Canada (167), Italy (112), Austria (88), Denmark (87), Sweden (83), Norway (82), Belgium (78), Singapore (71), Finland (68), Philippines (62), Czech Republic (43), Ireland, Portugal (35 each), Greece, Republic of South Korea, Romania (30 each), Brazil (28), New Zealand (20), Chile (18), Switzerland (15), Israel (14), Hungary, Poland, Thailand (12 each), Mexico (11), Luxembourg (10); the remaining 84 cases were distributed among 26 countries.
- Subjects' gender: female (4707), male (2615) and unknown (416).
- Subjects' age in years: n = 6707, range: 1.0 – 102.0, mean: 53.6, median: 55.0.
- Medical history (n = 4182): the most frequently (≥2%) reported relevant medical conditions included Hypertension (709), Drug hypersensitivity (530), Asthma (510),

COVID-19 (448), Hypersensitivity (234), Hypothyroidism (206), Obesity (196), Depression (188), Food allergy (176), Diabetes mellitus (151), Seasonal allergy (150), Blood cholesterol increased (136), Type 2 diabetes mellitus (130), Suspected COVID-19 (128), Gastrooesophageal reflux disease (124), Non-tobacco user (107), Anxiety (89), Immunodeficiency (87), Migraine (86).

- COVID-19 Medical history (n = 614): COVID-19 (448), Suspected COVID-19 (128), Post-acute COVID-19 syndrome (36), SARS-CoV-2 test positive (19), Coronavirus infection (7), Exposure to SARS-CoV-2 (6), COVID-19 pneumonia, Occupational exposure to SARS-CoV-2 (2 each).
- Co-suspect medications (n = 3719 cases); the most frequently (≥10) reported included COVID-19 vaccine (2133), elasomeran (878), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (747), COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (64), davesomeran elasomeran (34), COVID-19 vaccine inact (Vero) CZ02 (28), influenza vaccine (26), COVID-19 vaccine NRVV MVA (20), ocrelizumab (17).
- Number of relevant events: 7964.
- Relevant event seriousness[64]: serious (7326), non-serious (639).
- Relevant PTs most frequently reported (≥2%): COVID-19 (6168), Suspected COVID-19 (1035), Ageusia (246), Anosmia (223), Post-acute COVID-19 syndrome (156).
- Time to event onset[58]: n = 3667, range: <24 hours to 798 days, median: 167 days.
  - <24 hours: 136 events (0 fatal event);
  - 1 day: 141 events (0 fatal events);
  - 2-7 days: 246 events (1 fatal event);
  - 8-14 days: 111 events (3 fatal events);
  - 15-30 days: 131 events (2 fatal events);
  - 31-181 days: 1191 events (15 fatal events);
  - ≥ 182 days: 1711 events (13 fatal events).
- Duration of relevant events[59]: n = 550, range: 24 hours to 713 days, median: 9 days.
  - <24 hours: 0 events;
  - 1 day: 10 events;
  - 2-7 days: 201 events;
  - 8-14 days: 223 events;
  - 15-30 days: 84 events;
  - 31-181 days: 19 events;
  - 182-365 days: 5 events;
  - >365-713 days: 8 events.

[64] One case reported the occurrence of the same event in 2 different periods; the 1st occurrence was assessed as serious, the 2nd as non-serious.

- Relevant event outcome[65]: fatal (52), resolved/resolving (1784), resolved with sequelae (126), not resolved (1152), unknown (4852).

Fatal cases (52)

In 52 cases (reporting 55 relevant events of which 52 relevant events reported a fatal outcome), the reported causes of death (≥2) included COVID-19 (26), Drug ineffective (22), COVID-19 pneumonia, Vaccination failure (15 each), Respiratory failure (7), Suspected COVID-19 (6), Acute respiratory distress syndrome (5), Dyspnoea, Interchange of vaccine products (4 each), Cardiac arrest, Multiple organ dysfunction syndrome, Pyrexia (3 each), Cardiac failure, Coronavirus infection, Pneumonia, Shock (2 each).

16.3.3.1.2.1. Long COVID

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

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

Number of relevant cases: 156 (original [139], bivalent Omi BA.1 [8], bivalent Omi BA.4/BA.5 [9]; 0.2% of 74,102 cases, the total PM dataset), compared to 178 cases (0.06%) retrieved in the PSUR #4.

- MC cases (56), NMC cases (100).
- Country/region of incidence: Germany (62), UK (21), US (14), France (9), Sweden (8), Netherlands (7), Finland (6), Ireland (5), Australia, Austria, Japan (3 each), Belgium, Italy, Luxembourg, Norway (2 each), Canada, Indonesia, Lithuania, Romania, South Africa, Spain, Switzerland (1 each).
- Subjects' gender: female (103), male (50) and unknown (3).
- Subjects' age in years: n = 135, range: 14 – 86, mean: 46.3, median: 46.0. When the subjects' age group was provided (n=137), there were 7 paediatric, 113 adults, and 17 elderly subjects.
- Medical history (n = 94): the most frequently (≥2%) reported medical conditions included COVID-19 (27), Post-acute COVID-19 syndrome (16), Asthma, Seasonal allergy (10 each), Suspected COVID-19 (9), Hypothyroidism (7), Obesity (6), Food allergy, Hypersensitivity, Hypertension, Immunodeficiency (5 each), Chest pain, Depression, Tobacco abuse, Tobacco user, Type 2 diabetes mellitus (4 each), Appendicectomy, Arthritis, Autoimmune thyroiditis, Caesarean section, Crohn's disease, Drug hypersensitivity, Lyme disease, Migraine, Mitral valve incompetence, Osteoarthritis,

[65] 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.

Tinnitus (3 each), Ageusia, Alcohol use, Allergy to animal, Anosmia, Anxiety disorder, Apathy, Blood pressure increased, Cardiac disorder, Dermatitis contact, Diabetes mellitus, Dust allergy, Dyslipidaemia, Essential hypertension, Ex-tobacco user, Hepatic steatosis, Herpes zoster, Hypercholesterolaemia, Ileocaecal resection, Intervertebral disc protrusion, Metabolic disorder, Mite allergy, Mitral valve disease, Myocardial infarction, Non-Hodgkin's lymphoma, Non-tobacco user, Overweight, Pain, Pneumonia, Psoriasis, Stricturoplasty, Surgery, Uterine leiomyoma, Ventricular extrasystoles (2 each).

- COVID-19 Medical history (n = 45): COVID-19 (27), Post-acute COVID-19 syndrome (16), Suspected COVID-19 (9), Coronavirus infection (1).

Analysis by age group

PM: Paediatric (120), Adults (4868), Elderly (2036), Unknown (714).

– No significant difference was observed in the reporting proportion of COVID-19 relevant PTs between adult and elderly populations. Due to the relative low volume of cases in the paediatric population, a meaningful comparison with other age groups was not possible.

Analysis Original versus Bivalent Vaccines

The majority of the long COVID-19 cases was reported after administration of the original vaccine (89%), therefore a meaningful comparison of the PTs reported in the 3 vaccines groups was not possible.

O/E Analysis

O/E analysis was performed for Ageusia/anosmia (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest* and Appendix 5.8.1 for age of stratified observed cases with O/E ratio > 1).

Conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue and long COVID-19 will be discussed in the next PSUR if warranted.

16.3.3.1.3. Immune-mediated/autoimmune AESIs

Search criteria - SMQ Immune-mediated/autoimmune disorders (Narrow and Broad) OR HLGT (All Path) Autoimmune disorders OR PTs Cytokine storm; Hypersensitivity; Thrombocytopenia; Thyroiditis subacute.[66]

[66] Due to MedDRA upgrade to version 26.0: 11 new PTs have been included in the search strategy (Adenosine deaminase 2 deficiency; Anti IFN gamma autoantibody syndrome; Antibody-dependent enhancement; CANOMAD syndrome; Enhanced respiratory disease; Gestational alloimmune liver disease;

Clinical Trial Data

During the reporting interval, there were no serious clinical trial cases that reported events coded to MedDRA PTs indicative of Immune-mediated/autoimmune.

Post-Authorisation Data

- Number of cases: 3215 (original [2846], bivalent Omi BA.1 [138], bivalent Omi BA.4/BA.5 [248]; 4.3% of 74,102 cases of the total PM dataset), compared to 6155 cases (2.2%) retrieved in the PSUR #4.
- MC cases (1550), NMC cases (1665).
- Country/region of incidence: Germany (867), UK (308), Japan (273), Denmark (249), France (233), US (227), Finland (131), Sweden (106), Italy (86), Norway (84); the remaining 651 cases were distributed among 50 countries.
- Subjects' gender: female (2064), male (1066) and unknown (85).
- Subjects' age in years: n = 2975, range: 2 – 97, mean: 51.5, median: 53.0.
- Medical history (n = 1612); the most frequently (>50) reported relevant medical conditions included Hypertension (285), Asthma (118), Seasonal allergy (113), Psoriasis (104), Hypothyroidism (96), Diabetes mellitus (76), Hypersensitivity (75), Autoimmune thyroiditis, Drug hypersensitivity (73 each), Food allergy (56), Hypercholesterolaemia (55), and Depression (52).
- COVID-19 Medical history (n = 172): COVID-19 (129), Suspected COVID-19 (36), Post-acute COVID-19 syndrome (7), Coronavirus infection (3), Exposure to SARS-CoV-2 (2), Breakthrough COVID-19, and SARS-CoV-2 test positive (1 each).
- Co-suspect medications (n = 192); the most frequently (>5) reported relevant co-suspect medications included elasomeran (48), influenza vaccine inact split 4V (19), influenza vaccine (18), adalimumab (13), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (11), COVID-19 vaccine (8), and influenza vaccine inact SAG 4V (7).
- Number of relevant events: 3690.
- Relevant event seriousness: serious (2733) and non-serious (957).
- Most frequently (≥2%) reported relevant PTs: Hypersensitivity (413), Psoriasis (177), Polymyalgia rheumatica (160), Autoimmune disorder (156), Dermatitis (86), Thrombocytopenia (79), Alopecia areata (77), Myositis (69), Hyperthyroidism (65), Autoimmune thyroiditis, Hypothyroidism (64 each), and Graves' disease (63).

Graves' disease; Immune-mediated myelitis; Immune-mediated polyserositis; Incomplete thymus involution; S100 protein increased) and 1 PT (Basedow's disease) has been removed.

- Time to event onset: n = 1571, range: <24 hours to 740 days, median: 166 days.
  - <24 hours: 219 events (2 of which had a fatal outcome);
  - 1 day: 154 events (2 of which had a fatal outcome);
  - 2-7 days: 304 events (2 of which had a fatal outcome);
  - 8-14 days: 182 events (none reported a fatal outcome);
  - 15-30 days: 203 events (2 of which had a fatal outcome);
  - 31-181 days: 318 events (6 of which had a fatal outcome);
  - 182-240 days: 53 events (4 of which had a fatal outcome);
  - 241-365 days: 75 events (2 of which had a fatal outcome);
  - 366-740 days: 63 events (none reported a fatal outcome).

- Duration of relevant events: n = 162, range: <24 hours to 713 days, median: 137 days.
  - <24 hours: 19 events;
  - 1 day: 12 events;
  - 2-7 days: 29 events;
  - 8-14 days: 16 events;
  - 15-30 days: 5 events;
  - 31-181 days: 33 events;
  - 182-240 days: 8 events;
  - 241-365 days: 12 events;
  - 366-713 days: 28 events.
- Relevant event outcome: fatal (38), resolved/resolving (823), resolved with sequelae (240), not resolved at the time of reporting (1497), and unknown (1092).

Fatal cases (46)

In 46 cases (reporting 38 relevant events with a fatal outcome), the reported causes of death (≥3) included Interstitial lung disease, Thrombocytopenia (6 each), Multiple organ dysfunction syndrome, Myocarditis (5 each), Cardiac arrest, Pneumonia (4 each), Acute respiratory failure, Cerebral haemorrhage, COVID-19, Death, Dyspnoea, and Shock (3 each). Most (30 of 43 cases that provided age) of the fatal cases involved elderly subjects. When the medical history was provided (28 cases), significant medical conditions reported in more than 2 cases included Hypertension (11), Dyslipidaemia, Type 2 diabetes mellitus (4 each), Chronic kidney disease, Hospitalisation, and Renal failure (3 each).

Analysis by age group

PM: Paediatrics (107), Adults (2106), Elderly (775), and Unknown (227).

- Among the frequently (≥2%) reported Immune-mediated/autoimmune AESIs, it was observed that:
  - PTs Polymyalgia rheumatica, Thrombocytopenia, and Myositis were reported at a higher frequency in the elderly population when compared to paediatric and adult populations (Polymyalgia rheumatica [13.0% in elderly vs none in paediatrics and 2.6% in adults], Thrombocytopenia [4.0% in elderly vs 2.8% in paediatrics and 1.7% in adults], and Myositis [3.7% in elderly vs 0.9% in paediatrics and 1.8% in adults]).

- PTs Psoriasis, Dermatitis, and Hyperthyroidism were reported at a higher frequency in the adult and elderly populations when compared to the paediatric population (Psoriasis [5.9% in adults and 5.2% in elderly vs 0.9% in paediatrics], Dermatitis [2.8% in adults and 2.7% in elderly vs 0.9% in paediatrics], and Hyperthyroidism [2.0% in adults and 1.7% in elderly vs none in paediatrics]).
- PT Graves' disease was reported at a higher frequency in the adult population when compared to the paediatric and elderly populations (2.6% in adults vs none in paediatrics and 0.4% in elderly).
- PTs Hypersensitivity, Autoimmune disorder, Alopecia areata, Autoimmune thyroiditis, and Hypothyroidism were reported at a higher frequency in the paediatric and adult populations when compared to the elderly population (Hypersensitivity [14.0% in paediatrics and 13.5% in adults vs 8.3% in elderly], Autoimmune disorder [8.4% in paediatrics and 5.2% in adults vs 1.9% in elderly], Alopecia areata [2.8% in both paediatrics and adults vs 0.9% in elderly], Autoimmune thyroiditis [1.9% in paediatrics and 2.7% in adults vs 0.6% in elderly], and Hypothyroidism [2.8% in paediatrics and 2.1% in adults vs 1.5% in elderly]).

Analysis Original versus Bivalent Vaccines

PM: original (2846), bivalent Omi BA.1 (138), bivalent Omi BA.4/BA.5 (248).

– Among the frequently (≥2%) reported Immune-mediated/autoimmune AESIs by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:

  - PTs Hypersensitivity, Dermatitis, Myositis were reported at a higher frequency in patients administered bivalent Omi BA.1 when compared to subjects administered original and bivalent Omi BA.4/BA.5 (Hypersensitivity [21.0% in bivalent Omi BA.1 vs 12.6% in original and 11.3% in bivalent Omi BA.4/BA.5], Dermatitis [8.7% in bivalent Omi BA.1 vs 2.5% in original and 2.4% in bivalent Omi BA.4/BA.5], and Myositis [5.8% in bivalent Omi BA.1 vs 1.9% in original and 2.8% in bivalent Omi BA.4/BA.5]).
  - PTs Psoriasis, Autoimmune disorder, Alopecia areata, Hyperthyroidism, and Autoimmune thyroiditis were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (Psoriasis [5.7% in original vs 3.6% in bivalent Omi BA.1 and 4.4% in bivalent Omi BA.4/BA.5], Autoimmune disorder [5.1% in original vs 2.2% in bivalent Omi BA.1 and 2.8% in bivalent Omi BA.4/BA.5], Alopecia areata [2.6% in original vs 1.5% in bivalent Omi BA.1 and 0.8% in bivalent Omi BA.4/BA.5], Hyperthyroidism [2.1% in original vs none in bivalent Omi BA.1 and 0.8% in bivalent Omi BA.4/BA.5], and Autoimmune thyroiditis [2.1% in original vs none in bivalent Omi BA.1 and 1.6% in bivalent Omi BA.4/BA.5]).
  - PTs Polymyalgia rheumatica, and Thrombocytopenia were reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to subjects administered original (Polymyalgia rheumatica [9.4% in bivalent Omi BA.1 and 9.7% in bivalent Omi BA.4/BA.5 vs 4.4% in original], and

Thrombocytopenia [3.6% in bivalent Omi BA.1 and 4.4% in bivalent Omi BA.4/BA.5 vs 2.2% in original]).

- PT Hypothyroidism was reported at a higher frequency in subjects administered original and bivalent Omi BA.4/BA.5 when compared to subjects administered bivalent Omi BA.1 (2.1% in original and 1.6% in bivalent Omi BA.4/BA.5 vs 0.7% in bivalent Omi BA.1).
- PT Graves' disease was reported at a higher frequency in subjects administered original and bivalent Omi BA.1 when compared to subjects administered bivalent Omi BA.4/BA.5 (2.0% in original and 2.9% in bivalent Omi BA.1 vs 0.8% in bivalent Omi BA.4/BA.5).

O/E Analysis

O/E analysis was performed for Acute disseminated encephalomyelitis (ADEM), ADEM and encephalitis, Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.4. Multisystem Inflammatory Syndrome in Children / Adults

Search criteria – PTs: Cytokine release syndrome; Distributive shock; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Systemic inflammatory response syndrome.

Please refer to Appendix 5.2 *Multisystem Inflammatory Syndrome* for the review of the MIS-C/MIS-A cases received in the reporting interval.

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #4.

Post-Authorisation Data

- Number of relevant cases: 55 (original [45], bivalent Omi BA.1 [3], bivalent Omi BA.4/BA.5 [8]; 0.07% of 74,102 cases in the total PM dataset), compared to 92 (0.03%) retrieved in PSUR #4.
- MC cases (43), NMC cases (12).
- Country/region of incidence (≥3): Germany (18), Japan (7), UK (5), US (4), Denmark, France and Spain (3 each); the remaining 12 cases were distributed among 11 countries.

- Subjects' gender: female (28), male (25) and unknown (2).
- Subjects' age in years: n = 52, range: 5– 90, mean: 54.1, median: 59.0.
- Medical history (n = 42); the most frequently (≥3) reported medical conditions included Hypertension (8), Hyperlipidaemia (7), Hypothyroidism and Rheumatoid arthritis (6 each), Migraine (5), Adrenal cyst, Collagen disorder, Glomerulonephritis, Hypercholesterolaemia, Hypertriglyceridaemia, Lyme disease, Obesity, Overlap syndrome, Overweight, Polyarthritis, Presbyacusis, Presbyopia, Psoriasis, Tinnitus, Trigeminal neuralgia and Type 2 diabetes mellitus (4 each), Abstains from alcohol, Drug hypersensitivity and Non-tobacco user (3 each).
- COVID-19 medical history (n = 6): COVID-19 (4), Coronavirus infection (2) and Post-acute COVID-19 syndrome (1). Of the 6 cases, the COVID infection was past medical history (2), unknown (4).
- Co-suspect medications (n = 5): COVID-19 vaccine (2), elasomeran, influenza vaccine inact split 4V and teriflunomide (1 each).
- Number of relevant events: 56.
- Relevant event seriousness: serious (56).
- Relevant PTs: Multiple organ dysfunction syndrome (22), Multisystem inflammatory syndrome (15), Multisystem inflammatory syndrome in children (7), Multisystem inflammatory syndrome in adults (5), Systemic inflammatory response syndrome (4), Distributive shock (3).
- Time to event onset[58]: n = 20, range: <24 hours to 491 days, median: 23 days.
  - <24 hours: 2 events;
  - 1 day: 1 event;
  - 2-7 days: 3 events (1 of which had a fatal outcome);
  - 8-14 days: 1 event;
  - 15-30 days: 4 events (1 of which had a fatal outcome);
  - 31-180 days: 5 events (4 of which had a fatal outcome);
  - >180 days: 4 events (3 of which had a fatal outcome).
- Duration of relevant events[59]: n = 0 (in none of the 5 relevant events with clinical outcome 'resolved' the duration was provided).
- Relevant event outcome: fatal (16), resolved/resolving (14), not resolved (11), unknown (15).

Fatal cases (15)

In 15 fatal cases (reporting 16 relevant events with fatal outcome), the reported causes of death were coded to Multiple organ dysfunction syndrome (14), Renal failure and Thrombosis (4 each), Septic shock (3), Pancreatitis acute, Cardiogenic shock, Cerebrovascular accident, Necrosis ischaemic, Confusional state, Pulmonary embolism, COVID-19 pneumonia, Sepsis, Thrombocytopenia, Cerebral infarction, Cardiac arrest, Infarction and Ischaemic stroke (2 each). Of 15 cases, 11 involved elderly subjects. When

the medical history was provided (12 cases), the most frequently (≥2) reported medical conditions included Hypertension (4), Type 2 diabetes mellitus (3), Cholecystectomy, Diverticulitis, Dyslipidaemia, Glomerulonephritis, Hypothyroidism and Obesity (2 each).

Analysis by age group

PM: Paediatric (8 [1 Child, 7 Adolescents]), Adult (25), Elderly (19), Unknown (3).

– Among the relevant multisystem inflammatory syndrome events, it was observed that:
  - PT Multiple organ dysfunction syndrome was reported at a higher frequency in the elderly population compared to the adult population (78.9% of the elderly population vs 24.0% of the adult population). No cases were reported in the paediatric population.
  - PT Multisystem inflammatory syndrome was reported at a higher frequency in the adult population compared to paediatric and elderly populations (48% of the adult population vs 12.5% of the paediatric population and 10.5% of the elderly population).
  - PT Multisystem inflammatory syndrome in children was reported, as expected, primarily in the paediatric population (87.5% were in the paediatric population).
  - PT Multisystem inflammatory syndrome in adults was reported only in the adult and elderly populations (12.0% in the adult population and 10.5% in the elderly population); no cases, as expected, were reported in the paediatric population.
  - PT Systemic inflammatory response syndrome was reported only in patients of unknown age and in adults (66.7% in the population of unknown age and 8.0% in the adult population); no cases were reported in the paediatric population.
  - PT Distributive shock was observed only in the adult and elderly populations (8.0% in the adult population and 5.3% in the elderly population; no cases in paediatric population).

Analysis Original versus Bivalent Vaccines

PM: original (45 cases), bivalent Omi BA.1 (3 cases), bivalent Omi BA.4/BA.5 (8 cases). There were no paediatric patients administered bivalent vaccines.

Among the three groups, the PT Multiple organ dysfunction syndrome was the most frequently reported: there were 17 cases in the original group, 4 cases in the bivalent Omi BA.4/BA.5 group and 2 cases in the bivalent Omi BA.1 group.

The remaining relevant PTs were distributed as follows:

- PT Multisystem inflammatory syndrome was reported in cases involving patients administered the original vaccine (13 cases) and the bivalent Omi BA.4/BA.5 vaccine (2 cases);
- PTs Multisystem inflammatory syndrome in children and Systemic inflammatory response syndrome were reported exclusively in cases involving patients administered the original vaccine (7 cases and 4 cases, respectively);

- PT Multisystem inflammatory syndrome in adults was reported in cases involving patients administered the original vaccine (3 cases) and the bivalent Omi BA.4/BA.5 vaccine (2 cases);
- PT Distributive shock was reported in cases involving patients administered the original vaccine (2 cases) and the bivalent Omi BA.1 vaccine (1 case).

O/E Analysis

O/E analysis was performed for Multisystem inflammatory syndrome (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.5. Myocarditis and Pericarditis AESIs

Please refer to the Risk 'Myocarditis and Pericarditis' in Section 16.3.1.1 *Important Identified Risks – Myocarditis* and in Section 16.3.1.1.2. *Important Identified Risks – Pericarditis.*

16.3.3.1.6. Neurological AESIs (including demyelination)

Search criteria - SMQ Generalised convulsive seizures following immunisation (Narrow) OR SMQ Demyelination (Narrow and Broad) OR PTs Ataxia; Cataplexy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Meningitis viral; Miller Fisher syndrome; Narcolepsy; Neuropathy peripheral; Polyneuropathy.[67]

Clinical Trial Data

- Number of cases: 2 (original [1], blinded therapy [1]; 2.4% of 82 cases in the total CT dataset), compared to 8 cases (2.6%) retrieved in the PSUR #4.
- Country/region of incidence: US, Germany (1 each).
- Subjects' gender: female, male (1 each).
- Subjects' age in years: n = 2; ages 3 years and 45 years.
- Medical history (n = 1); the subject had a history of epilepsy.
- COVID-19 medical history: none.
- Co-suspect medications: none.

[67] Due to MedDRA upgrade to version 26.0: 1 new PT (Immune-mediated optic neuritis) have been included in the search strategy.

- Reported relevant PTs: Epilepsy, Seizure (1 each). None of these SAEs were assessed as related to original/blinded therapy.
- Relevant event outcome: resolved with sequelae (2).

Post-Authorisation Data

- Number of relevant cases: 1263 (original [1040], bivalent Omi BA.1 [80], bivalent Omi BA.4/BA.5 [149], BNT162b2 Multivalent NOS [4]; 1.7% of 74,102 cases in the total PM dataset), compared to 2597 cases (0.9%) retrieved in the PSUR #4. Please note that in some cases the subject received more than vaccine formulation.
- MC cases (591), NMC cases (672).
- Country/region of incidence (> 25): Germany (396), UK (132), Japan (122), US (97), France (68), Finland (62), Italy (50), Denmark (47), Australia (30), Norway (29), and Austria (27). The remaining 203 cases were distributed among 31 countries.
- Subjects' gender: female (743), male (470) and unknown (50).
- Subjects' age in years: n = 1158, range: 2 – 102, mean: 49.6, median: 51.0.
- Medical history (n = 637); the most frequently (> 2% of cases that reported history) reported medical conditions included Hypertension (115), Epilepsy (51), Multiple sclerosis (35), Depression, Fibromyalgia (34 each), Diabetes mellitus, Drug hypersensitivity (30 each), Hypothyroidism (28), Seasonal allergy (27), Asthma (26), Type 2 diabetes mellitus (25), Obesity (24), Tobacco user (21), Pain (20), Alcohol use, Atrial fibrillation (19 each), Non-tobacco user (18), Osteoporosis, (17), Dyslipidaemia, Migraine, Osteoarthritis (16 each), Rheumatoid arthritis (15), Hypercholesterolaemia, Hypersensitivity (14 each), Autoimmune thyroiditis, Back pain, polyneuropathy (13 each).
- COVID-19 Medical history (n = 87): COVID-19 (64), Suspected COVID-19 (22), Coronavirus infection, COVID-19 pneumonia (1 each).
- Co-suspect medications (n = 69 cases); the most frequently (≥ 2) reported included elasomeran (22), influenza vaccine, ocrelizumab (8 each), influenza vaccine inact split 4V (7), adalimumab, influenza vaccine inact SAG 4V (3 each), cortisone acetate, COVID-19 vaccine NRVV AD26 (JNJ 78436735), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), prednisone (2 each).
- Number of relevant events: 1419.
- Relevant event seriousness: serious (1280), non-serious (139).
- Most frequently (> 2% of cases) reported relevant PTs: Seizure (212), Neuropathy peripheral (149), Polyneuropathy (139), Guillain-Barre syndrome (130), Epilepsy (115), Fibromyalgia (110), Multiple sclerosis (93), Myelitis transverse (65), Trigeminal

neuralgia (51), Ataxia (43), Generalised tonic-clonic seizure, Myokymia (33 each), Optic neuritis (31), Multiple sclerosis relapse (26).

- Time to event onset[58]: n = 749, range: < 24 hours to 648 days, median: 7 days.

  - < 24 hours: 144 events (1 of which had a fatal outcome);
  - 1 day: 109 events (2 of which had a fatal outcome);
  - 2-7 days: 129 events (1 of which had a fatal outcome);
  - 8-14 days: 64 events (1 of which had a fatal outcome);
  - 15-30 days: 77 events (2 of which had a fatal outcome);
  - 31-180 days: 152 events (2 of which had a fatal outcome);
  - 181-365 days: 44 events (1 of which had a fatal outcome);
  - > 365 days: 33 events (none of which had a fatal outcome).

- Duration of relevant events[59]: n = 101, range: <24 hours to 673 days, median: 8 days.

  - < 24 hours: 28 events;
  - 1 day: 6 events;
  - 2-7 days: 17 events;
  - 8-14 days: 4 events;
  - 15-30 days: 7 events;
  - 31-180 days: 17 events;
  - 181-365 days: 5 events;
  - > 365 days: 17 events.

  Relevant event outcome[65]: fatal (14), resolved/resolving (299), resolved with sequelae (127), not resolved (562), unknown (420).

Fatal cases (13)

In 13 cases (reporting 14 relevant events with fatal outcome), the reported causes of death included Seizure (5), Guillain-Barre syndrome, Status epilepticus (3 each), Epilepsy (2), and Demyelination (1). Over half (7 of 13 cases) of the fatal cases involved elderly subjects. When the medical history was provided (10 cases), medical conditions reported in 2 or more cases included Hypertension (5), Epilepsy, Non-tobacco user, and Tobacco user (2 each). The subjects in all 10 cases reported a history of other neurologic disorders (PTs Cerebral palsy, Cerebrovascular accident, Dementia, Encephalopathy, Generalised tonic-clonic seizure, Haemorrhage intracranial, Hemiparesis, Hydrocephalus, Paraparesis, and Seizure; 1 each) and 6 reported a history of cardiac disorders (PTs Atrial fibrillation, Cardiac arrest, Cardiac valve sclerosis, Coronary artery disease, Myocardial infarction, Myocardial ischaemia; 1 each).

Analysis by age group

CT: Paediatric 1 Child], Adult (1).

– A meaningful comparison between the different age groups is not possible due to the low number of cases.

PM: Paediatric (62 [1 Infant, 19 Child, 42 Adolescent]), Adult (813), Elderly (287), Unknown (101).

– Among the most frequently (> 2% of all cases) reported relevant neurological events, it was observed that:

  - Frequently reported seizure-related AEs (PTs Epilepsy, Febrile convulsion, Generalised tonic-clonic seizure, and Seizure) were reported at higher frequencies in the paediatric population compared to the adult population and the elderly population (19.4%, 9.7%, 9.7%, and 38.7%, respectively, in the paediatric population vs 9.5%, 1.0%, 2.7% and 16.5%, respectively, in the adult population, and 7.7%, none, 1.7%, and 14.3%, respectively, in the elderly population). This pattern is consistent with the known epidemiology of seizures.
  - The PTs Neuropathy peripheral and Polyneuropathy were reported at higher frequencies in the elderly population compared to the paediatric population and the adult population (11.5% and 19.9%, respectively, in the elderly population vs 4.8%% and none, respectively, in the paediatric population, and 12.6% and 9.4%, respectively, in the adult population).
  - The PTs Multiple sclerosis and Multiple sclerosis relapse were reported at higher frequencies in the adult population compared to the paediatric population and the elderly population (9.6% and 2.7%, respectively, in the adult population vs 4.8% and none, respectively, in the paediatric population, and 2.4% and 1.1% in the elderly population, respectively).
  - The PTs Trigeminal neuralgia and Fibromyalgia were reported more frequently in the adult population and the elderly population compared to the pediatric population (4.8% and 10.0%, respectively, in the adult population and 2.4% and 5.2%, respectively, in the elderly population vs none in the pediatric population).
  - The PT Guillain-Barre syndrome was reported more frequently in the elderly population than in the adult or pediatric populations (17.8% vs 8.0% and 4.8%, respectively).

Analysis Original versus Bivalent Vaccines

PM: original (1035), bivalent Omi BA.1 (79), and bivalent Omi BA.4/BA.5 (149).

– Among the frequently (≥2%) reported Neurological AESIs (including demyelination) by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:

  - PTs Polyneuropathy, Multiple sclerosis, Myelitis transverse, Myokymia, Optic neuritis, and Multiple sclerosis relapse were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5

PT	Original	Bivalent Omi BA.1	Bivalent Omi BA.4/BA.5
Polyneuropathy	**12.1%**	6.3%	6.0%
Multiple sclerosis	**8.3%**	1.3%	4.0%
Myelitis transverse	**5.7%**	1.3%	3.4%
Myokymia	**3.1%**	0	0.7%
Optic neuritis	**3.0%**	0	0
Multiple sclerosis relapse	**2.4%**	0	0.7%

  - PT Trigeminal neuralgia was reported at a higher frequency in subjects administered bivalent Omi BA.1 when compared to subjects administered original and bivalent Omi BA.4/BA.5
  - PTs Seizure was reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to subjects administered original (34.2% in bivalent Omi BA.1 and 25.5% in bivalent Omi BA.4/BA.5 vs 14.2% in original).
  - PT Generalised tonic-clonic seizure was reported at a higher frequency in subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 when compared to original (6.3% in bivalent Omi BA.1 and 5.4% in bialent Omi BA.4/BA.5 vs 1.9% in original).
  - PT Fibromyalgia was reported at a higher frequency in subjects administered original and bivalent Omi BA.1 when compared to subjects administered bivalent Omi BA.4/BA.5 (9.9% in original and 7.6% in bivalent Omi BA.1 vs 1.3% in bivalent Omi BA.4/BA.5).
  - PT Guillain-Barre syndrome was reported at a higher frequency in subjects administered bivalent Omi BA.4/BA.5 when compared to subjects administered original and bivalent Omi BA.1 (24.8% in bivalent Omi BA.4/BA.5 vs 8.3% in original and 8.9% in bivalent Omi BA.1).

O/E Analysis

O/E analysis was performed for Generalized convulsive, Fibromyalgia, Guillain-Barré syndrome, Meningitis, Narcolepsy, Multiple sclerosis (MS) and Polyneuropathy. See

Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest* and Appendix 5.8.1 *Ageusia-anosmia, multiple sclerosis and stress cardiomyopathy* for an assessment of multiple sclerosis stratified observed cases with O/E ratio > 1.

Conclusion

No new significant safety information was identified based on a review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.7. Pregnancy related AESIs

Search criteria – PTs: Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal death; Maternal death affecting foetus; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Renal failure neonatal; Renal impairment neonatal; Stillbirth; Uterine rupture; Vasa praevia.

For relevant cases, please refer to Section 16.3.5.2 *Use in Pregnant/Lactating Women.*

16.3.3.1.8. Glomerulonephritis and Nephrotic Syndrome AESIs

Search criteria – HLT Glomerulonephritis and nephrotic syndrome (All Path).[68]

Clinical Trial Data

- Number of cases: none; no cases were retrieved in PSUR #4.

Post-Authorisation Data

- Number of cases: 103 (original [93], bivalent Omi BA.1 [3], bivalent Omi BA.4/BA.5 [8]; 0.07% of 74,102 cases, the total PM dataset), compared to 198 (0.07%) retrieved in PSUR #4. Please note that in 1 case the subject received more than vaccine formulation.
- MC cases (73), NMC cases (30).
- Country/region of incidence: Japan (25), Germany (24), UK (14), US (10), France (7), Sweden (5); the remaining 18 cases were distributed among 12 countries.
- Subjects' gender: female (47), male (53) and unknown (3).
- Subjects' age in years: n = 97, range: 9 – 91, mean: 53, median: 57.0.
- Medical history (n = 66); the most frequently (≥ 2) reported medical conditions included Hypertension (16), Asthma, Haematuria, Non-tobacco user (7 each), Diabetes mellitus, Nephrotic syndrome (5 each), Atrial fibrillation, Dyslipidaemia, Glomerulonephritis

[68] Due to MedDRA upgrade to version 26.0: 1 new PT (Galloway Mowat syndrome) have been included in the search strategy.

minimal lesion, Steroid therapy (4 each), Abstains from alcohol, Drug hypersensitivity, Hospitalization, Hypoalbuminaemia, Immunodeficiency, Proteinuria, Seasonal allergy, Tobacco user, Type 2 diabetes mellitus (3 each), Adrenal insufficiency, Allergy to animal, Arthralgia, Carpal tunnel decompression, Deep vein thrombosis, Gastrooesophageal reflux disease, Gilbert's syndrome, Hyperlipidaemia, IgA nephropathy, Osteopenia, Pyeloplasty, Renal failure, Urinary occult blood (2 each).

- COVID-19 Medical history (n = 5): COVID-19 (5), Suspected COVID-19 (2).
- Co-suspect medications (n = 5); the reported relevant co-suspect medications included COVID-19 vaccine, elasomeran, encorafenib, and influenza (1 each).
- Number of relevant events: 115.
- Relevant event seriousness: serious (114), non-serious (1).
- Relevant PTs: Nephrotic syndrome (35), IgA nephropathy (19), Granulomatosis with polyangiitis (16), Glomerulonephritis membranous (11), Glomerulonephritis minimal lesion (8), Glomerulonephritis (6), Focal segmental glomerulosclerosis (5), Glomerulonephritis rapidly progressive, Microscopic polyangiitis (4 each), C3 glomerulopathy, Glomerulonephritis membranoproliferative (2 each), Anti-glomerular basement membrane disease, Nephritic syndrome, and Primary coenzyme Q10 deficiency (1 each).
- Time to event onset[58]: n = 33, range: < 24 hours - 606 days, median: 16 days.
  - < 24 hours: 4 events;
  - 1 day: 4 events;
  - 2-7 days: 3 events;
  - 8-14 days: 5 events;
  - 15-30 days: 5 events;
  - 31-180 days: 8 events;
  - 181-304 days: 3 events;
  - > 305 days: 1 event.
- Duration of relevant events[59]: n = 2, duration 171 days and 605 days.
- Relevant event outcome: fatal (3), resolved/resolving (31), resolved with sequelae (8), not resolved (37), unknown (36).

Fatal cases (3)

In 3 cases (reporting 3 relevant events with fatal outcome), the reported causes of death were coded to Granulomatosis with polyangiitis (2) and Nephrotic syndrome (1). Medical history was provided in all 3 cases and included Fluid retention, Haemodialysis, and Glomerulonephritis and Renal failure (1 each).

Analysis by age group

PM: Paediatric (8 [1 Child, 7 Adolescent]), Adult (59), Elderly (31) and Unknown (5).

- The most frequently reported Glomerulonephritis and Nephrotic Syndrome AE in adults and elderly subjects coded to the PT Nephrotic syndrome (28.8% and 41.9% of adults and elderly, respectively). The PT IgA nephropathy was higher in adult population when compared to elderly population (25.4% in adults vs 3.2% in elderly). Other PTs were reported in similar reporting proportions in both adults and the elderly. Due to the relative low volume of cases in the paediatric population and for cases with age unknown, a meaningful comparison of the same with the other age groups was not possible.

Analysis Original versus Bivalent Vaccines

PM: original (92), bivalent Omi BA.1 (3), and bivalent Omi BA.4/BA.5 (8). The number of cases for bivalent Omi BA.1, and bivalent Omi BA.4/BA.5 (5 and 8, respectively) are too small to all for a meaningful comparison to the occurrence of Glomerulonephritis/nephrotic syndrome in cases treated with BNT162b2.

O/E Analysis

O/E analysis was performed for Glomerulonephritis/nephrotic syndrome (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information has emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.9. Stroke

Search criteria – HLT Central nervous system haemorrhages and cerebrovascular accidents (All path); Cerebrovascular venous and sinus thrombosis (Primary Path).

Clinical Trial Data

- Number of cases: 2 (original, BNT162b2 [B.1.1.7 + B.1.617.2] [1 each]; 2.4% of 82 cases in the total CT dataset), compared to 11 cases (3.5%) retrieved in the PSUR #4.
- Country/region of incidence: South Africa (1), US (1).
- Subjects' gender: female (1), male (1).
- Subjects' age in years: 44.0 and 52.0 years.
- Medical history PTs (n = 1): Clinical trial participant, Hypercholesterolaemia, Hyperlipidaemia, Sexual abstinence, Stress urinary incontinence, Tobacco user, Type 2 diabetes mellitus

- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PTs: Cerebrovascular accident (2), Vertebral artery occlusion (1). However, both these SAEs were assessed as unrelated to BNT162b2.
- Relevant event outcome: resolved with sequelae (3).

Post-Authorisation Data

- Number of cases: 764 (original [571], bivalent Omi BA.1 [52], bivalent Omi BA.4/BA.5 [141]; 1.0% of 74,102 cases in the total PM dataset), compared to 1132 cases (0.4%) retrieved in the PSUR #4.
- MC cases (358), NMC cases (406).
- Country/region of incidence (>50): Germany (254), US (98), UK (89), Japan (58), France (54); the remaining 211 cases were distributed among 37 countries.
- Subjects' gender: female (351), male (383), unknown (30).
- Subjects' age in years: n = 683, range: 5 – 99, mean: 62.2, median: 64.0.
- Medical history (n = 436): the most frequently (>20) reported medical conditions were coded to the PTs Hypertension (171), Atrial fibrillation (34), Hypothyroidism (30), Diabetes mellitus, Dyslipidaemia, Hypercholesterolaemia, Type 2 diabetes mellitus (29 each), Tobacco user (27), Cerebrovascular accident, Obesity (23 each), Drug hypersensitivity (22), Non-tobacco user (21).
- COVID-19 medical history (n = 38): COVID-19 (28), Suspected COVID-19 (8), COVID-19 immunisation, Post-acute COVID-19 syndrome (1 each).
- Co-suspect medications (n = 37): the most frequently (≥2) reported included elasomeran (10), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (7), influenza vaccine inact split 4V (5), apixaban, COVID-19 vaccine, influenza vaccine inact SAG 4V (3 each), influenza vaccine, mepolizumab, rivaroxaban (2 each).
- Number of relevant events: 898.
- Relevant event seriousness: serious (898).
- Most frequently (≥10) reported relevant PTs: Cerebrovascular accident (357), Cerebral infarction (107), Ischaemic stroke (86), Cerebral haemorrhage (57), Cerebral venous sinus thrombosis (40), Cerebral ischaemia (24), Subarachnoid haemorrhage (23), Cerebral thrombosis (18), Embolic stroke (17), Cerebellar infarction, Haemorrhagic stroke (13 each), Brain stem infarction, Ischaemic cerebral infarction (10 each).

- Time to event onset: n = 541, range: <24 hours to 581 days, median: 18 days.
  - <24 hours: 45 events (5 of which had a fatal outcome);
  - 1 day: 55 events (5 of which had a fatal outcome);
  - 2-7 days: 84 events (8 of which had a fatal outcome);
  - 8-14 days: 56 events (4 of which had a fatal outcome);
  - 15-30 days: 93 events (8 of which had a fatal outcome);
  - 31-180 days: 135 events (20 of which had a fatal outcome);
  - >180 days: 73 events (7 of which had a fatal outcome).
- Duration of relevant events[59]: n = 59, range: <24 hours to 649 days, median 15 days.
  - <24 hours: 8 events;
  - 1 day: 5 events;
  - 2-7 days: 7 events;
  - 8-14 days: 8 events;
  - 15-30 days: 8 events;
  - 31-180 days: 9 events;
  - >180 days: 14 events.
- Relevant event outcome: fatal (92), resolved/resolving (175), resolved with sequelae (154), not resolved (193), unknown (287).

Fatal cases (78)

In 78 cases (reporting 92 relevant events with fatal outcome), the reported causes of death (≥3) were coded to the PTs Cerebrovascular accident (24), Cerebral haemorrhage (15), Ischaemic stroke (12), Cerebral infarction (8), Cerebral thrombosis (7), Subarachnoid haemorrhage (5), Haemorrhage intracranial (3).

Analysis by age group

CT: Adult (2).

- A meaningful comparison between the different age groups is not possible due to the low number of cases.

PM: Paediatric (8 [3 Child, 5 Adolescent]), Adult (357), Elderly (333), Unknown (66).

- Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible. Among the most frequently (≥10 occurrences) reported relevant stroke-related events, there were no PTs that had a greater than 3-fold reporting proportion between the elderly and adult populations.

Analysis Original versus Bivalent Vaccines

PM: original (571), bivalent Omi BA.1 (52), and bivalent Omi BA.4/BA.5 (141).

- Among the frequently (≥3%) reported stroke related events by original cases, bivalent Omi BA.1 cases, and bivalent Omi BA.4/BA.5 cases during the reporting interval, it was observed that:

  - PTs Cerebral ischaemia and Cerebral venous sinus thrombosis were reported at a higher frequency in subjects administered original when compared to subjects administered bivalent Omi BA.1 and bivalent Omi BA.4/BA.5 (Cerebral ischaemia [3.5% in original vs none in bivalent Omi BA.1 and 2.8% in bivalent Omi BA.4/BA.5], Cerebral venous sinus thrombosis [6.5% in original vs none in bivalent Omi BA.1 and 2.1% in bivalent Omi BA.4/BA.5]).

  - PT Cerebral haemorrhage was reported at a higher frequency in subjects administered bivalent Omi BA.4/BA.5 (11.3%) when compared to subjects administered original (6.8%) and bivalent Omi BA.1 (3.8%). No significant difference observed in the other most frequently reported events among these groups.

O/E Analysis

O/E analysis was performed for CVST, Ischaemic stroke and Haemorrhagic stroke, respectively (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information have emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.10. Sudden Death

Search criteria – PT Sudden Death.

Clinical Trial Data

- Number of cases: none; no cases were retrieved in PSUR #4.

Post-Authorisation Data

- Number of cases: 23 (original [11], bivalent Omi BA.1 [4], bivalent Omi BA.4/BA.5 [8]; 0.03% of 74,102 cases, the total PM dataset), compared to 48 (0.02%) retrieved in PSUR #4.
- MC cases (18), NMC cases (5).

- Country/region of incidence: Japan (10), Germany (7), Spain, UK (2 each), France, and Italy (1 each).
- Subjects' gender: female (8), and male (15).
- Subjects' age in years: n = 19, range: 14 – 93, mean: 72.5, median: 80.0.
- Medical history (n = 14); the most frequently (≥2) reported relevant medical conditions included Hypertension (6), Atrial fibrillation, Cerebral infarction, and Diabetes mellitus (2 each).
- COVID-19 Medical history: none.
- Co-suspect medications (n = 2); the reported relevant co-suspect medications included influenza vaccine inact split 4V (2).
- Number of relevant events: 23.
- Relevant event seriousness: serious (23), non-serious (0).
- Time to event onset[58]: n = 18, range: 0 - 571 days, median: 9 days.
  - <24 hours: 2 events;
  - 1 day: 2 events;
  - 2-7 days: 3 events;
  - 8-14 days: 3 events;
  - 15-30 days: 1 event;
  - 31-180 days: 4 events;
  - 181-571 days: 3 events.

Analysis by age group

PM: Paediatric (1, Adolescent), Adult (3), Elderly (16) and Unknown (3).

- Elderly subjects account for 70% of cases reporting the PT Sudden death. Due to the relative low volume of cases in the paediatric and in the adult population, a meaningful comparison of the PT Sudden death with the other age groups was not possible.
- The paediatric case involved a 14-year-old female subject from Japan; Sudden death was reported along with the fatal events Myopericarditis, Cardiac failure, Arrhythmia, Atrial arrhythmia, Arrhythmia supraventricular, Myocarditis and Pericarditis. This case is described in Section 16.3.1.1.1 (Subjects aged 12 – 15 years – Fatal cases).

Analysis Original versus Bivalent Vaccines

There are no differences in reporting proportion between cases involving administration of original vaccine (11 cases) compared to cases involving administration of bivalent vaccines (12 cases, of which 4 bivalent Omi BA.1 and 8 bivalent Omi BA.4/BA.5).

Sudden death was the only reported PT in 15 cases (of which 4 bivalent Omi BA.1, 6 bivalent Omi BA.4/BA.5, and 5 original vaccine).

In the remaining 8 cases, other fatal SAEs were reported along with Sudden death:

- Six (6) cases involved administration of the original vaccine; in 5 of these cases, along with the PTs Sudden death, cardiac SAEs (3 cases), or Pulmonary embolism (2 cases) were reported; in the last case the co-reported fatal PTs were Musculoskeletal chest pain, Dyspnoea, Loss of consciousness, Syncope, and Resuscitation.

- Two (2) cases involved administration of the bivalent Omi BA.4/BA.5; cardiac SAEs were the co-reported fatal PTs in both cases.

O/E Analysis

O/E analysis was performed for Sudden death (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information has emerged based on the review of these cases and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

16.3.3.1.11. Thromboembolic AESIs

Search criteria - HLGT (All path) Embolism and thrombosis (excluding PTs reviewed as Stroke AESIs) OR PT Coagulopathy.[69]

Clinical Trial Data

- Number of cases: 1 (Original [1]; 1.2% of 82 cases in the total CT dataset), compared to 5 cases (1.6%) retrieved in the PSUR #4.
- Country of incidence: [redacted]
- Subjects' gender: female.

[69] Due to MedDRA upgrade to version 26.0: 2 new PTs (Renal infarct, Tricuspid valve thrombosis) have been included in the search strategy.

- Subjects' age in years: 79.
- Medical history: Hypertension, Drug hypersensitivity, Osteoarthritis, Pulmonary embolism, Gastrooesophageal reflux disease, Blood cholesterol increased, Malignant melanoma, Pulmonary thrombosis, Scarlet fever, Skin neoplasm excision.
- COVID-19 medical history: none.
- Co-suspects: none
- Reported relevant PTs: Deep vein thrombosis, Pulmonary embolism. However, both these SAEs were assessed as unrelated to BNT162b2.
- Relevant event outcome: resolving (1), not resolved (1)

Post-Authorisation Data

- Number of cases: 1217 (original [968], bivalent Omi BA.1 [89], bivalent Omi BA.4/BA.5 [160]; 1.6% of 74,102 cases in the total PM dataset), compared to 2064 cases (0.7%) retrieved in the PSUR #4.
- MC cases (562), NMC cases (655).
- Country of incidence (>50): Germany (414), UK (159), US (102), France (99), Japan (57); the remaining 386 cases were distributed among 43 countries.
- Subjects' gender: female (586), male (586), unknown (45).
- Subjects' age in years: n = 1086, range: 2 – 98, mean: 57.1, median: 57.0.
- Medical history (n = 639): the most frequently (>50) reported medical conditions were coded to the PT Hypertension (156).
- COVID-19 Medical history (n = 75): COVID-19 (63), Suspected COVID-19 (11), Coronavirus infection (2), SARS-CoV-2 test positive (1).
- Co-suspect medications (n = 65): the most frequently (≥3) reported included elasomeran (17), influenza vaccine inact split 4V (10), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (8), influenza vaccine inact SAG 4V, influenza vaccine (5 each), apixaban, COVID-19 vaccine (3 each).
- Number of relevant events: 1457.
- Relevant event seriousness: serious (1369), non-serious (88).
- Most frequently (>50 occurrences) reported relevant PTs: Pulmonary embolism (388), Thrombosis (339), Deep vein thrombosis (211).

- Time to event onset[58]: n = 780, range: < 24 hours to 747 days, median: 22 days.

  - <24 hours: 42 events (10 of which had a fatal outcome);
  - 1 day: 40 events (3 of which had a fatal outcome);
  - 2-7 days: 148 events (8 of which had a fatal outcome);
  - 8-14 days: 81 events (7 of which had a fatal outcome);
  - 15-30 days: 126 events (8 of which had a fatal outcome);
  - 31-180 days: 201 events (10 of which had a fatal outcome);
  - >180 days: 142 events (10 of which had a fatal outcome).

- Duration of relevant events[59]: n = 54, range: <24 hours to 718 days, median 33 days.

  - <24 hours: 6 events;
  - 1 day: 1 event;
  - 2-7 days: 8 events;
  - 8-14 days: 6 events;
  - 15-30 days: 6 events;
  - 31-180 days: 11 events;
  - >180 days: 16 events.

- Relevant event outcome[65]: fatal (105), resolved/resolving (377), resolved with sequelae (119), not resolved (396), unknown (462).

Fatal cases (82)

In 82 cases (reporting 105 relevant events with fatal outcome), the reported causes of death (≥3 occurrences) were coded to the PTs Pulmonary embolism (34), Thrombosis (21), Deep vein thrombosis (10), Embolism (9), Coronary artery thrombosis, Pulmonary thrombosis (5 each), Thrombosis with thrombocytopenia syndrome (4), Disseminated intravascular coagulation, Intracardiac thrombus (3 each). Most (48 of 82 cases) of the fatal cases involved elderly subjects. When the medical history was provided (56 cases), the most frequently (≥5 occurrences) reported medical conditions included the PTs Hypertension (25), Type 2 Diabetes mellitus (9), Atrial fibrillation, Dyslipidaemia, Obesity (7 each), Chronic kidney disease (5).

Analysis by age group

CT: Elderly (1).

- A meaningful comparison between the different age groups is not possible due to the low number of cases.

PM: Paediatric (14 [3 Child, 11 Adolescent]), Adults (689), Elderly (408), Unknown (106).

- Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible. No significant difference was observed in the reporting proportion of the most frequently (≥50 occurrences) reported thromboembolic AESIs, between the adult and elderly populations.

Analysis Original versus Bivalent Vaccines

PM: original (968), bivalent Omi BA.1 (89), and bivalent Omi BA.4/BA.5 (160). No significant difference observed in the most frequently (≥5%) reported events among these groups.

O/E Analysis

O/E analysis was performed for Arterial thromboembolism, Deep vein thrombosis, Disseminated intravascular coagulation, Thrombotic thrombocytopenia syndrome and Venous thromboembolism respectively (see Appendix 5.8 *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new significant safety information has emerged based on the review of these cases, and on the analyses by age group, O/E and original vs bivalent vaccines. Safety surveillance will continue.

Overall AESI Conclusion

Considering that the review of the cases reporting AESIs identified no new significant safety information, the MAH proposes to include and discuss AESIs in future PSURs only if the reporting pattern changes and/or significant new safety information is evident.

At this time, the BNT162b2 vaccines have been administered to an unprecedented number of individuals worldwide and approximately 30 months of clinical trial safety data review, post-authorization surveillance and signal management activities have elapsed. The safety profile of the COVID-19 vaccine is well-characterized, however surveillance will continue.

Based on regulatory authority feedback, knowledge gained about the product safety profile, and the recognition that AESIs for products will evolve over time as knowledge about a product's safety profile grows, it is appropriate to review the AESI/TME list and revise it as needed to stay current and improve surveillance. Pfizer will continue to utilize and refine the AESI list as appropriate for signal detection activities (including O/E analyses) and in preparation for safety aggregate reports. At present, the AESI list is synonymous with the targeted medical event (TME) list which is a MedDRA-based list of >1900 unique PTs, leading to more of a SOC-based approach of aggregate case review. Commensurate with the safety profile of the vaccine, the future AESI list will reflect specific medical conditions coupled with appropriate MedDRA-derived search strategies for each AESI.

16.3.4. Evaluation of Special Situations

In the PRAC AR of the PSUR #3 (EMEA/H/C/PSUSA/00010898/202206), the following request was made: *For future PSURs in the section 'Evaluation of special situations', the overdose, abuse, misuse, and drug dependency, occupational exposure, off-label use, and/or unexpected therapeutic effect should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Upon review of the incremental data of cases evaluated for all the above-mentioned topics, no new safety issues/signals or reporting pattern changes were detected. These topics have been removed from the evaluation of special situations discussed in Section 16.3.4. *Evaluation of Special Situations* of the PSUR.

New data identified during the reporting interval for use of BNT162b2 by special subject situations is described below.

16.3.4.1. Lack of Therapeutic Efficacy

Lack of efficacy cases

Search criteria - PTs Drug ineffective; Vaccination failure.

Of the 7062 cases, 14 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Two (2) cases are not considered as true lack of efficacy cases because the subjects developed COVID-19 infection between days 1-13 from the first dose.
- In 3 cases, subjects did not develop COVID-19 infection.
- In 9 cases, the lack of efficacy PT did not refer to original or bivalent COVID-19 vaccine.

Clinical Trial Data

There was no lack of efficacy cases in the clinical trial dataset for both this reporting period and for the reporting period of PSUR #4.

Post-Authorisation Data

- Number of cases: 7048 (original [4896], bivalent Omi BA.1 [196], bivalent Omi BA.4/BA.5 [1956]) (9.5% of 74,102 cases, the total PM dataset), compared to 56,095 cases (19.8%) in PSUR #4.
- MC cases (2010), NMC cases (5038).

- Country/region of incidence: US (2766), UK (1252), Germany (636), France (429), Japan (360), Netherlands (185), Spain (178), Australia (166), Canada (158), Italy (107). The remaining 811 cases were distributed among 48 countries.
- Subjects' gender: female (4273), male (2396) and unknown (379).
- Subjects' age in years: n = 6085, range: 1 – 102 years, mean: 53.8 years, median: 55.0 years.
- Relevant lack of efficacy events[70]: 7048 (Vaccination failure [1057] and Drug ineffective [5991]). For more details, please refer Table 53 and Table 54.
- Relevant event seriousness: all serious[71].

[70] LOE PTs recorded in 7048 cases were Vaccination failure (1062) and Drug ineffective (5986). Upon review after DLP, some cases were re-assessed: in 5 cases the PT Vaccination failure was reassessed to Drug ineffective.

[71] Includes 3 cases where LOE was captured as non-serious and upgraded to serious after the PSUR DLP.

Vaccination failure (1057 cases)

Table 53. Demographic Information of All Post-Marketing Cases Reporting PT Vaccination failure by Age Group

Characteristics		Age Group[a]		
		5 – 11 years N = 2	**12 years and older N = 1006**	**Unknown N = 49**
MC	Yes	1	431	18
	No	1	575	31
Gender	Female	-	635	17
	Male	2	350	21
	Unknown/ No data	-	21	11
Country/region of incidence		[redacted](2)	US (530), Germany (90), Spain (78), France (52), Austria, Italy (30 each), Japan (21); the remaining 175 cases were distributed among 35 countries	Singapore (19), Italy (13), US (6), Germany (3), Australia (2), Austria, Belgium, Canada, France, Republic of South Korea, and Spain (1 each)
Subject's age in years	N	2	965	-
	Min – Max	8 and 10	13 - 98	-
	Mean	9.0	57.5	-
	Median	9.0	60.0	-
Number of cases involving original vaccine		2 (of which 1 subject received dose 3)	582 (of which 237 subjects received dose 3, 66 subjects received dose 4, and 7 subjects received dose 5)	40 (of which 28 subjects received dose 3, and 4 subjects received dose 4)
Number of cases involving Bivalent Omi BA.1		-	2	1
Number of cases involving Bivalent Omi BA.4/BA.5		-	422	8
Reported COVID-19 infection related events[b]		COVID-19 (2)	COVID-19 (975), COVID-19 pneumonia (30), Breakthrough COVID-19 (6), and Post-acute COVID-19 syndrome (5)	COVID-19 (49)
Outcome of COVID-19 infection related events		resolved/resolving (2)	resolved/resolving (292), resolved with sequelae (6), not resolved (142), unknown (552), and fatal (24)	resolved/resolving (10), unknown (38), and not resolved (1)

a. There were no cases reporting PT Vaccination failure in the age group 6 months to 4 years.
b. Some cases reported more than 1 PT referring to COVID-19 infection

Drug ineffective (5991 cases)

Table 54. Demographic Information of All Post-Marketing Cases Reporting PT Drug ineffective by Age Group

Characteristics		Age Groups			
		6 months – 4 years N = 6	**5 – 11 years N = 28**	**12 years and older N = 5336**	**Unknown N = 621**
MC	Yes	5	14	1336	205
	No	1	14	4000	416
Gender	Female	4	10	3390	217
	Male	1	12	1857	153
	Unknown/ No data	1	6	89	251
Country/region of incidence		Japan (5) and Germany (1)	Japan (11), US (5), Philippines (3), Australia, Brazil, Germany, UK (2 each), and Canada (1)	US (2057), UK (1163), Germany (453), France (368), Japan (218), Netherlands (172), Canada (134), Australia (124), Italy (58); the remaining 589 cases were distributed among 46 countries	US (166), Japan (105), Germany (87), UK (84), Spain (51), Australia (25); the remaining 103 cases were distributed among 29 countries
Subject's age in years	N	6	23	5089	-
	Min – Max	1 – 4 years	5 – 11 years	12 – 102 years	-
	Mean	2.7	7.8	53.4	-
	Median	3.0	8.0	54.0	-
Number of cases involving original vaccine		6 (none completed primary series)	27 (of which 2 subjects received dose 3)	3741 (of which 1449 subjects received dose 3, 307 subjects received dose 4, 62 subjects received dose 5, and 3 subjects received dose 6)	498 (of which 80 subjects received dose 3, 27 subjects received dose 4, and 30 subjects received dose 5)
Number of cases involving Bivalent Omi BA.1		-	-	165	28
Number of cases involving Bivalent Omi BA.4/BA.5		-	1	1430	95

Table 54. Demographic Information of All Post-Marketing Cases Reporting PT Drug ineffective by Age Group

Characteristics	Age Groups			
	6 months – 4 years N = 6	**5 – 11 years N = 28**	**12 years and older N = 5336**	**Unknown N = 621**
Reported COVID-19 infection related events[a]	COVID-19 (5) and Suspected COVID-19 (1)	COVID-19 (23) and Suspected COVID-19 (5)	COVID-19 (4558), Suspected COVID-19 (746), COVID-19 pneumonia (27), Post-acute COVID-19 syndrome (25), Breakthrough COVID-19 (5), Coronavirus infection (3), SARS-CoV-2 test positive (2), Coronavirus test positive, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, and Pneumonia viral (1 each)	COVID-19 (414), Suspected COVID-19 (206), and Post-acute COVID-19 syndrome (3)
Outcome of COVID-19 infection related events	resolved (1) and unknown (5)	resolved/ resolving (11), not resolved (2), and unknown (15)	resolved/resolving (1166), resolved with sequelae (85), not resolved (629), unknown (3472), and fatal (19)	resolved/resolving (106), resolved with sequelae (8), not resolved (18), unknown (486), and fatal (5)

a. Some cases reported more than 1 PT referring to COVID-19 infection

SARS-CoV-2 Variants (48 cases)

In 48 of the 7048 cases, information on SARS-CoV-2 variants was provided.

- *Delta variant (10 cases)*[72]
  - Product: original (10).
  - Country/region of incidence: France (3), Germany, Italy (2 each), New Zealand, Romania, and US (1 each).
  - Lack of efficacy events: Vaccination failure (3) and Drug ineffective (7).
  - Outcome of COVID-19 infection related events: resolved/resolving (4), unknown (4), and fatal (2).

- *Omicron variant (40 cases)*[72]
  - Product: original (37), bivalent Omi BA.1 (2), bivalent Omi BA.4/BA.5 (1).
  - Country/region of incidence (≥2 cases): Germany, US (7 each), France, Japan, Netherlands (4 each), Australia (3), Italy and UK (2 each).
  - Lack of efficacy events: Vaccination failure (6) and Drug ineffective (34).
  - Outcome of COVID-19 infection related events: resolved/resolving (17), not resolved (1), unknown (21), and fatal (1).

Literature

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

Conclusion

No new safety signals have emerged based on a review of these cases.

[72] Includes 2 cases where both Delta and Omicron variants were reported in separate episodes.

16.3.5. Update on Special Patient Populations

In the PRAC AR of the PSUR #3 (EMEA/H/C/PSUSA/00010898/202206), the following request was made: *For future PSURs in the section 'Update on special patient populations', the use in frail patients with co-morbidities, and/or interactions with other vaccines should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

Upon review of the incremental data of cases reported in frail patients with comorbidities and/or interactions with other vaccines, no new safety issues/signals or reporting pattern changes were detected. These populations have been removed from the populations discussed in Section 16.3.5 *Update on Special Patient Populations* of the PSUR.

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 BNT162b2 in this population.

In the AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the following request was made: *For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.*

Response

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

The populations of immunocompromised patients and of patients with autoimmune or inflammatory disorders are summarised in Section 16.4.2 *Description of Missing information.*

16.3.5.1. Use in Paediatric Patients

Search criteria - Paediatric cases are identified as cases where the Age Range derived field value for the patient is "Less than or equal to 17 years". Cases indicative of exposure to the vaccine during the mother's pregnancy or through breastfeeding were excluded.

Of the 2962 cases, 1 case was determined to be non-contributory and was not included in the discussion because the subject was older than 17 years.

16.3.5.1.1. Paediatric Subjects <5 Years of Age

Clinical Trial Data

- Number of cases: 41 (blinded therapy [17], original [13], and bivalent Omi BA.4/BA.5 [11] originated from clinical studies C4591007, C4591007-OPENLABEL, C4591048-SSA, and C4591048-SSB; 50% of 82 cases, the total CT dataset), compared to 62 cases (20.1%) retrieved in the PSUR #4.
- Country/region of incidence: US (25), Brazil (7), Poland (5), Spain (2), Finland, and Mexico (1 each).
- Subjects' gender: female (19), male (22).
- Subjects' age in years: n = 41, range: 13 months – 4 years, mean: 2.4, median: 2.0.
- Medical history (n = 21); the most frequently (≥2) reported included Eczema, Otitis media (4 each), Dermatitis atopic (3), Bronchial hyperreactivity, Ear infection, Food allergy, Hydronephrosis, and Rhinitis allergic (2 each).
- COVID-19 Medical history (n = 3): COVID-19 (3).
- Co-suspect medications: none.
- Most frequently (>1 occurrence) reported PTs (n = 53): Bronchiolitis (6), Pneumonia (5), Asthma (3), Acute respiratory failure, and Pyelonephritis (2 each).
- All events were assessed as unrelated to blinded therapy, BNT162b2, or bivalent Omi BA.4/BA.5.
- Time to event onset: n = 53, range: from 2 to 293 days, median: 123.5 days.
  - 2-7 days: 2 events;
  - 8-40 days: 5 events;
  - 41-180 days: 33 events;
  - 181-293 days: 13 events.
- Duration of relevant events: n = 51, range: <24 hours to 45 days, median: 9.5 days.
  - <24 hours: 1 event;
  - 1 day: 9 events;
  - 2-7 days: 19 events;
  - 8-14 days: 15 events;
  - 15-45 days: 7 events.
- Event outcome: resolved/resolving (51) and resolved with sequelae (2).

Post-Authorisation Data

- Number of cases: 396 (original [294], bivalent Omi BA.1 [2], bivalent Omi BA.4/BA.5 [176]; 0.5% of 74,102 cases in the total PM dataset), compared to 606 cases (0.2%) retrieved in the PSUR #4.
- MC cases (324), NMC cases (72).
- Country/region of incidence: US (285), Japan (51), Brazil (27), Australia (15), Taiwan, Province of China (7), Canada (4), Germany (2). The remaining 5 cases were distributed among 5 countries.
- Subjects' gender: female (160), male (172), and unknown (64).
- Subjects' age in years: n = 389, range: 6 months – 4 years, mean: 2.4, median: 2.0.
- Medical history (n = 42); the most frequently (≥2) reported medical conditions included Gastrooesophageal reflux disease (7), Asthma (4), Astigmatism, Hypersensitivity (3 each), Autism spectrum disorder, Ear infection, Hypertension, Jaundice, Plagiocephaly, Speech disorder developmental, Urticaria, and Weight decreased (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect medications (n = 27); the most frequently (≥2) reported included elasomeran (8), influenza vaccine (7), COVID-19 vaccine NRVV MVA, davesomeran/elasomeran, diphtheria vaccine toxoid/pertussis vaccine acellular/tetanus vaccine toxoid, hepatitis A vaccine, hepatitis A vaccine inact, and influenza vaccine inact split 4V (2 each).
- Number of events: 858.
- Most frequently reported PTs (≥ 2) in subjects with ages of 6 months through 4 years (n = 858):
  - Following dose 1
    - Formulation 3 mcg (Maroon cap) (n = 206): Wrong product administered (28), Pyrexia (19), Poor quality product administered (17), Overdose, Product administration error (14 each), Product preparation error (13), COVID-19 (6), Urticaria (5), Drug ineffective, Product administered at inappropriate site (4 each), Expired product administered, Rash, Vomiting (3 each), Cellulitis, Dyspnoea, Fatigue, Headache, Peripheral swelling, Pharyngeal erythema, Product packaging confusion, Suspected COVID-19, Vaccination site pain, and Vaccination site swelling (2 each).
    - Formulation other/unknown (n = 104): Product administered to patient of inappropriate age (25), Overdose (24), Wrong product administered (8), Pyrexia (6), Off label use, Pain in extremity (3 each), Poor quality product administered, Product administration error, Product use issue, and Vomiting (2 each).
  - Following dose 2
    - Formulation 3 mcg (Maroon cap) (n = 184): Poor quality product administered (22), Wrong product administered (20), Inappropriate schedule of product

administration, Product administration error (19 each), Pyrexia (11), Overdose, Product preparation error (8 each), Off label use (6), Interchange of vaccine products, Vomiting (5 each), Expired product administered, Product administered at inappropriate site, Rash (4 each), Constipation, Cough, Diarrhoea, Gastrooesophageal reflux disease, Product use issue, and Pruritus (2 each).
  - Formulation other/unknown (n = 49): Overdose, Product administered to patient of inappropriate age (11 each), Wrong product administered (5), Expired product administered, Inappropriate schedule of product administration, and Seizure (2 each).
- Following dose 3
  - Formulation 3 mcg (Maroon cap) (n = 125): Poor quality product administered, Product administration error (23 each), Wrong product administered (22), Inappropriate schedule of product administration, Interchange of vaccine products (9 each), Product preparation error (5), Off label use, Overdose (4 each), Fatigue, Pyrexia, and Underdose (2 each).
  - Formulation other/unknown (n = 8): Poor quality product administered, and Product administration error (2 each).
- Following dose other/unknown
  - Formulation 3 mcg (Maroon cap) (n = 102): Poor quality product administered (35), Product administration error (33), Incorrect dose administered, Product preparation error (7 each), Overdose (6), Pyrexia, Wrong product administered (3 each), and Expired product administered (2).
  - Formulation other/unknown (n = 90): Overdose, Product administered to patient of inappropriate age (18 each), Poor quality product administered, Product administration error (11 each), Wrong product administered (6), Asthma, Cough, Expired product administered, Pyrexia, and Rhinorrhoea (2 each).

  Please refer to Table 26 and Table 27 in Section 9.2 *Medication Errors* for the categorisation of the PTs indicative of medication errors reported in this population.

- Event seriousness: serious (109), non-serious (749).
- Time to event onset: n = 587, range: from <24 hours to 60 days, median: 10 days.
  - <24 hours: 473 events;
  - 1 day: 26 events;
  - 2-7 days: 56 events;
  - 8-14 days: 12 events;
  - 15-60 days: 20 events.

- Duration of relevant events: n = 46, range: from <24 hours to 60 days, median: 5.5 days.
  - <24 hours: 5 events;
  - 1 day: 8 events;
  - 2-7 days: 26 events;
  - 8-14 days: 5 events;
  - 15-60 days: 2 events.

- Event outcome: fatal (9), resolved/resolving (128), not resolved (49), unknown (672).

Fatal cases (3)

- Age: 1 year, 2 years, and 4 years (1 each).
- MC cases (2), NMC cases (1).
- Gender: males (3).
- Country/region of incidence: Japan, Taiwan, Province of China, and US (1 each).
- Fatal PTs (9): Arrhythmia, Cardio-respiratory arrest, Cyanosis, Death, Loss of consciousness, Muscle rigidity, Seizure, Sinus tachycardia, and Supraventricular tachycardia (1 each).
- Medical history (n = 15): Blood calcium abnormal, Blood phosphorus abnormal, Cardiac failure, Cardiac hypertrophy, Congenital nephrotic syndrome, Gastrooesophageal reflux disease, Gene mutation, Hypertension, Hypertensive heart disease, Hyperuricaemia, Peritoneal dialysis, Respiratory disorder, Respiratory muscle weakness, Therapeutic aspiration, and Upper respiratory tract inflammation (1 each).

The 3 fatal cases are summarised below:

The 1st case (NMC) reported only PT Death as the fatal AE. Neither cause of death nor information on autopsy was provided in this case involving a 2-year-old male subject "who died after being vaccinated (timing of vaccination and date of death was not reported.)". Limited information was provided, precluding any meaningful assessment.

The 2nd case (MC) originated from Japanese Pharmaceuticals and Medical Devices Agency (PMDA), in which the 1-year-old male subject received dose 3 (maroon cap) for COVID-19 immunisation on 16 February 2023. On the next day, he experienced minor pyrexia and productive cough. On 18 February 2023, the subject developed cardio-respiratory arrest and his body temperature decreased and died on the same day, although treatments included Endotracheal intubation, gastric intubation, intraosseous needle placement, adrenaline intravenous injection, and Meylon (sodium bicarbonate) intravenous injection. In this case, the subject had severe underlying diseases (such as blood calcium abnormal, blood phosphorus abnormal, cardiac failure, cardiac hypertrophy, congenital nephrotic syndrome, gastrooesophageal reflux disease, gene mutation [Pierson syndrome], hypertension, hypertensive heart disease, hyperuricaemia, peritoneal dialysis, respiratory disorder, respiratory muscle weakness, therapeutic aspiration, and upper respiratory tract

inflammation), making it difficult to determine the causal relationship between the vaccination and the fatal event (PT coded to Cardio-respiratory arrest).

The 3rd case (MC) originated from Taiwan Center for Disease Control, which involved a 4-year-old male subject, who experienced events with PTs coded to Arrhythmia, Loss of consciousness, Seizure, Sinus tachycardia, Supraventricular tachycardia, Muscle rigidity, and Cyanosis and died 11 days after the second dose of BNT162b2. The subject's medical history and concomitant medications were not reported. No autopsy was performed. Causality assessment from the reporter and BioNTech was "possible".

16.3.5.1.2. Paediatric Subjects ≥5 Years and ≤ 11 Years of Age

Clinical Trial Data

- Number of cases: 7 (original [4] and blinded therapy [3], originated from clinical studies C4591007, C4591007-OPENLABEL, and C4591024; 8.5% of 82 cases, the total CT dataset), compared to 34 cases (11.0%) retrieved in the PSUR #4.
- Country/region of incidence: Brazil (3), Finland, Poland, Spain, and US (1 each).
- Subjects' gender: female (3), male (4).
- Subjects' age in years: n = 7, range: 5 – 7, mean: 5.4, median: 5.0.
- Medical history (n = 4); the reported medical conditions included Asthma, Food allergy, Mechanical ventilation, Tonsillar hypertrophy, Dermatomyositis, Dust allergy, Jaundice, Laryngitis, Premature baby, Pulmonary haemorrhage, Pulmonary hypertension, Pulmonary valve stenosis, Respiratory distress, and Sepsis neonatal (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: none.
- Reported PTs (7): Pneumonia (3), Arthropod bite, Asthma, Eyelid injury, and Synovitis (1 each). All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset: n = 7, range: 57 days to 350 days, median: 222 days.
  - 57-350 days: 7 events.
- Duration of relevant events: n = 7, range: 2 to 35 days, median: 9 days.
  - 2-7 days: 3 events;
  - 8-35 days: 4 events.
- Event outcome: resolved (6) and resolved with sequelae (1).

Post-Authorisation Data

- Number of cases: 1225 (original [949], bivalent Omi BA.4/BA.5 [384]; 1.7% of 74,102 cases, the total PM dataset), compared to 4983 cases (1.8%) retrieved in the PSUR #4.
- MC cases (1063), NMC cases (162).

- Country/region of incidence (≥2%): US (509), Japan (266), Brazil (127), and Philippines (95).
- Subjects' gender: female (425), male (493) and unknown (307).
- Subjects' age in years: n = 968, range: 5-11, mean: 8.1, median: 8.0.
- Medical history (n = 110); the most frequently (≥5) reported medical conditions included Asthma (15), Rhinitis allergic (9), Food allergy (7), Attention deficit hyperactivity disorder, Hypersensitivity (6 each), Immunodeficiency, and Seasonal allergy (5 each).
- COVID-19 Medical history (n = 22): COVID-19 (19), and Suspected COVID-19 (3).
- Co-suspect medications (n = 47); the most frequently (≥5) reported included influenza vaccine, sodium chloride (9 each), influenza vaccine inact split 3V (6), and HPV vaccine (5).
- Number of events: 2693.
- Event seriousness: serious (547), non-serious (2146).
- Most frequently reported PTs (≥3% of cases): Poor quality product administered (318), Product administration error (189), Expired product administered (183), Overdose (150), Pyrexia (136), Wrong product administered (120), Product colour issue (99), Product administered to patient of inappropriate age (92), Product preparation error (82), Headache (60), Vaccination site swelling (59), Vomiting (55), Inappropriate schedule of product administration (48), and Cough (39).
- Time to event onset: n = 1724, range: from <24 hours to 622 days, median: 193 days.
  - <24 hours: 1096 events;
  - 1 day: 169 events;
  - 2-7 days: 122 events;
  - 8-14 days: 44 events;
  - 15-40 days: 29 events;
  - 41-100 days: 72 events;
  - 101-180 days: 38 events;
  - 181-240 days: 80 events;
  - 241-360 days: 67 events;
  - 361-622 days: 7 events.

- Duration of relevant events: n = 173, range: from <24 hours to 40 days, median: 9 days.
  - <24 hours: 36 events;
  - 1 day: 28 events;
  - 2-7 days: 72 events;
  - 8-14 days: 29 events;
  - 15-40 days: 8 events.

- Relevant event outcome: resolved/resolving (603), resolved with sequelae (12), not resolved (207), fatal (3), unknown (1868).

Fatal cases (2)

- Age: 9 years, and unknown (1 each).
- MC cases (1), NMC cases (1).
- Gender: females (2).
- Country/region of incidence: Philippines, and Taiwan, Province of China (1 each).
- Fatal PTs (3): Abdominal pain upper, Death, Pyrexia (1 each).
- Medical history: not reported in 2 fatal cases.

The 2 fatal cases are summarised below:

The 1st NMC case recorded the subject's (unspecified age) death (PT coded to Death) as the only event, in which cause of death was unknown. This case provided limited information pertaining to dose and date of immunisation, medical history, concomitant medications, and date of the fatal outcome, which precluded a meaningful clinical assessment.

In the 2nd case, a 9-year-old female subject experienced pyrexia and upper abdominal pain 15 days after COVID-19 immunisation (unknown dose number). The subject's medical history and concomitant medications were not reported, and she died on an unknown date with the cause of death coded to the PTs Abdominal pain upper and Pyrexia.

16.3.5.1.3. Paediatric Subjects ≥12 to ≤ 17 Years of Age

Clinical Trial Data

- Number of cases: 5 (blinded therapy [5], originated from clinical studies C4591007, and C4591044; 6.1% of 82 cases, the total CT dataset), compared to 11 cases (3.6%) retrieved in the PSUR #4.
- Country/region of incidence: Spain, US (2 each), Mexico (1).
- Subjects' gender: female (3), male (2).
- Subjects' age in years: n = 5, range: 12 – 14, mean: 13.2, median: 14.0.
- Medical history (n = 5); the most frequently (≥2) reported medical conditions included Asthma, Anxiety, Depression, Intentional self-injury, Suicidal ideation, and Suicide attempt (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect medications: none.
- Reported PTs (6): Abortion spontaneous, Alcohol poisoning, Bronchitis, Condition aggravated, Myalgia, and Suicidal ideation (1 each). All events were assessed as unrelated to blinded therapy.

- Time to event onset: n = 6, range: from 154 days to 308 days, median: 186 days.
  - 154-308 days: 6 events.
- Duration of relevant events: n = 4, range: from 1 day to 8 days, median: 7 days.
  - 1 day: 1 event;
  - 2-8 days: 3 events.
- Event outcome: resolved (4), not resolved (2).

Post-Authorisation Data

- Number of cases: 1287 (original [1062], bivalent Omi BA.1 [55], bivalent Omi BA.4/BA.5 [229], BNT162b2 Multivalent NOS [3]; 1.7% of 74,102 cases, the total PM dataset), compared to 7064 cases (2.5%) retrieved in the PSUR #4.
- MC cases (824), NMC cases (463).
- Country/region of incidence (>2%): US (244), Germany (160), Japan (142), France (101), Sweden (85), Philippines, UK (66 each), and Spain (64).
- Subjects' gender: female (683), male (555) and unknown (49).
- Subjects' age in years: n = 1260, range: 12 - 17, mean: 14.6, median: 15.0.
- Medical history (n = 289); the most frequently (≥10) reported medical conditions included Asthma (43), Seasonal allergy (29), Food allergy, Hypersensitivity (16 each), Allergy to animal (13), Mite allergy (11), Attention deficit hyperactivity disorder, and Rhinitis allergic (10 each).
- COVID-19 Medical history (n = 71): COVID-19 (62), Suspected COVID-19 (5), Coronavirus infection (4), and Post-acute COVID-19 syndrome (1).
- Co-suspect medications (n = 51); the most frequently (≥3) reported included COVID-19 vaccine (12), influenza vaccine (8), adalimumab, elasomeran, HPV vaccine (4 each), influenza vaccine inact split 4V (3).
- Number of events: 3857.
- Relevant event seriousness: serious (1653), non-serious (2207).
- Most frequently reported PTs (≥3%): Headache (182), Pyrexia (174), Poor quality product administered (124), Product administration error (115), Fatigue (102), Inappropriate schedule of product administration (77), Wrong product administered (76), Dizziness, Malaise (74 each), Nausea (70), Chest pain (60), Vomiting (59), COVID-19 (57), Myocarditis (55), Asthenia (51), Dyspnoea (45), Vaccination site pain (43), Abdominal pain, and Lymphadenopathy (38 each).

- Time to event onset: n = 2442, range: from <24 hours to 643 days, median: 148 day.
  - <24 hours: 1001 events;
  - 1 day: 413 events;
  - 2-7 days: 324 events;
  - 8-14 days: 131 events;
  - 15-40 days: 176 events;
  - 41-100 days: 130 events;
  - 101-180 days: 78 events;
  - 181-240 days: 36 events;
  - 241-360 days: 93 events;
  - 361-643 days: 60 events.

- Duration of relevant events: n = 422, range: <24 hours to 613 days, median: 25 days.
  - <24 hours: 87 events;
  - 1 day: 96 events;
  - 2-7 days: 151 events;
  - 8-14 days: 34 events;
  - 15-40 days: 25 events;
  - 41-100 days: 14 events;
  - 101-613 days: 15 events.

- Relevant event outcome[65]: fatal (42), resolved/resolving (1224), not resolved (1038), resolved with sequelae (73), unknown (1481).

Fatal cases (13)

- Age: 14 years, 15 years (3 each), 16 years, 17 years, unknown (2 each), and 12 years (1).
- MC cases (9), NMC cases (4).
- Gender: females, males (5 each), and unknown (3).
- Country/region of incidence (> 2): Philippines (4), and Germany (3).
- Fatal PTs (42): the most frequently (≥ 2) reported AEs included Cardiac arrest (4), Myocarditis, Pyrexia, Dyspnoea, Malaise, Pericarditis, Poisoning, and Vomiting (2 each).
- Medical history (n = 14): Becker's muscular dystrophy, Cerebral palsy, Cochlea implant, Hypoacusis, Intellectual disability, Language disorder, Mental disability, Myeloid leukaemia, Neuromyopathy, Orthostatic intolerance, Physical disability, Quadriparesis, Severe myoclonic epilepsy of infancy, and Wheelchair user (1 each).

The 13 fatal cases are summarised below:

In 4 MC cases, limited information was provided, precluding any meaningful assessment. The subjects' medical history/underlying conditions, concomitant medications, or date of death were not reported. Neither lab data nor information on autopsy was provided in these 4 cases.

In 2 NMC cases reported by a lawyer, both adolescents (unspecified ages) were reported to have sudden cardiac arrest within a week of BNT162b2 vaccination. Although it was not reported if autopsies were performed, the reporter stated that "pathologists recognized signs of poisoning and concluded that poisoning by the vaccine-induced spike protein was more likely to lead to death." Information on subject's medical history, concomitant medications and date of death was not provided.

In 1 MC case, a 17-year-old male subject received expired BNT162b2 for COVID-19 immunisation (PT coded to Expired product administered). The subject experienced fatal events (acute myocardial infarction, headache, pain, and vomiting) about 2 months after vaccination. The subject's medical history, concomitant medications, date of death and information on autopsy were not reported.

In 4 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

- One (1) MC case involved a 14-year-old male subject, who received BNT162b2 dose 1, 0.3 ml single for COVID-19 immunisation and neuromuscular disease (fatal PT coded to Off label use). Other fatal PTs were coded to Circulatory collapse, Pyrexia, Dyspnoea, Hypotonia, Hyperpyrexia, Chills, Pericarditis, and Myocarditis. The subject's death was possibly due to his severe underlying conditions, coded as Becker's muscular dystrophy, cerebral palsy, cochlea implant, COVID-19, hypoacusis, intellectual disability, language disorder, mental disability, neuromyopathy, physical disability, quadriparesis, and wheelchair user.
- One (1) NMC case involved a 15-year-old female subject who had underlying myeloid leukaemia, which could attribute to her fatal events (myocarditis, disease recurrence, and myeloid leukaemia).
- In 1 MC case, a 14-year-old female subject had severe underlying condition of Dravet syndrome and COVID-19 and was medicated with multiple antiepileptic drugs, which were confounding factors for the causality assessment between BNT162b2 vaccination and her fatal events (vaccination failure, COVID-19, hyperthermia, shock, COVID-19 pneumonia, and cardiac arrest).
- In 1 MC case, although the medical history was not reported, the 17-year-old female subject received multiple concomitant medications (such as amitriptyline, azathioprine, buprenorphine, colecalciferol, etanercept, paracetamol, piroxicam, prednisolone, and zoledronic acid), which were confounding factors for determination of the causal relationship between BNT162b2 vaccination and the fatal events (arrhythmogenic right ventricular dysplasia, Escherichia sepsis, and vomiting).

In the remaining 2 cases, potential explanations other than vaccination for death are not evident in the reports however in the first case there is very limited information provided:

- In 1 NMC case, a 12-year-old female subject died of myocardial infarction 5 days after receiving BNT162b2 as dose 1, single for COVID-19 immunisation. The subject's medical history, concomitant medications, and information on autopsy were not reported.
- In 1 MC literature case[73] reporting a 14-year-old female subject with following fatal PTs Myopericarditis, Cardiac failure, Arrhythmia, Arrhythmia supraventricular, Myocarditis, Pericarditis, and Sudden death, no confounding factors have been identified. Autopsy result showed inflammatory findings of pericardial tissue.

Analysis of confounders and risk factors

Among the 2961 cases involving paediatric subjects, 763 cases included one or more confounders that prevented a clear causality assessment: co-suspect and/or concomitant drugs (355 cases) and/or underlying medical history (546 cases).

Literature

During the reporting period, a literature article reporting important safety information about the use of bivalent vaccines and children aged 5-11 years was identified. Please refer to Section 11 *Literature* for further details.

Conclusion

Upon review, the most frequently reported AEs indicative of vaccination errors had a higher reporting proportion in paediatric groups < 5 years and ≥5 Years and ≤ 11 Years of Ages compared to the ≥ 12 years of age; while the most frequent AEs indicative of reactogenicity type had a higher reporting proportion in paediatric group ≥ 12 years of age compared to groups of < 5 years and ≥5 Years and ≤ 11 Years of Ages. Of the frequently reported AEs (≥2%) in the paediatric dataset, Pyrexia had a higher reporting proportion compared to the non-paediatric dataset (4.7% vs 2.6%). 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[74] 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 CDS.

[73] Nishida H. A case of fatal multi-organ inflammation following COVID-19 vaccination. *Legal Medicine* 2023, 63: 102244(1-4).

[74] For the CT cases, the analysis was focused on AEs assessed as related to BNT162b2 or blinded therapy.

16.3.5.2. Use in Pregnant/Lactating Women[75,76]

Clinical Trial Data

- Number of pregnancy cases: 2 (2.4% of the total 82 cases from the CT dataset). Cases originated from clinical studies BNT162-17 and C4591007 (1 each) and study treatment was reported as BNT162b2 B.1.1.7, BNT162b2 B.1.617.2 (1) and blinded therapy (1).
- Country/region of incidence: [redacted] and [redacted] (1 each).
- Two (2) serious retrospective maternal cases reported event coded to the PT Abortion spontaneous (1 each), which occurred in the vaccinated pregnant females. In these 2 cases only the event of abortion spontaneous was reported and the trimester of exposure was unknown. Of these 2 cases, in 1 case the subject had a medical history of hypertension and was on concomitant medication ethinylestradiol, levonorgestrel which might have contributed to the reported event. In the remaining case there was limited information regarding the obstetric history which precluded meaningful causality assessment.

Post-Authorisation Data

- Number of pregnancy cases: 464 (original [397], bivalent Omi BA.1 [34], bivalent Omi BA.4/BA.5 [33]; 0.6% of 74,102 cases, the total PM dataset), compared to 988 cases (0.3%) retrieved in the PSUR #4. These 464 cases represent 422 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 41 pregnancies).
- Country/region of incidence (≥20): Sweden (152), UK (76), Germany (53), US (29), France (26), Norway (20).
- Of the 407 mother cases, 62 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 (47), Maternal exposure timing unspecified (13), Maternal exposure before pregnancy (2).
- There were 345 mother cases of which 169 were serious and 176 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females.

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[75] Exposure *in utero* cases are included.

[76] 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.

The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (204), Maternal exposure timing unspecified (21), Maternal exposure before pregnancy (10). Additional pregnancy related events reported in these cases (≥10) were coded to the PTs Abortion spontaneous (69), Heavy menstrual bleeding, Stillbirth (10 each). Other frequently reported (>20) clinical events coded to the PTs Vaccination site pain (67), Headache (53), Fatigue (48), Malaise (37). Pyrexia (31), Nausea (30), Vomiting (27), Chills (26), Myalgia (24), Arthralgia (22), COVID-19, Dizziness (21 each).

- Fifty-seven (57) baby/foetal cases, 51 serious and 6 non-serious. Cases are classified according to pregnancy outcome.

  - Pregnancy outcome: Live birth with congenital anomaly: 12 of these cases reported 30 congenital anomalies that coded to the PTs Cerebral palsy (3), Myoclonus, Hypospadias, Foot deformity (2 each), Abdominal hernia, Acrodermatitis enteropathica, Cerebral calcification, Congenital aortic stenosis, Congenital cystic kidney disease, Congenital hand malformation, Congenital hydronephrosis, Congenital musculoskeletal disorder of spine, Congenital ureterocele, Dextrocardia, Heart disease congenital, Intestinal obstruction, Kidney duplex, Kidney malformation, Multiple fractures, Nervous system disorder, Oesophageal atresia, Osteoporosis, Pulmonary aplasia, Single umbilical artery, VACTERL syndrome (1 each). Of these 12 cases, information regarding trimester of exposure was available in 7 cases. Of these 7 cases, in 3 cases foetus was exposed during 1st trimester, in 3 cases foetus was exposed during 2nd trimester and in 1 case foetus was exposed during 3rd trimester. Of these 12 cases, in 1 case mother of the baby had a medical history of tobacco use which might have contributed to the reported event i.e., hypospadias and cerebral calcification. In the remaining 11 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

  - Pregnancy outcome: Spontaneous abortion: 14 cases reported spontaneous abortion. Of these 14 cases, information regarding trimester of exposure was provided in 2 cases. Of these 2 cases, in 1 case foetus was exposed during 1st trimester, in 1 case foetus was exposed during 2nd trimester. The clinical events in these 14 cases other than exposure related events were coded to PTs Congenital anomaly (5), Foetal growth restriction (4), Foetal cardiac disorder, Foetal chromosome abnormality (2 each), Brain malformation, Cerebellar hypoplasia, Double outlet right ventricle, Foetal cardiac arrest, Foetal death, Foetal disorder, Foetal malformation, Skeletal dysplasia (1 each). In these 14 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.

  - Pregnancy outcome: Elective termination: 3 cases reported elective termination of pregnancy due to foetal defects. In all these 3 cases, foetus was exposed during 1st trimester. The events reported in these 3 cases other than exposure related events were coded to PTs Abortion induced, Congenital central nervous system anomaly, Exomphalos, Foetal cystic hygroma, Foetal death, Foetal heart rate abnormal

(1 each). In these 3 cases, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Stillbirth: 1 case reported foetal death/ neonatal death. This case reported stillbirth with foetal defects. In this case foetus was exposed during 1st trimester. The events reported in this case other than exposure related events were coded to PTs Bronchopulmonary dysplasia, Congenital anomaly, Ecchymosis, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Joint contracture, Muscle contracture, Neonatal asphyxia, Polyhydramnios, Posthaemorrhagic hydrocephalus, Premature baby, Premature baby death, Umbilical cord short (1 each). In this case, there was limited information regarding obstetric history or co-suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Live birth without congenital anomaly: 27 cases reported live birth babies without congenital anomaly. Of these 27 cases, information regarding trimester of exposure was available in 7 cases. Of these 7 cases, in 1 case, foetus was exposed during 1st trimester, in 1 case, foetus was exposed during 2nd trimester, and in 5 cases, foetus was exposed during 3rd trimester. The frequently reported events (≥2) in these 27 cases other than exposure related events were coded to PTs Premature baby (6), Foetal heart rate deceleration abnormality, Infantile apnoea, Jaundice neonatal (2 each). In these remaining 27 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 464 cases, 356 cases provided pregnancy outcomes which are provided in Table 55 below. Pregnancy outcome was pending or not provided in the remaining 108 cases.

Table 55. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a,b]

Pregnancy outcome	Prospective cases 210 (45.3% of pregnancy cases)				Retrospective cases 146 (31.5% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1st trimester	After 1st trimester	During all pregnancy	Unknown	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	1	0	0	0	0
Spontaneous abortion	2	0	0	4	12	1	0	39
Elective termination (foetal defects)	1	0	0	0	5	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	0	1	0	0
Stillbirth with foetal defects	0	0	0	0	2	0	0	1

Table 55. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a,b]

Pregnancy outcome	Prospective cases 210 (45.3% of pregnancy cases)				Retrospective cases 146 (31.5% of pregnancy cases)			
	Timing of exposure in pregnancy				Timing of exposure in pregnancy			
	1st trimester	After 1st trimester	During all pregnancy	Unknown	1st trimester	After 1st trimester	During all pregnancy	Unknown
Stillbirth without foetal defects	0	1	0	1	1	4	0	5
Live birth with congenital anomaly	0	0	0	3	5	4	0	3
Live birth without congenital anomaly	45	92	0	60	4	18	0	41
Total	***48***	***93***	***0***	***69***	***29***	***28***	***0***	***89***

a. 19 December 2022 through 18 June 2023.
b. None of the prospective or retrospective cases reported receipt of COVID-19 vaccine doses before conception.

Lactation cases

- Number of lactation cases: 119 (original [94], bivalent Omi BA.1 [19], bivalent Omi BA. 4/BA.5 [6]; 0.2% of 74,102 cases, the total PM dataset), compared to 302 cases (0.1%) retrieved in the PSUR #4.

  – Breast feeding baby cases: 88, of which:

  – Sixty-eight (68) cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events.

  – Twenty (20) cases, 6 serious and 14 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk); the frequently reported clinical events (≥2) were coded to the PTs Pyrexia (6), Infantile vomiting (4), Insomnia, Restlessness, Pain, Infant irritability (3 each), Fatigue, Decreased appetite, Diarrhoea (2 each).

  Breast feeding mother cases: 31, of which:

  – Ten (10) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.

  – Twenty-one (21) cases, 6 serious and 15 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>2) were coded to the PTs Pyrexia (6), Nausea, Myalgia (5 each), Pain in extremity (4), Paraesthesia, Chills, Fatigue, Vaccination site pain, Lymphadenopathy, Malaise (2 each).

Literature

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

Conclusion

There were no safety signals regarding use in pregnant/lactating women that emerged from the review of these cases or the medical literature.

16.4. Characterisation of Risks

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

16.4.1. Characterisation of Important Identified and Potential Risks

A typical medicinal product has multiple risks associated with it and individual risks vary in terms of severity, effect on individual patients, and public health impact.

What constitutes an important risk depends upon several factors including the impact on the individual subject, the seriousness of the risk and its severity, and the impact on public health. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered. Risks may be related to nonclinical or clinical safety or quality issues. The intended purpose and impact of the product e.g., whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease must also be considered when characterising risks.

The following were considered in characterising risk(s) of this product:

- frequency of risk;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life or could lead to serious consequences if left untreated);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (ie, predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

Internal and external datasets were used to populate the table below with available data. In addition to literature searches for the drug itself and its class, external data sources were consulted.

Please see Appendix 8 for the characterisation of the important identified and important potential risks[77] of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU-RMP version 10.0 approved on 22 June 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 June 2023 is provided in Section 16.4.1.1 and Section 16.4.1.2.

16.4.1.1. Cumulative Characterisation of Important Identified Risks

Table 56. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
Myocarditis and Pericarditis	Cumulatively, there were 7 cases of Myocarditis and Pericarditis: 4 cases reported myocarditis and 3 cases reported pericarditis (none of these 7 cases reported developing both the events- myocarditis and pericarditis). *Myocarditis* • No. of cases: 4 [original]. • No. of SAEs: 4. • Relevant PTs: Myocarditis, Myopericarditis (2 each). • Related SAEs: Myopericarditis (2), Myocarditis (1). *Pericarditis* • No. of cases: 3 [original]. • No. of SAEs: 3. • Relevant PTs: Pericarditis (3). • Related SAEs: none.	Cumulatively, there were 23,250 cases of Myocarditis and Pericarditis: 14,346 cases reported myocarditis and 11,114 cases reported pericarditis (in 2210 of these 23,250 cases, the subjects developed both myocarditis and pericarditis). *Myocarditis* • No. of cases: 14,346 (original [14,223], bivalent Omi BA.1 [66], bivalent Omi BA.4/BA.5 [67]). • Relevant PTs: Myocarditis (12,066), Myopericarditis (2196), Carditis (188), Eosinophilic myocarditis (18), Giant cell myocarditis, Hypersensitivity myocarditis (7 each), Immune-mediated myocarditis (6), Autoimmune myocarditis, Chronic myocarditis (4 each). • Frequently co-reported PTs (≥2%): Chest pain (4769), Dyspnoea (3108), Fatigue (2473), Palpitations (2286), Pericarditis (2206), Pyrexia (2114), Tachycardia (1568), Chest discomfort (1518), Headache (1237), Off label use (919), Dizziness (913),

[77] None.

Table 56. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
	Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.	Immunisation (898), Troponin increased (883), Interchange of vaccine products (821), Malaise (696), Inappropriate schedule of product administration (675), Asthenia (666), Arrhythmia (651), Nausea (584), Myalgia (559), Pain (551), Pain in extremity (535), Chills (483), Pericardial effusion (470), Angina pectoris (450), Syncope (433), Arthralgia (410), Vomiting (369), Heart rate increased (364), Cough (332), Paraesthesia (311), Cardiac failure (310), Dyspnoea exertional, Hyperhidrosis (302 each), Diarrhoea (288), Influenza like illness (261), C-reactive protein increased (257), Hypertension (245), COVID-19 (238), Lymphadenopathy (230), Vaccination site pain (229), Back pain (225), Hypoaesthesia (224). • Subjects' gender: female (4903), male (8931) and unknown (512). • Subjects' age in years (n = 12,930), range: 5 – 102 years, mean: 35.6 years, median: 32.0 years. • Age group: Paediatric (2087), Adults (10,173), Elderly (1086) and Unknown (1000). • Case source: Spontaneous (13,819), Literature (464), Clinical study (31), Other Solicited (32). • Event seriousness: serious (14,496) Event outcome[65]: fatal (271), resolved/resolving (5533), resolved with sequelae (417), not resolved (4109), unknown (4179). <u>*Pericarditis*</u> • No. of cases: 11,114 (original [11,037], bivalent Omi BA.1 [43], bivalent Omi BA.4/BA.5 [41]). • Relevant PTs: Pericarditis (11,030), Pleuropericarditis (83), Pericarditis constrictive (23), Autoimmune pericarditis, Pericarditis adhesive (1 each). • Frequently co-reported PTs (≥2%): Chest pain (4641), Dyspnoea (2854), Myocarditis (2058), Fatigue (1990), Palpitations (1827), Pyrexia (1284), Tachycardia (1225), Chest discomfort (1180), Pericardial effusion (910), Headache (870), Immunisation (684), Dizziness (652), Off label use (646),

Table 56. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		Interchange of vaccine products (585), Malaise (512), Myalgia, Nausea (449 each), Pain (448), Asthenia (430), Arthralgia, Pain in extremity (419 each), Inappropriate schedule of product administration (386), Paraesthesia (316), Syncope (299), Cough (275), Chills (271), Angina pectoris (263), Heart rate increased (260), Electrocardiogram abnormal (251), Lethargy (225), Back pain (216), Arrhythmia (213), Hyperhidrosis (207), Dyspnoea exertional (206), Pleural effusion (203), Lymphadenopathy (202), Vomiting (199), Influenza like illness (198), C-reactive protein increased (190), Vaccination site pain (186), Myopericarditis (183), Hypoaesthesia (182), Diarrhoea (179), Hypertension (175), Troponin increased (173). • Subjects' gender: female (5238), male (5627) and unknown (249). • Subjects' age in years (n = 10260), range: 2 – 98 years, mean: 39.9 years, median: 37.0 years. • Age group: Paediatric (737), Adults (8522), Elderly (1064), and Unknown (791). • Case source: Spontaneous (10,941), Literature (111), Clinical study (46), Other solicited sources (16). • Event seriousness[78]: serious (11,138). • Event outcome[65]: fatal (44), resolved/resolving (4100), resolved with sequelae (201), not resolved (3765), unknown (3039). Based on the cumulative PM data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.

16.4.1.2. Cumulative Characterisation of Important Potential Risks

None.

[78] 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.

16.4.2. Description of Missing Information

Table 57 describes missing information associated with the use of BNT162b2.

Table 57. Description of Missing Information

Topic	Description	
Use in pregnancy and while breast feeding	The safety profile of the vaccine in pregnant and/or breastfeeding women was not studied in the pivotal clinical trial and the maternal clinical trial was terminated early due to participant recruitment difficulties. Many pregnant women have chosen to be vaccinated despite the lack of clinical trial safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.2 *Use in Pregnant/Lactating Women*.	
Use in immunocompromised patients[79]	The vaccine is being studied in an ongoing clinical trial of individuals with immunocompromised conditions.	
	Clinical Study Data	**Post-Marketing Data**
	• No. of cases: 3 (BNT162b2; 3.7% of 82 cases, the total CT dataset) compared to 32 cases (10.4%) retrieved in the PSUR #4. • Subjects' gender: female (3). • Subjects' age in years: n = 3, range: 55 – 85 years, mean: 73.0, median: 79.0. • Reported clinical PTs: Breast cancer, COVID-19, Deep vein thrombosis, Pulmonary embolism, Syncope (1 each). • Related SAEs: none.	• No. of cases: 2628 (original [1743], bivalent Omi BA.1 [430], bivalent Omi BA.4/BA.5 [455]; 2.5% of 74,102 cases, the total PM dataset) compared to 4879 cases (1.7%) retrieved in the PSUR #4. • Subjects' gender: female (1708), male (826) and unknown (94). • Subjects' age in years: n = 2428, range: 6 months – 104 years, mean: 60.5, median: 62.0. • Most frequently reported clinical PTs (≥3%): COVID-19 (458), Fatigue (314), Headache (251), Pyrexia (223),

[79] 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 57. Description of Missing Information

Topic	Description	
Use in immunocompromised patients *Cont'd*	• Reported event outcome: resolved/resolving (4), not resolved (1). • Relevant medical history: Malignant melanoma (2), Radiotherapy (1).	Pain in extremity (159), Arthralgia (153), Dyspnoea (152), Dizziness (143), Nausea (137), Malaise (124), Vaccination failure (120), Myalgia (119), Asthenia (118), Pain (114), Chills (113), Lymphadenopathy (106), Chest pain (99), Palpitations (97), Vaccination site pain (92), Vomiting (89), Diarrhoea (86). • Event seriousness: serious (6560), non-serious (4019). • Event outcome: fatal (242), resolved/resolving (2548), resolved with sequelae (429), not resolved (2681), unknown (4695). • Relevant medical history (>100): Immunodeficiency (506), Breast cancer (279), Neoplasm malignant (187), Thyroidectomy (135), Prostate cancer (127), Chemotherapy (116), Radiotherapy (105), Hysterectomy (104).

Table 57. Description of Missing Information

<table>
<tr><th>Topic</th><th colspan="2">Description</th></tr>
<tr><td rowspan="3">Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)[80]</td><td colspan="2">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.</td></tr>
<tr><td>Clinical Study Data</td><td>Post-Marketing Data</td></tr>
<tr><td>• No. of cases: 19 (original [3], BNT162b2 B.1.1.7, BNT162b2 B.1.617.2 [5], bivalent Omi BA.4/BA.5 [3], blinded therapy [8]; 23.2% of 82 cases, the total CT dataset) compared to 80 cases (25.9%) retrieved in the PSUR #4.
• Subjects' gender: female (11) and male (8).
• Subjects' age in years: n = 19, range: 2 – 79, mean: 35.7, median: 44.0.
• Relevant PTs most frequently reported (>1): Asthma and Hypoglycaemia (2 each).
• Related SAEs: 0.
• Relevant event outcome: fatal (1), not resolved (3), resolved with sequelae (2), resolved/resolving (20).</td><td>• No. of cases: 5738 (original [4389], bivalent Omi BA.1 [570], bivalent Omi BA.4/BA.5 [1036]; 7.7% of 74,102 cases, the total PM dataset) compared to 11,803 cases (4.2%) retrieved in the PSUR #4.
• Subjects' gender: female (3654), male (1979) and unknown (105).
• Subjects' age in years: n = 5531, range: 1 - 99, mean: 58.1, median: 60.0.
• Relevant PTs most frequently reported (≥2%): COVID-19 (879), Drug ineffective (743), Fatigue (709), Interchange of vaccine products (600), Headache (571), Pyrexia (451), Dyspnoea (394), Pain in extremity (383), Arthralgia (377), Inappropriate schedule of product administration (334), Myalgia (322), Dizziness (314), Pain (295), Malaise (284), Asthenia (267), Vaccination site pain (261), Nausea (256), Vaccination failure (235), Chills (228), Off label use (189), Chest pain, Diarrhoea, Palpitations (171 each), Vomiting (160), Condition aggravated (154), Lymphadenopathy (149), Asthma (144), Cough (140), Paraesthesia (132), Peripheral swelling (114), and Pruritus (112).
• Relevant event seriousness: serious (11,767), non-serious (11,176).</td></tr>
</table>

[80] 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 57. Description of Missing Information

Topic	Description	
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) *Cont'd*		• Relevant event outcome: fatal (702), resolved/resolving (5906), resolved with sequelae (781), not resolved (6424), unknown (9151).
Use in patients with autoimmune or inflammatory disorders[81]	There is limited clinical trial information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.	
	Clinical Study Data	**Post-Marketing Data**
	• Number of cases: 3 (original [2], blinded therapy [1]; 3.7% of 82 cases in the total CT dataset), compared to 46 cases (14.9%) retrieved in the PSUR #4. • Number of events: 3. • Reported PTs: Arthropod bite, Post procedural infection, Syncope (1 each). • None of the 3 events were assessed as related to BNT162b2 or blinded therapy by the investigator and Sponsor. • Event outcome: resolved (3).	• Number of cases: 5856 (original [4500], bivalent Omi BA.1 [627], bivalent Omi BA.4/BA.5 [955], BNT162b2 Multivalent NOS [20];(7.9% of 74,102 cases, the total PM dataset), compared to 12,868 cases (4.5%) retrieved in the PSUR #4. • MC cases (2161), NMC cases (3695). • Number of events: 23,462. • Of the 5856 cases, the most frequently PTs (≥300) reported included: COVID-19 (882), Drug ineffective (777), Fatigue (733), Interchange of vaccine products (576), Headache (568), Pyrexia (454), Arthralgia (430), Pain in extremity (409), Inappropriate schedule of product administration (383), Myalgia (356), Dizziness (347), Pain (304). • Event seriousness: serious (12,177), non-serious (11,297). • Event outcome: fatal (341), resolved/resolving (5714), resolved with sequelae (837), not resolved (7099), unknown (9501). • In 95 cases (reporting 341 relevant events with a fatal outcome), the reported causes of death (≥ 5 occurrences) were coded to the PTs: Interchange of vaccine products (12), Cardiac arrest, Death (9 each),

[81] 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 57. Description of Missing Information

Topic	Description	
Use in patients with autoimmune or inflammatory disorders *Cont'd*		Dyspnoea, Myocardial infarction (7 each), Pyrexia (6), Cardio-respiratory arrest, Cerebral infarction, Cerebrovascular accident, Fatigue, Multiple organ dysfunction syndrome, Pneumonia (5 each). • The most frequently reported events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.
	Exacerbation or flare-up No relevant cases were retrieved.	***Exacerbation or Flare-up*** Of the 330 cases that reported PTs indicative of exacerbation or flare, 130 cases were determined to be non-contributory and were not included in the discussion for the following reason: – The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (e.g., pain, fatigue, menstruation, COVID-19/long COVID). Therefore, 200 cases are included in the analysis below. • Number of cases: 200 (original [169], bivalent Omi BA.1 [12], bivalent Omi BA.4/BA.5 [21], BNT162b2 Multivalent NOS [1]; 0.3% of 74,102 cases, the total PM dataset), compared to 340 cases (0.1%) retrieved in the PSUR #4. • MC cases (96), NMC cases (104). • Country of incidence (≥10): Germany (32), France, UK, US (22 each), Japan (19), Denmark (18), Norway (16), Italy (15). • Subjects' gender: female (136), male (58), unknown (6). • Subjects' age in years: n = 190, range: 13 – 90, mean: 53.9, median: 54.0. • Relevant medical history; the most frequently (≥5) reported medical conditions included: Autoimmune thyroiditis (18), Psoriasis (16), Hypothyroidism (14), Sjogren's syndrome (11), Alopecia areata, Diabetes mellitus (10 each), Autoimmune disorder (9), Arthritis,

Table 57. Description of Missing Information

Topic	Description	
Use in patients with autoimmune or inflammatory disorders *Cont'd*		Crohn's disease, Scleroderma (7 each), Ankylosing spondylitis, Colitis ulcerative, Osteoarthritis, Rheumatoid arthritis (6 each), Autoimmune hepatitis, Graves' disease, Hyperthyroidism, Optic neuritis, Raynaud's phenomenon, Thyroid disorder, Type 1 diabetes mellitus (5 each). • Number of events: 1210 (of which 201 were events of interest ie, exacerbation/flare AEs). • Relevant event seriousness: serious (153), non-serious (48). • Most frequently reported relevant PTs: Condition aggravated (138), Disease recurrence (51), Concomitant disease aggravated (11), Symptom recurrence (1). • Relevant event outcome: resolved/resolving (47), resolved with sequelae (6), not resolved (73), unknown (75); there were no relevant events with a fatal outcome.
Interaction with other vaccines *Search criteria: HLT Interactions (All Paths)*	During the reporting interval, 2 PM cases (of which 1 serious) reported the interaction with the influenza vaccine inact split 4V and pneumococcal vaccine. The non-serious case reporting an interaction with the original COVID-19 vaccine and pneumonia vaccine did not report any additional AEs. The serious case reporting an interaction with the bivalent Omi BA.4/BA.5 and influenza vaccine inact split 4V co-reported the following AEs: Encephalopathy, Decreased appetite, and Constipation (1 each).	
Long term safety data	At the time of the initial submission, 2-month post dose 2 safety data were available for approximately half of the patients who have received BNT162b2 mRNA vaccine in Study C4591001. The ongoing non-interventional safety studies will collect longer term post-marketing safety data.	

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 6 months of age and older.[82]

17.1.1. Clinical Study Data in Individuals ≥12 Years of Age

Study C4591001 is a multicenter, placebo controlled- efficacy study in participants 12 years of age and older. 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.[83] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[82] 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,[84] were included as were participants with known stable infection with HIV, HCV, or HBV.[82]

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.

Table 58. 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*,[85]			
Subgroup	**TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)

[82] As per information reported in the CDS version 21.0 dated 25 May 2023, in effect at the end of the reporting period.

[83] Ref #12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2.

[84] Ref #21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

[85] 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.

Table 58. 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

16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[86]			
Subgroup	**TRADENAME Na=22,166 Cases n1b Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1b Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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).

[86] 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.

Subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after dose 2 (with a cut-off date of 13 March 2021) are presented in Table 59[87] and Table 60.

Table 59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after dose 2 [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk [g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese [h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

[87] Ref #55 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 60. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after dose 2 [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk [g]			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)

Table 60. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Obese [h]			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 61) 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 61. 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[88,89]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After dose 1 [d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after dose 2 [f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition[90,91]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After dose 1 [d]	1 8.427[e] (22,473)	45 8.269[e] (22,394)	97.8 (87.2, 99.9)
7 days after dose 2 [f]	0 6.514[g] (21,620)	32 6.391[g] (21,693)	100 (88.0, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[92]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);

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[88] 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.

[89] 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.

[90] 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.

[91] 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.

[92] 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 61. 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

- 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:[92]

- 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.[93]
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.[93]
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 62.

[93] Ref #62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 62. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 to 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*,[94]			
	TRADENAME N[a]=1005 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=978 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection[95]			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1110 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In C4591001 an analysis of SARS-CoV-2 neutralising titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses comparing adolescents 12 to 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to

[94] 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.

[95] Ref #47 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 through 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titers at 1 month after dose 2. The GMT ratio of the adolescents 12 to 15 years of age group to the participants 16 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the GMR >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 through 25 years of age.[96]

Efficacy and immunogenicity in participants ≥ 16 years of age after booster dose

Neutralizing SARS-CoV-2 antibody titers and S1-binding IgG antibodies were evaluated at 6 months after dose 2 for Study C4591001. The data noted the persistence of a robust immune response elicited by BNT162b2 30 µg vaccination in adults for up to 6 months; and also suggest, based on the modest decline in GMTs and GMCs from 1 month to 6 months after receiving dose 2, that vaccinees may benefit from a booster dose at 6 months or thereafter. Study C4591031 was designed to assess a booster dose in this participant population.

Study C4591031 Substudy A is a Phase 3 randomised, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 in Study C4591001, at least 6 months prior to randomisation, were enrolled and participants were randomised at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomisation was stratified by age, such that approximately 60% of participants enrolled were to be ≥16 to 55 years of age and approximately 40% of participants >55 years of age.

Considering the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards and those randomised to receive a booster dose of placebo were offered a dose of BNT162b2 30 µg to receive a booster of active vaccine.

In the 6-month interim report for Substudy A, efficacy analysis of a single booster dose of BNT162b2 30 µg from 7 days after booster dose during the blinded placebo-controlled follow-up period was evaluated; also, incidence of COVID-19 cases through the entire study follow-up period in participants who received BNT162b2 initially or subsequently after unblinding was analysed.

Demographics of participants in the evaluable efficacy populations without evidence of infection prior to 7 days after booster vaccination were similar in the BNT162b2 and placebo groups. This analysis population had similar demographics compared to the overall safety

[96] Ref #48 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population.

population, as did the evaluable efficacy population participants with or without evidence of infection prior to 7 days after booster vaccination and the all-available efficacy population.

For participants without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, the median duration of blinded follow-up after booster vaccination was 2.8 months as of the data cutoff date and was similar to the safety population. Of these participants originally randomized to the BNT162b2 group, the total exposure from booster vaccination to the data cutoff date was ≥6 months for most participants (99.0%).

Follow-up times after booster vaccination for participants with or without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population were similar to the evaluable efficacy population.

After unblinding, in the all-available efficacy population, there were 7 cases meeting severe criteria; all occurred after 20 December 2021, when the Omicron variant was the predominant strain, in participants who were baseline SARS-CoV-2 negative. In original BNT162b2 participants, there were 5 severe cases: 3 met the FDA definition, 1 met the CDC definition, and 1 met both definitions. In placebo participants who later received BNT162b2, there were 2 severe cases that met the FDA definition.

These results indicate that a booster dose of BNT162b2 30 μg given ≥6 months after the primary 2-dose series of BNT162b2 30 μg vaccination provided protection against COVID-19, and protection was strongest during the Delta variant wave, and sustained up to 4 months after vaccination; longer term protection against Delta variant relative to placebo cannot be estimated from this study due to unblinding and crossover of placebo control participants. For the same reason, RVE of boosted to non-boosted participants during the Omicron variant wave cannot be estimated in this study. Although the IR during Omicron wave is much higher than that of Delta wave, the IR in those participants that were 'later' vaccinated is lower than those participants that were 'early' vaccinated, which implies better protection against Omicron with recent vaccination.

Clinical Study Data for Omicron BA.1-Adapted Vaccines in Individuals ≥18 Years of Age

Substudy D of C4591031 is a randomized substudy composed of open-labeled and observer-blinded groups to evaluate the safety, tolerability, and immunogenicity of a 2-dose primary series of BNT162b2 Omi, and as a booster (third, fourth, or fifth) dose. Participants ≥18 years of age to ≤55 years of age were enrolled. The study consists of 3 cohorts:

Participants in Cohort 1 completed a 2-dose primary series of BNT162b2 (30-μg doses), with their last dose 90 to 240 days prior to enrollment. Participants were randomized at a ratio of 1:1:1 either to receive 1 dose (third) of BNT162b2 Omi (Group 1), 2 doses (third and fourth) of BNT162b2 Omi, 4 weeks apart (Group 2), or 1 dose (third) of BNT162b2 (Group 2b). Randomization was stratified by age (stratified as 18-30 and 31-55 years of age).

Participants in Cohort 2, enrolled from Study C4591001 and C4591031 Substudy A, completed a 2-dose primary series and received a single booster (third) dose of BNT162b2,

with their last dose 90 to 180 days prior to randomization. Participants were randomized at a ratio of 1:1 to receive a fourth dose of either BNT162b2 Omi (Group 3) or BNT162b2 (Group 4). Participants in both groups were offered a dose of BNT162b2 Omi at the 3-month follow-up visit. Randomization was stratified by age (stratified as 18-30 and 31-55 years of age).

In Cohort 3, participants 18 through 55 years of age who were COVID-19 vaccine–naïve and had not experienced COVID-19 were enrolled to receive 2 doses (primary series) of BNT162b2 Omi, 3 weeks apart, with a dose of BNT162b2 approximately 5 months later (Group 5).

Interim analysis performed at 1 month post dose for cohort 2 demonstrated, for the primary and secondary immunogenicity analyses for the Omicron variant, BNT162b2 Omi 30 µg met the pre-specified criteria for simple superiority with respect to GMR and noninferiority with respect to seroresponse rate when compared to BNT162b2 30 µg when administered as a fourth dose.

In participants without prior evidence of infection up to 1 month after Dose 4, for the Omicron (BA.1) variant:

- The ratio of GMTs for the BNT162b2 Omi group to BNT162b2 group (GMR) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was >1, the simple superiority of BNT162b2 Omi to BNT162b2 for the Omicron variant was achieved based on GMR at 1 month after Dose 4.
- Seroresponse rates to the Omicron variant were 62.3% in the BNT162b2 Omi group and 39.3% in the BNT162b2 group, and the difference in proportions of participants who achieved seroresponse to Omicron variant between the BNT162b2 Omi and BNT162b2 groups was 23.0% (2-sided 95% CI: 11.1%, 34.3%). As the lower bound of the 2-sided 95% CI for GMR was greater than the prespecified margin of -5%, noninferiority of BNT162b2 Omi to BNT162b2 for the Omicron variant was achieved based on seroresponse rates at 1 month after Dose 4. The lower bound of the 2-sided 95% CI was greater than 0%, suggesting higher seroresponse to Omicron variant in BNT162b2 Omi recipients than BNT162b2 recipients.
- The GMR (BNT162b2 Omi / BNT162b2) was 1.75 (2-sided 95% CI: 1.39, 2.22). As the lower bound of the 2-sided 95% CI for GMR was not >1.5, "super" superiority of BNT162b2 Omi to BNT162b2 for the Omicron variant was not achieved at 1 month after Dose 4 based on the prespecified criterion.

Substudy E of C4591031 is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of high-dose BNT162b2 (60 µg), high-dose BNT162b2 Omi (60 µg), and a high-dose combination of BNT162b2 and BNT162b2 Omi at 60 µg (30 µg each), given as a single dose. Participants in two age groups; 18 to 55 years and >55 years of age who have received 3 prior doses of BNT162b2 (30-µg doses), with the most recent dose being 5 to 12 months (150 to 360 days) prior to randomization. Participants >55 years of age were randomized at a ratio of 1:1:1:1:1:1 to receive BNT162b2 at 30 µg, BNT162b2 at 60 µg, BNT162b2 Omi at 30 µg, BNT162b2 Omi at 60 µg, a combination of BNT162b2 and BNT162b2 Omi at 30 µg (15 µg each), or a combination of BNT162b2 and

BNT162b2 Omi at 60 µg (30 µg each) as a fourth dose. Participants 18 to 55 years of age were randomized to receive bivalent BNT162b2 and BNT162b2 Omi at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 Omi at 30 µg (15 µg each), or BNT162b2 Omi at 60 µg as a fourth dose.

Individuals >55 Years of Age (Study C4591031 Substudy E)

For the primary and secondary immunogenicity analyses for the Omicron variant, BNT162b2 Omi 30 µg and 60 µg and the BNT162b2 +BNT162b2 Omi 30 µg and 60 µg groups met the prespecified criteria for superiority with respect to GMR and noninferiority with respect to seroresponse rate when compared to BNT162b2 30 µg group, when administered to BNT162b2-experienced participants as fourth dose.

- 'Simple' superiority of BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg were met, as the lower bound of the 2-sided 95% CI for GMR was >1 for each of the three comparisons.
- Noninferiority based on seroresponse for BNT162b2 Omi 60 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and bivalent BNT162b2 + BNT162b2 Omi 30 µg to BNT162b2 30 µg were met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5% for each of the three comparisons. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 Omi 30 µg also had lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse (>-5%) consistent with noninferiority criterion.
- "Super" superiority of BNT162b2 Omi 60 µg to BNT162b2 30 µg for the Omicron variant was achieved based on the prespecified criterion, as the lower bound of the 2-sided 95% CI for GMR was >1.5. Although not formally claimed due to multiplicity, monovalent Omicron-modified vaccine BNT162b2 Omi 30 µg also had GMR and lower bound of 95% CI (>1.5) consistent with the super superiority criterion.
- Noninferiority for reference strain based on the GMR was met in both bivalent vaccine groups (BNT162b2 + BNT162b2 Omi 30 µg and 60 µg) as the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion).
- Overall, for all BNT162b2, BNT162b2 Omi and BNT162b2 Omi + BNT162b2 recipients, there were no clinically meaningful differences between subgroups for neutralizing GMTs and seroresponse rates, for the Omicron variant except for baseline SARS-CoV-2 status. GMTs at 1 month-post-dose were substantially higher while seroresponse rates were generally lower for participants who were baseline positive compared to those who were baseline negative for SARS-CoV-2.

Individuals 18 through 55 Years of Age (Study C4591031 Substudy E)

For BNT162b2-experienced participants 18 through 55 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after study

vaccination, the GMTs for Omicron BA.1 neutralizing titers across all vaccine groups evaluated were higher when compared to participants >55 years of age:

- The ratio of GMTs for participants 18 through 55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg and monovalent BNT162b2 Omi 60 µg groups, respectively, to participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg was 1.47 (2-sided 95% CI: 1.11, 1.94), 1.68 (2-sided 95% CI: 1.26, 2.25), and 3.34 (2-sided 95% CI: 2.50, 4.46), respectively. GMRs for the reference strain were also >1 for all vaccine groups.
- Seroresponse rates to the Omicron BA.1 variant for participants 18 through 55 years of age were 87.6%, 88.5%, and 95.6% in the bivalent BNT162b2 + BNT162b2 Omi 30 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg and monovalent BNT162b2 Omi 60 µg groups, respectively. The difference in percentages of participants 18 through 55 years of age with seroresponse to Omicron BA.1 variant in the bivalent BNT162b2 + BNT162b2 Omi 30 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg and monovalent BNT162b2 Omi 60 µg groups, respectively compared with participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group was 20.7% (2-sided 95% CI: 9.8%, 31.3%), 21.5% (2-sided 95% CI: 10.7%, 32.0%) and 28.6% (2-sided 95% CI: 18.9%, 38.4%), respectively. Seroresponse rates for reference strain were similarly high for all vaccine groups.
- GMTs were substantially elevated over levels observed before study vaccination for Omicron BA.1 in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group (1245.3 and 80.9, respectively), while GMTs in participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group at 1-month post-dose compared with prevaccination were 846.9 and 107.1, respectively. The monovalent BNT162b2 Omi 60 µg showed the highest response against Omicron BA.1 (increased from 114.9 to 2828.3) followed by the bivalent BNT162b2 + BNT162b2 Omi 60 µg group (increased from 83.2 to 1424.7). GMTs were also substantially elevated over levels observed before study vaccination for the reference strain, across all vaccine groups.
- The GMFRs from study vaccination to 1 month post dose for the Omicron BA.1 variant were higher for the bivalent BNT162b2 +BNT162b2 Omi 30 µg (15.4 [2-sided 95% CI: 12.4, 19.2]), bivalent BNT162b2 +BNT162b2 Omi 60 µg (17.1 [2-sided 95% CI: 13.7, 21.4]) and monovalent BNT162b2 Omi 60 µg (24.6 [2-sided 95% CI: 19.3, 31.4]) compared to participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group (7.9 [2-sided 95% CI: 6.2, 10.2]). In participants 18 to 55 years of age, monovalent BNT162b2 Omi 60 µg showed the highest Omicron BA.1 GMFR compared to bivalent vaccines at either dose level. GMFRs from study vaccination to 1 month post vaccination against the reference strain were high for participants 18 through 55 years of age across all vaccine groups than participants >55 years of age in the bivalent BNT162b2 + BNT162b2 Omi 30 µg group.
- The proportion of participants 18 through 55 years of age who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1-month post-dose for the Omicron BA.1 variant was 87.6%, 88.5% and 95.6% in the bivalent BNT162b2 + BNT162b2 Omi 30 µg, bivalent BNT162b2 + BNT162b2 Omi 60 µg, and monovalent BNT162b2 Omi 60 µg

groups, respectively. Proportion of participants achieving seroresponse for reference strain were similarly high for all vaccine groups.

Analysis of immunogenicity data from C4591031 Substudy E demonstrated a robust vaccine-elicited immune response to both monovalent and bivalent Omicron BA.1-modified vaccines when administered as a booster (dose 4) to BNT162b2-experienced participants 18 through 55 years of age. In vaccine-experienced individuals, a booster dose elicited robust neutralization titers to Omicron BA.1 and the reference strain.

17.1.2. Clinical Study Data in Children 5 Through <12 Years of Age

Efficacy and immunogenicity after 2 doses

Study C4591007 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomized, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

An initial descriptive efficacy analysis of Study C4591007 was performed in 1968 children 5 through <12 years of age without evidence of infection prior to 7 days after dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of 08 October 2021.[97]

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 63. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[96]

Table 63. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population

First COVID-19 Occurrence from 7 days after dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 Infection*			
	TRADENAME± 10 mcg/dose Na=1305 Cases n1b Surveillance Timec (n2d)	**Placebo Na=663 Cases n1b Surveillance Timec (n2d)**	**Vaccine Efficacy % (95% CI)**
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

[97] 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.

Table 63. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population

First COVID-19 Occurrence from 7 days after dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 Infection*			
	TRADENAME± 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

A formal efficacy analysis to assess the secondary vaccine efficacy hypotheses was also performed, as the required number of SARS-CoV-2 cases for hypotheses testing has been accrued. In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days after dose 2, the observed VE was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days after dose 2 to before dose 3 through the blinded follow-up period. This VE is consistent with the primary series results of previous studies of BNT162b2 in adolescent and adult populations. Importantly, while participants were randomized 2:1 to BNT162b2 or placebo, there were fewer (10 versus 42) first cases confirmed in the BNT162b2 group than in the placebo group. Notably, most of the COVID-19 cases in this VE analysis accrued from Summer to Autumn 2021, during a time that the highly transmissible Delta variant was circulating in the US and globally. This was confirmed by next-generation sequencing which showed that the majority of cases in the BNT162b2 and placebo groups were of the Delta variant lineage. Among the small number of participants who were unblinded in late December 2021 or later, few Omicron variant cases were identified in the BNT162b2 and placebo groups. This is notable because this VE analysis captures only the earliest stages of the first global Omicron variant wave.

Among confirmed COVID-19 cases, it was more common (31.0% versus 20.0%) for participants in the placebo group to report ≥4 signs and symptoms of COVID-19 than those in the BNT162b2 group. New or increased cough, fever, and sore throat were commonly reported (greater than 46.2% overall) among cases in both the BNT162b2 and placebo groups. In contrast, new or increased muscle pain was much more common (28.6% versus 0%) in the placebo group compared to the BNT162b2 group.

Subgroup analyses identified no clinically meaningful differences in efficacy parameters; however, some subgroups had small sample sizes in the study population, so caution is warranted in extrapolating these efficacy findings to all demographic subgroups.

Taken together, these results indicate that a 2-dose series of BNT162b2 10 µg in children 5 to 12 years of age provided protection against COVID-19 during the peak of the global Delta variant wave.

An analysis of SARS-CoV-2 50% neutralising titers (NT50) 1 month after dose 2 in a randomly selected subset of participants, demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study C4591007 to participants 16 through 25 years of age in the Phase 2/3 part of Study C4591007 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 64.[98]

Table 64. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (C4591007) to Participants 16 Through 25 Years of Age (C4591001) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		TRADENAME		5 Through <12 Years/ 16 Through 25 Years	
		10 mcg/Dose 5 Through <12 Years n[a]=264	30 mcg/Dose 16 Through 25 Years n[a]=253		
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after dose 2, SARS-

[98] Ref #73 of the CDS. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults.

Table 64. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (C4591007) to Participants 16 Through 25 Years of Age (C4591001) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		TRADENAME		5 Through <12 Years/ 16 Through 25 Years	
		10 mcg/Dose 5 Through <12 Years n[a]=264	30 mcg/Dose 16 Through 25 Years n[a]=253		
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)

CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 65.[97]

Table 65. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to C4591007 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		TRADENAME		5 Through <12 Years / 16 Through 25 Years	
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253		
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Immunogenicity after booster (3rd) dose

Administration of a booster (third) dose of BNT162b2 10-µg to children 5 through <12 years of age in Study C4591007 elicited robust neutralizing titers against the wild-type variant of SARS-CoV-2 in an evaluable immunogenicity population of 67 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

- Observed GMTs at 1-month post-dose 3 were substantially increased (2720.9) compared with those at 1-month post-dose 2 (1253.9) and prior to booster (dose 3) vaccination (271.0).

- The GMR for participants with available titers at 1-month post-dose 3 compared to those with available titers at 1-month post-dose 2 was 2.17 (2-sided 95% CI: 1.76, 2.68).
- The observed proportion of participants who achieved seroresponse (ie, ≥4-fold rise in SARS-CoV-2 neutralizing titers from pre-dose 1, or ≥4 × LLOQ for a pre-dose 1 measurement <LLOQ) was high (100.0%) at 1-month post-dose 2, waned by pre-dose 3 (77.6%), and was increased at 1 month after dose 3 (98.5%). The difference in seroresponse rates at 1-month post-dose 3 compared with at 1-month post-dose 2 was -1.5% (2-sided 95% CI: -8.0%, 2.4%).

Additionally, based on the FFRNT (a supportive assay), a third (booster) dose of BNT162b2 10-µg elicited neutralizing titers against a recombinant SARS-CoV-2 Omicron variant and recombinant wild-type (reference) strain of SARS-CoV-2 in an evaluable immunogenicity population of 29 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

- The observed 1-month post-dose 2, neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively which increased at 1-month post-dose 3 to 614.4 and 1702.8 and, respectively, representing an increase from post-two-dose primary series to post-booster vaccination of 22-fold for Omicron and 5-fold for the reference strain.
- The GMR of neutralizing titers against Omicron versus the reference strain at 1-month post-dose 2 was 0.09 (2-sided 95% CI: 0.07, 0.10) and increased to 0.36 (2-sided 95% CI: 0.28, 0.47) at 1-month post-dose 3, representing a fold-rise from 1-month post-dose 2 to 1-month post-dose 3 that was 4-times higher for the Omicron titers than for the reference strain titers obtained in the FFRNT assay.

The immune response associated with a booster (third) dose of BNT162b2 10 µg administered approximately 6 months after the second dose to children 5 to <12 years of age is expected to confer protection against COVID-19 including disease caused by Omicron. This is in the context of previously observed immunogenicity and efficacy results across paediatric, adolescent, and adult populations in the clinical development program and available real-world data, which have collectively shown that a booster (third) dose of BNT162b2 substantially increases the magnitude and breadth of neutralization and provides protection against symptomatic SARS-CoV-2 infection caused by variants including Omicron.

17.1.3. Clinical Study Data in Children 6 Months Through <5 Years of Age

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. The paediatric vaccination series for children 6 months to <5 years of age was initially planned as a two-dose series given 3 weeks apart. The Phase 2/3 primary immunogenicity objective in children from 6 months to <5 years of age was immunobridging the immune responses against SARS-CoV-2 wild-type strain from children 2 to <5 years and 6 months to <2 years of age in Study C4591007 compared to young adults 16 to 25 years of age in the Phase 3 efficacy Study C4591001. Immunobridging data after dose 2 met success criteria for the 6 months to <2

years group and did not meet GMR success criteria (but met seroresponse criteria) for the 2 to <5 years of group, compared to young adults 16 to 25 years of age.

Immunogenicity after 3 doses

Given emerging real-world data in the Omicron wave that two-dose protection against symptomatic infection was only modest, a third dose was evaluated for children <5 years of age. Immunobridging data after dose 3 met success criteria for the 6 months to <5 years age group, compared to young adults 16 to 25 years of age.

Immunobridging (i.e., effectiveness) data were analysed from approximately 4500 children across the 6 months to <5 years of age groups who were randomized 2:1 to receive three doses of BNT162b2 3 µg or placebo with median follow-up of approximately 2 months after dose 3 (inclusive of blinded and open-label periods).

Immunobridging Results

Immunobridging success criteria were met for both age groups, comparing the GMR and seroresponse for each C4591007 group who received three doses of BNT162b2 3-µg to adults 16 to 25 years of age in C4591001 who received two doses of BNT162b2 30-µg. Note, the CI lower bounds of the GMRs were ≥1, indicating statistical significance.

- For children 2 to <5 years of age, the GMR for titers at 1-month post-dose 3 of BNT162b2 3 µg compared to young adults 16 to 25 years of age at 1-month post-dose 2 of BNT162b2 30 µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.30 (2-sided 95% CI: 1.13, 1.50) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -1.5%, 4.2%).
- For children 6 months to <2 years of age, the GMR for titers at 1-month post-dose 3 of BNT162b2 3 µg compared to young adults 16 to 25 years of age at 1-month post-dose 2 of BNT162b2 30 µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.19 (2-sided 95% CI: 1.00, 1.42) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -3.4%, 4.2%).

Wild-type Strain SARS-CoV-2 Neutralization

Three doses of BNT162b2 elicited robust immune responses to wild-type SARS-CoV-2 in children who received 3-µg doses and in young adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.7) was increased prior to dose 3 (401.1) and then substantially increased at 1-month post-dose 3 (1535.2). The GMFR at 1-month post-dose 3 was 73.3 and the seroresponse rate was 100%.
- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.8) was increased prior to dose 3 (317.0) and was substantially increased at 1-month post-dose 3 (1406.5). The GMFR at 1-month post-dose 3 was 68.4 and the seroresponse rate was 100%.

Patterns observed for children in wild-type SARS-CoV-2 neutralization at 1-month post-dose 3 were generally comparable to young adults 16 to 25 years of age at 1-month post-dose 2.

Omicron Variant SARS-CoV-2 Neutralization

Three doses of BNT162b2 increased neutralizing titers to Omicron and Delta variants of SARS-CoV-2 in children who received 3-µg doses and in adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, FFRNT assay results showed neutralizing titers against a recombinant Omicron variant increased from before dose 3 (14.0) to 1-month post-dose 3 (82.5). This represents a 5.9-fold increase in Omicron neutralizing titers from before dose 3 to 1-month post-dose 3.
- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, FFRNT assay results showed neutralizing titers against a recombinant Omicron variant increased from before dose 3 (16.3) to 1-month post-dose 3 (127.5). This represents a 7.8-fold increase in Omicron neutralizing titers from before dose 3 to 1-month post-dose 3.
- Substantial increases in titers against a recombinant Delta variant and a wild-type reference strain were also observed after the second and third doses in both paediatric age groups.

Efficacy

Descriptive efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <2 years of age were initially based on symptomatic COVID-19 cases accrued from dose 1 to a data cutoff date of 29 April 2022 due to the urgency of ensure an available vaccine for this age group. VE was estimated across the total population of participants 6 months to <5 years of age randomized 2:1 to receive BNT162b2 3-µg vs placebo, which included 992 BNT162b2 recipients and 464 placebo recipients who received three doses of study intervention. Based on COVID-19 cases confirmed from at least 7 days post-dose 3 to the cutoff date, observed VE was 80.3% (2-sided 95% CI: 13.9%, 96.7%). Based on cases from dose 1 onwards, observed VE was 25.5% (2-sided 95% CI: 7.7%, 39.6%).

Protocol-specified efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <5 years of age were based on symptomatic COVID-19 cases accrued from dose 1 to a data cutoff date of 17 June 2022, with a median follow-up of 2.2 months post-dose 3 of the three-dose series. These analyses were based on all cases confirmed since dose 1 to the data cutoff date, and cases confirmed from at least 7 days after dose 3 to the data cutoff date among participants without or with or without evidence of prior SARS-CoV-2 infection. These analyses were triggered by the protocol objective to evaluate VE after accrual of at least 21 confirmed cases across the combined age groups of 2 to <5 years and 6 months to <2 years of age who both previously met immunobridging success criteria.

Observed Vaccine Efficacy in Population of Children 6 Months to <5 Years

The per protocol efficacy analysis was based on cases confirmed at least 7 days post-dose 3 to the data cutoff date of 17 June 2022, observed VE in the dose 3 evaluable population was ⩾72.5%, irrespective of population and/or evidence of prior SARS-CoV-2 infection. Post-dose 3 case sequence analysis identified all cases with determinant sequencing results as Omicron sublineages, with observed VE of approximately 71% to 83% against the most frequently identified sublineages (BA.2.12.1 and BA.2). Few cases were identified as BA.4 or BA.5, precluding reliable estimation or meaningful interpretation of VE against these sublineages whether considered separately or combined. Excluding cases involving coinfection with other respiratory pathogens did not meaningfully impact observed VE. This notably corresponds to a period of Omicron variant predominance, during which substantial infection surges have continued in the US and globally. This was confirmed by sequencing data and analyses showing high VE against Omicron BA.2 and BA.2.12.1 sublineages, at a time when BA.4 and BA.5 were just beginning to emerge.

The overall observed VE for each age group was generally consistent with the combined population results.

The totality of available data indicates vaccinating children 6 months to <5 years of age with three doses of BNT162b2 3-µg affords a high level of protection against symptomatic COVID-19 accrued up to a data cutoff date of 17 June 2022 in the evaluable efficacy population without evidence of prior infection.

17.1.4. Real World Data for Omicron Variant

Omicron-specific VE for the time period 19 December 2022 to 18 June 2023

The following two real world data studies reported on the effectiveness and durability of the original vaccines during periods of Omicron BA.4/5 and XBB dominance, the strains predominant during the reporting period. These studies were selected as they provided the most recent evidence available for the present reporting period.

On 15 March 2023, the *Journal of American Medical Association (JAMA) Network Open* published a study by Link-Gelles et al.[2] estimating original COVID-19 mRNA vaccine effectiveness against illness and severe disease by vaccination status during Omicron BA.4 and BA.5 sublineage periods. Brand specific effectiveness estimates were not reported. This test negative case-control study was conducted in 10 US states with data from 82,229 emergency department (ED) and urgent care (UC) encounters and 21,007 hospitalizations with COVID-19-like illness and a molecular test for SARS-CoV-2 from 16 December 2021 to 20 August 2022. Estimated effectiveness of 2 doses of original mRNA vaccine against hospitalization was 25% (95% CI, 17%-32%) at 150 days or more after vaccination, 68% (95% CI, 50%-80%) for a third dose 7 to 119 days after vaccination, and 36% (95% CI, 29%-42%) for a third dose 120 days or more after vaccination. Among patients aged 65 years or older who had received a fourth vaccine dose, VE against hospitalization was 66% (95% CI, 53%-75%) at 7 to 59 days after vaccination and 57% (95% CI, 44%-66%) at 60 days or more after vaccination. Among hospitalized patients with COVID-19, ICU admission or in-hospital death occurred in 21.4% of patients during the BA.1 period vs 14.7% during the

BA.4 and BA.5 period (standardized mean difference: 0.17). In this study, VE associated with protection against medically attended COVID-19 illness was lower with increasing time since last dose and estimated VE was higher after receipt of 1 or 2 booster doses compared with a primary series alone.

On 6 June 2023, Wee et al.[3] reported in the journal Clinical Infectious Diseases a study of long-term real-world protection afforded by third mRNA doses against symptomatic SARS-CoV-2 infections, COVID-19-related emergency attendances and hospitalizations amongst Singaporeans aged 60 years and over during an Omicron XBB wave. The study reported on a population-based cohort that included all Singaporeans aged ≥60 years with no documented prior SARS-CoV-2 infection who had previously received 3 or more doses of original mRNA vaccines, over a 4-month period during transmission of Omicron XBB. 506,856 boosted adults were included, contributing 55,846,165 person-days of observation. The authors reported adjusted incidence-rate-ratio (IRR) for symptomatic infections, ED attendances and hospitalizations at different time-intervals from both first and second boosters, using Poisson regression; with the reference group being those who received their first booster 90 to 179 days prior. Brand specific effectiveness estimates were not reported. Protection against symptomatic infections among those who received a third vaccine dose (first booster) waned after 180 days with increasing adjusted IRRs. Adjusted IRR against symptomatic infection at ≥360 days following third vaccine dose was 1.45 (95% CI, 1.33 to 1.57). However, protection against ED attendances and hospitalizations did not wane, with comparable or lower adjusted IRRs with increasing time from third vaccine doses. Adjusted IRR against ED attendance and hospitalization ≥360 days from third dose was 0.73 (95% CI: 0.62–0.85) and 0.58 (95% CI: 0.49 - 0.70), respectively. This study shows the effectiveness of a booster dose in reducing ED attendances and hospitalizations amongst older adults aged ≥60 years with no documented prior SARS-CoV-2 infection, during an Omicron XBB wave; up to and beyond 360 days post-booster.

17.2. Newly Identified Information on Efficacy and Effectiveness

17.2.1. Clinical Study Data for Omicron-Adapted Vaccines in Individuals ≥12 Years of Age

Individuals ≥12 Years of Age (Study C4591044)

Analysis of immunogenicity data at 1 month post study vaccination from Study C4591044 Cohort 2 and Cohort 2 and 3 combined for BNT162b2-experienced participants >12 years of age who received a booster (dose 4) of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg or 60 µg demonstrated a robust vaccine-elicited immune response.

These data show that a booster (dose 4) dose of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg or 60 µg elicited higher Omicron BA.4/BA.5 specific neutralization titers at 1 month after study vaccination in both age groups of 18 to 55 and >55 years compared with comparator groups of BNT162b2-experienced participants 18 to 55 years and >55 years of age from C4591031 Substudy E who received a booster (dose 4) dose of BNT162b2 Bivalent (WT/Omi BA.1) 30 µg vaccine.

Increased neutralizing responses with the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) vaccine and the BNT162b2 Bivalent (WT/Omi BA.1) vaccine were observed regardless of baseline SARS-CoV-2 infection status, with the greatest GMFRs observed in participants without prior infection and the higher titers observed in participants with prior infection. Within baseline positive or baseline negative groups, anti-Omicron BA.4/BA.5 and anti-reference strain neutralizing titers were higher in participants 12 through 17 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg compared with other age and vaccine groups at both prevaccination and 1 month after vaccination.

Superiority of BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg to BNT162b2 30 µg in the >55-year age group from C4591031 Substudy E was met with respect to anti-Omicron BA.4/BA.5 neutralizing titers. Noninferiority based on Omi BA.4/BA.5 seroresponse and anti-reference strain immune response based on GMR was also met in the >55 years of age group.

Noninferiority of the anti-Omicron BA.4/BA.5 response based on GMR and seroresponse for BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg participants 18 through 55 years of age to participants >55 years of age in the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) 30 µg were also met.

Immune response against Omicron BA.4/BA.5 was higher in all age groups (18 through 55 and >55 years) when compared to control groups from Study C4591031 Substudy E who received BNT162b2 Bivalent (WT/Omi BA.1) vaccine, with a substantially larger increase in baseline negative participants. Immune responses against the Omicron BA.1 and the reference strain were comparable for both bivalent vaccines in baseline positive participants, and a trend of higher increases for baseline negative participants was observed in participants who received BNT162b2 Bivalent (WT/Omi BA.4/BA.5). Immune responses against Omicron sublineages (BA.4.6, BA.2.75.2 and BQ.1.1) were also higher compared to BNT162b2 vaccine. Immune responses against Omicron XBB were limited.

In summary, these data indicate the BNT162b2 Bivalent (WT/Omi BA.4/BA.5) vaccine is more immunogenic against circulating Omicron sublineages and suggest that vaccines containing contemporary versions of SARS-CoV-2 may provide increased protection against COVID-19.

17.2.2. Clinical Study Data in Children 5 Through <12 Years of Age

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.

17.2.3. Clinical Study Data in Children 6 Months Through <5 Years of Age

Based on the 1-month post dose immunogenicity data in the 60 participants (≥6 months to <5 years of age) and new variants of concern neutralization data in 31 participants (≥6 months to <5 years of age) from C4591048 Substudy B Group 2 for BNT162b2-experienced (i.e., they had 3 prior doses of 3 µg original BNT162b2, with the last dose being 60 to 240 days before enrollment), the 3-µg dose of the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine elicited a robust immune response.

Analysis of immunogenicity data at 1 month after study vaccination in the evaluable immunogenicity population with or without evidence of infection for participants ≥6 months to <5 years of age who received a fourth dose of bivalent BNT162b2 at 3 µg demonstrated a higher vaccine-elicited immune response against Omicron BA.4/5 compared to a subset of participants ≥6 months to <5 years of age in the C4591048 Substudy B Group 2 who received 3 prior doses of BNT162b2 at 3 µg.

Overall, as previously observed in adults the postvaccination Omicron XBB.1.5 and BQ.1.1 neutralization titers were reduced compared with the Omicron BA.4/BA.5 neutralization titers. The reduced difference in Omicron XBB.1.5 neutralizing titers among baseline negative participants who received the bivalent BNT162b2 (Original/Omi BA.4/BA.5) vaccine compared with those that received the original BNT162b2 suggests that the advantage of the bivalent vaccine as the fourth dose may diminish as the variant becomes more distant. Overall, the collective data reinforce the importance of a bivalent booster dose in this pediatric age group and deploying vaccines that are closely matched to current circulating strains.

17.2.4. Real World Data for Omicron-Adapted Vaccines

During the current reporting period, the Centers for Disease Control and Prevention published a real-world data study on 26 May 2023 reporting vaccine effectiveness for the adapted (bivalent) mRNA vaccines, which was subsequently updated and presented during the Advisory Committee on Immunization Practices meeting on 23 June 2023. This study was identified as the best study describing vaccine effectiveness for the adapted vaccine during the reporting period and is summarized below.

On 26 May 2023, Centers for Disease Control and Prevention published a report on updated bivalent BA.4/5 mRNA vaccine durability in preventing medically attended COVID-19-associated illness among adults.[4] The study applied a test-negative design on 18,943 and 66,141 hospitalized patients with and without immunocompromising conditions, respectively, within the VISION network during September 13, 2022–April 21, 2023, across five sites in seven states. Brand specific effectiveness estimates were not reported. During the first 7–59 days after vaccination, compared with no vaccination, VE for receipt of a bivalent vaccine dose was 62% (95% CI: 57%–67%) among adults without immunocompromising conditions and 28% (95% CI: 10%–42%) among adults with immunocompromising conditions. At 120-179 days after receipt of bivalent dose, VE against hospitalization declined to 24% (95 CI: 12%–33%) among adults without immunocompromising conditions and 13% (95% CI: -13%–33%) among adults with immunocompromising conditions. Effectiveness of a bivalent booster against critical COVID-19 illness did not show signs of waning durability with comparable VE estimates over time among both immunocompetent and immunocompromised patients. VE was generally lower for adults with immunocompromising conditions. This study showed that a bivalent booster dose provided the highest protection, and protection was sustained through at least 179 days against critical outcomes, including intensive care unit (ICU) admission or in-hospital death. These data support updated recommendations allowing additional optional bivalent COVID-19 vaccine doses for certain high-risk populations.

On 23 June 2023, the Centers for Disease Control and Prevention published updated data[5] on vaccine effectiveness of monovalent and bivalent doses from the VISION[6] and IVY[7] networks – two large networks of hospitals across 10 and 20 states, respectively. During January to May, 2023, a time when Omicron XBB sublineages were the predominant circulating virus strain, VISION reported waning VE against hospitalization among immunocompetent adults. Adjusted effectiveness of a bivalent BA.4/BA.5 booster against hospitalization was 51% (95% CI: 35%–63%) at 7-89 days after receipt of vaccine dose which waned to 20% (95% CI: 7%–32%) at 90-179 days after receiving the vaccine. There was no evidence of waning VE against critical illness in immunocompetent adults with VE of 58% (95% CI: 15%–79%) and 48% (95% CI: 23%–65%) at 7-89 and 90-179 days after receiving vaccine, respectively. In the XBB era, data from the IVY network found waning VE against hospitalization among immunocompetent adults from 54% (95% CI: 39 to 65) to 6% (95% CI: -27 to 30) at 7-59 and 120-179 days after receiving vaccine, respectively. Among immunocompromised adults in the VISION network, VE against both hospitalization and critical illness were generally lower compared to immunocompetent adults. Among immunocompromised adults, adjusted VE at 7-59 days after receiving bivalent vaccine was 27% (95% CI: 9%–41%) and 41% (95% CI: 8%–62%) against hospitalization and critical illness respectively.

Recently, the World Health Organization,[8] US Food and Drug Administration,[9] and European Medicines Agency[10] all provided updated guidelines and recommendations for SARS-CoV-2 antigen composition for updated COVID-19 vaccines beginning in the fall of 2023. The WHO and EMA affirm that currently available COVID vaccines, including those based on the original virus, continue to provide substantial protection against severe disease and death. All three agencies recommended that the SARS-CoV-2 vaccine composition be updated to a monovalent COVID-19 vaccine with an XBB-lineage of the Omicron variant

with a preference for XBB.1.5 to ensure cross-reactivity against current dominant and emerging strains.

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 and effectiveness 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.

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.[11] 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.[12]

Estimates of SARS-CoV-2 incidence change rapidly. The MAH obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organisation that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.[13]

As of 06 July 2023, the overall number of SARS-CoV-2 cases was over 691 million worldwide.[14]

Table 66 shows the cumulative number of cases and deaths as of 06 July 2023 for the US, UK, and EU-27 countries. In the EU and the UK, by 06 July 2023, the total number of confirmed cases had accumulated to almost 210 million people, or 408,583 per 1,000,000 population. Across countries in the EU, the cumulative number of confirmed cases ranged from 172,706 to 670,727 cases per 1,000,000 population. Poland, Romania, and Bulgaria

reported the lowest cumulative case rates while Austria, Slovenia, and France reported the highest.

In the US, the number of confirmed cases had reached over 107 million (320,622 per 1,000,000 population) by 06 July 2023.

Table 66. Incidence, Prevalence, and Mortality of COVID-19 as of 06 July 2023

	Total Cases	Total Cases/ 1,000,000 Pop	Active Cases	Active Cases/ 1,000,000	Total Deaths	Deaths / 1,000,000	Population
Global	691,192,021	88,673	20,565,129	2,557	6,898,077	885	8,042,703,470[a]
EU-27	185,243,743	416,109	1,350,756	3,034	1,237,894	2,781	445,181,267
UK	24,636,637	359,670	5,487	80	227,524	3,322	68,497,907
EU-27 + UK	209,880,380	408,583	1,356,243	2,640	1,465,418	2,853	513,679,174
US	107,346,013	320,622	679,489	2,030	1,168,414	3,490	334,805,269
EU-27 Countries							
Austria	6,081,287	670,727	3,811	420	22,542	2,486	9,066,710
Belgium	4,801,724	411,520	1,962	168	34,375	2,946	11,668,278
Bulgaria	1,309,209	191,276	1,425	208	38,430	5,615	6,844,597
Croatia	1,274,014	313,852	145	36	18,275	4,502	4,059,286
Cyprus	660,854	540,184	0		1,364	1,115	1,223,387
Czech Republic	4,642,786	432,419	200	19	42,811	3,987	10,736,784
Denmark	3,182,286	545,384	93	16	8,755	1,500	5,834,950
Estonia	619,297	468,487	91,306	69,071	3,001	2,270	1,321,910
Finland	1,482,363	266,854	1,002	180	9,974	1,796	5,554,960
France	40,138,560	612,013	19,398	296	167,642	2,556	65,584,518
Germany	38,428,685	458,119	13,733	164	174,352	2,078	83,883,596
Greece	6,101,379	591,412	0		37,089	3,595	10,316,637
Hungary	2,203,171	229,347	2,135	222	48,881	5,088	9,606,259
Ireland	1,713,613	341,344	959	191	9,058	1,804	5,020,199
Italy	25,897,801	429,748	113,365	1,881	190,868	3,167	60,262,770
Latvia	978,172	529,074	380	206	6,386	3,454	1,848,837
Lithuania	1,321,493	496,483	433	163	9,692	3,641	2,661,708
Luxembourg	319,959	498,091	2,037	3,171	1,232	1,918	642,371
Malta	119,063	268,140	563	1,268	844	1,901	444,033
Netherlands	8,610,372	500,270	0		22,992	1,336	17,211,447
Poland	6,517,903	172,706	1,062,334	28,149	119,629	3,170	37,739,785
Portugal	5,593,092	551,556	2,222	219	26,899	2,653	10,140,570
Romania	3,407,995	179,073	1,096	58	68,240	3,586	19,031,335
Slovakia	1,866,857	341,903	0		21,167	3,877	5,460,193
Slovenia	1,344,254	646,887	75	36	7,100	3,417	2,078,034
Spain	13,914,811	297,840	30,634	656	121,760	2,606	46,719,142
Sweden	2,712,743	265,461	1,448	142	24,536	2,401	10,218,971

a. World population based on https://www.worldometers.info/world-population/#:~:text=7.9%20Billion%20(2022),Nations%20estimates%20elaborated%20by%20Worldometer. Accessed 06 July 2023.

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested, as well as in the quality of reporting across countries. People who carry the

virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported.[13] Further, as at-home rapid testing kits have become more readily available[15] and formal testing resources reach capacity due to the Omicron variant, the true estimate of cases is expected to be larger than formally reported counts. The numbers should therefore be interpreted with caution. While there is limited information on number of cases attributable to specific variants, case counts for the majority of months in 2022 through current are likely to reflect the Omicron variant, which is currently the predominant strain in many countries, including in the US[16] where Omicron XBB.1.5 was responsible for 27.0%, XBB.1.16 was responsible for 19.9%, XBB.1.9.2 was responsible for 13.0%, XBB.1.9.1 was responsible for 11.4%, and XBB.2.3 was responsible for 10.6% of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 24 June 2023.

The main existing treatment options:

Through 18 June 2023, other COVID-19 vaccines were authorised[17] in the European Union including COVID-19 Vaccines (recombinant, adjuvanted) [BIMERVAX (EU/1/22/1709), Nuvaxovid (EU/1/21/1618), Valneva vaccine (EU/1/21/1624), and VidPrevtyn Beta (EU/1/21/1580)]; COVID-19 vaccine (Ad26.COV2-S [recombinant]) JCOVDEN [previously Janssen vaccine (EU/1/20/1525)]; COVID-19 Vaccine (CHADOX1-S [recombinant]) Vaxzevria [previously AstraZeneca vaccine (EU/1/21/1529)]; elasomeran [Spikevax (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[18-21] to critical illness and death. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities.[21] A meta-analysis has estimated that 46.7% of infections in children are asymptomatic.[21] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults.[22, 23] 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%.[24]

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.[25, 26] 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.[26] 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.[26, 27]

Progression and Timeline of Severe Disease Requiring Hospitalisation

Those with severe disease will require hospitalisation to manage their illness. Based on data that have been systematically collected for the US by the CDC between 01 August 2020 and 08 July 2023, there were 6,209,122 total hospital admissions for patients with confirmed COVID-19 in the US.[28] For the week ending 09 July 2023, 0.5 per 100,000 population (country range: 0.0–3.1) were hospitalised due to COVID-19 in 7 countries of the EU/EEA with available data.[28]

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 diarrhoea (33%)[29-32] COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[33] Among unhospitalised children < 18 years of age, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three.[31] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[30, 34, 35] 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.[36] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[37]

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 days and time from onset of illness to ICU admission was 9.5–12 days.[25] In 5 countries of the EU/EEA with available data, 0.1 per 100,000 population (country range 0.0-0.6) were in the ICU due to COVID-19 as of 09 July 2023.[28] 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.[19] 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.[38]

Mortality

As of 08 July 2023, there were 1,134,710 deaths reported in the US for all age groups.[28] As of the week ending on 09 July 2023, the mortality rate was 1.3 per million population (country range: 0.0 – 7.7) in the EU.[28]

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

As of 08 July 2023, the overall SARS-CoV-2 mortality for the EU + UK was 1,465,418 deaths, or 2,853 per 1,000,000 population. Reported mortality among EU countries and the UK ranged from 1,115 to 5,615 deaths per 1,000,000 population. Cyprus, Netherlands, and Denmark reported the lowest mortality; Bulgaria, Hungary, and Croatia reported the highest.[14]

In the US, as of 08 July 2023, the mortality was 1,168,414 deaths (3490 per 1,000,000 population). Mortality in the US was higher than that of the UK (3322 per 1,000,000).[14]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK and US.[35, 39-41]

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.[42]

Assuming at least 10% of COVID-19 survivors develop long COVID, it is estimated that 5 million people are facing long COVID globally.[43]

This illness is poorly understood as it affects COVID-19 survivors at all levels of disease severity, even younger adults, children, and those not hospitalised. While the precise definition of long COVID may be lacking, the most common symptoms reported in many studies are fatigue and dyspnoea that last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues.

Presently, there is limited literature discussing the possible pathophysiology, risk factors, and treatments in long COVID, which the current review aims to address. In brief, long COVID may be driven by long-term tissue damage (e.g., lung, brain, and heart) and pathological inflammation (e.g., from viral persistence, immune dysregulation, and autoimmunity). The associated risk factors may include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific systemic inflammatory or pro-inflammatory biomarkers (e.g., elevated D-dimer and CRP values, and low lymphocyte count), although more research is required to substantiate such risk factors.[43]

Studies that have evaluated a potential impact of SARS-CoV-2 vaccination on long COVID include:

Ayoubkhani et al.[44] 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.[44]

Furthermore, Kuodi et al.[45] showed that two doses of BNT162b2 vaccine reduced the risk of the most common long COVID symptoms after COVID-19 infection, in a cross-sectional study preformed between 15 March 2020–15 November 2021. They found that patients who received 2 doses of BNT162b2 were 54% to 82% less likely to report 7 of the 10 most commonly reported symptoms compared with unvaccinated patients (all P<0.04).

Post COVID has also been described in children. A national survey in the UK found 7-8% of children with COVID-19 reported continued symptoms at >12 weeks.[46]

Long COVID can appear after mild to severe infections, and after MIS-C. Most common symptoms: similar to adults and include fatigue, headache, insomnia, trouble concentrating, muscle and joint pain, and cough. Impact on quality of life: limitations of physical activity, feeling distressed about symptoms, mental health challenges, decreased school attendance/participation.

Post-COVID conditions may be less likely to occur after vaccine breakthrough in adolescents.[47, 48]

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. [47, 48]

Further research is needed, but vaccination may contribute to a reduction in the population health burden of long COVID.

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

Non-interventional (observational) study data:

a) There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.

b) Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also inherent limitations.

Post-marketing data:

a) Reports originate from multiple sources (consumer and healthcare professional) and they can be poorly characterised from a medical perspective.

b) Limited or incomplete information is common, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.

c) Difficult to contextualise quantitatively, as voluntary and sporadic reporting do not allow complete knowledge of total exposure or total number of events ever experienced in the exposed population. These data are generally not suitable to make between-drug comparisons.

18.2.1. Benefits

Please refer to Section 17 *Benefit Evaluation.*

18.2.2. Risks

An assessment of the important 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 67.

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:

- Dyspnoea, Palpitations and Tachycardia/Heart rate increase,
- Multisystem Inflammatory Syndrome,
- Pemphigus & pemphigoid, and
- Hemophagocytic lymphohistiocytosis.

Table 67. Summary of Important Risks

Risks	Clinical Study Data	Post-Marketing Data	Literature Sources	Conclusion
Important Identified Risks				
Myocarditis and Pericarditis	No new data from clinical studies were identified during the reporting interval.	Based on the review of post-marketing data, no new safety information was identified for BNT162b2 and myocarditis and pericarditis.	During the reporting interval, there were no new significant data received from literature sources.	The risk is communicated through the CDS in Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects and Appendix A and Appendix B and in the EU SmPC in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects. It is also included as an Important identified risk in the EU RMP and in the US PVP. Based upon review of the available information, no additional change to the RSI is warranted at this time.
Important Potential Risks				
None				

In the PSUR #4, the MAH, based on the review of clinical trial data, cumulative PM data, individual review of cases, (and real-world data on mRNA vaccine effectiveness, proposed to remove the important potential risk of VAED/VAERD from the list of the safety concerns. In the AR of the PSUR #4 (EMEA/H/C/PSUSA/00010898/202212), the PRAC agreed to remove VAED/VAERD from the list of safety concerns in both RMP and PSUR.

18.2.3. Overall Benefit-Risk

The important risks associated with the use of BNT162b2 are minimised through provision of relevant product information in the RSI to support safe use of the product. Risks have been evaluated in the context of the enumerated benefits of the product. Based on the available safety and efficacy/effectiveness data for BNT162b2 (original and bivalent presentations), the overall benefit-risk profile of BNT162b2 remains favourable for all age groups in which it is authorised.

Table 68. Overall Benefit-Risk for BNT162b2

Consideration	Favourable Benefit-Risk	Non Contributory	Unfavourable Benefit-Risk
Severity of condition	The severity of the condition being treated, as well as comorbidities and outcomes in the population to be treated were considered. (See Section 18.1)	NA	NA
Unmet medical need	BNT162b2 meets an unmet medical need because there is - lack of alternative therapies, or - although alternative products are available in this class, this product may be the preferred therapeutic option or preferred in a select group of patients. (See Section 18.1)	NA	NA
Clinical benefit	The nature, clinical importance, duration, and generalizability of benefits were considered. (See Section 18.1)	NA	NA
Risk associated with treatment	The nature, seriousness, frequency, predictability, reversibility, impact on patients and public health of the product's risks were considered. (See Section 18.2.2)	NA	NA
Risk management	Risk minimisation measures currently in place for this product support a favourable benefit-risk balance. (See Section 18.2.2)	NA	NA

Table was adapted from European Medicines Agency. Benefit-risk Methodology Project – Working package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010.

19. CONCLUSION AND ACTIONS

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

The MAH will continue to review the safety of BNT162b2, including all reports of adverse experiences and will revise the product documents if an evaluation of the safety data yields significant new information.

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