EMA/PRAC/849/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202206

Active substance(s): tozinameran (COMIRNATY)

Period covered by the PSUR: 19/12/2021 To: 18/06/2022

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

Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	15 September 2022	15 September 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	14 November 2022	14 November 2022
☐	MS/PRAC members and MAH comments	14 December 2022	14 December 2022
☐	PRAC Rapporteur's updated assessment report following comments	29 December 2022	22 December 2022
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	12 January 2023	12 January 2023

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Table of contents

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for tozinameran (COMIRNATY).

2. Assessment conclusions and actions

The MAH submitted the 3rd EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 18 Aug 2022) covering the period 19 Dec 2021 to 18 Jun 2022.

During the reporting interval, the posology recommendations for the booster use were updated to "individuals 12 years of age and older", further details on heterologous boosting were provided and the boosting interval was shortened to at least 3 months after completion of the primary series (EMEA/H/C/005735/II/0093, EMEA/H/C/005735/II/0104 and EMEA/H/C/005735/II/0111).

Comirnaty (tozinameran) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals aged 06 months and older.

During the reporting interval, an estimated 843,724,061 doses of Comirnaty were administered. Cumulatively, an estimated 2,693,922,584 doses of Comirnaty were administered.

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

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

- Appendicitis, Hemolytic anemia, Uveitis, Exacerbation and/ or flare of underlying autoimmune disease or inflammatory disorders, Capillary leak syndrome, Corneal graft rejection, Vasculitis, Cerebral venous sinus thrombosis, Lymphocytic colitis, Chronic urticaria, Polymyalgia rheumatica, Subacute thyroiditis, Cerebrovascular accident/Stroke, Amenorrhea, Loss of/altered taste and smell, and Irritability.

The following were ongoing signals during the reporting interval:

- Heavy menstrual bleeding - Please refer to the separate signal procedure heavy menstrual bleeding (EMEA/H/C/005735/SDA/053- EPITT 19783).
- Hearing loss and tinnitus - Through 18 Jun 2022, 212 HCP confirmed hearing loss and tinnitus cases (27 cases possible related to Comirnaty exposure, 110 cases unlikely, 75 cases unassessable), 295 HCP confirmed tinnitus cases (2 cases possible related, 161 cases unlikely, 132 cases unassessable), 352 HCP confirmed hearing loss cases (6 cases possible, 153 cases unlikely, 193 cases unassessable), and four relevant articles were retrieved. Despite the 27 cases reporting hearing loss and tinnitus and the 2 cases reporting tinnitus and the 6 cases reporting hearing loss that were considered possible related to Comirnaty exposure, there seems to be no causal association between Comirnaty exposure and occurrence of hearing loss and/or tinnitus in the post-marketing cases. In the observed to expected analyses all O/E ratios were below 1. In the clinical trial, there were more reports of hearing loss and of tinnitus in the placebo group compared to the Comirnaty group. The MAH's conclusion is endorsed that a causal association between Comirnaty and hearing loss or tinnitus cannot be concluded at this time.

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

- Acquired haemophilia, Autoimmune hepatitis, IgA nephropathy.

During the reporting interval, there were no changes in the important risks and missing information for the Comirnaty European Risk Management Plan (EU-RMP) version 4.0.

Based on the evaluation of the interval data provided, new important safety information for Comirnaty has emerged during the reporting period: Dizziness (with frequency Unknown) should be added as an ADR in section 4.8 of the Comirnaty SmPC. However, as the MAH already submitted a variation to amend the Comirnaty product information accordingly (procedure EMEA/H/C/005735/II/0152), this PSUSA procedure can be concluded with maintenance of the marketing authorisation(s).

The benefit-risk balance for the use of Comirnaty in its authorised indication remains unchanged.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing tozinameran (COMIRNATY) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

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

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

1. In future PSURs, the MAH should only report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases decreases below 99% as presented in the current 3rd PSUR.
2. The MAH should continue to closely monitor MIS-C/-A as outlined in PRAC's signal recommendation (EPITT 19732) and all new cases of MIS-C/-A should be reported in the future PSURs.
3. The MAH should focus the analysis of myocarditis/pericarditis cases on aspects of these ADRs not fully known or addressed in the Comirnaty product information (myocarditis/pericarditis is already an ADR stated in section 4.8), and if the warning in section 4.4 regarding myocarditis/pericarditis is still in line with current knowledge. Therefore, the myocarditis/pericarditis analysis should focus more on information concerning the course, subsequent dosing, outcome and possible risk factors (such as age of the participant) of the myocarditis/pericarditis cases following Comirnaty exposure.
4. 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.
5. The vaccination stress/anxiety related ADRs are considered well documented and adequately managed in clinical practice, and therefore could be removed from section 'Evaluation of other risks (not categorised as important)' in future PSURs.
6. 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.
7. 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.

8. After the DLP of the 3rd PSUR, Comirnaty has been variant updated (bivalent vaccines), approved and is currently being used in the EU. In light of this, in the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent Comirnaty or, indeed, when comparing the two different variant updated bivalent Comirnaty vaccines, should be discussed.
9. The MAH should present cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase, with special focus on the duration of the events not considered stress/anxiety-related reactions. The MAH should evaluate whether these events should be added in the section 4.8 of the Comirnaty SmPC.
10. 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.
11. Concerning post orthostatic tachycardia syndrome, the MAH is requested to discuss the publication of "Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8" concerning post orthostatic tachycardia syndrome and Comirnaty exposure and, if applicable, to perform a cumulative review on the association between Comirnaty and post orthostatic tachycardia syndrome. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.

5 PSUR frequency

☒ No changes to the PSUR frequency.

The current 6-month frequency for the submission of PSURs should remain unchanged.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the 3rd PSUR for BNT162b2 (Comirnaty) covering the period 19 Dec 2021 to 18 Jun 2022, which is assessed in this report.

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

BNT162b2 was approved in the EU through a centralised procedure (conditional approval) on 21 December 2020 and is currently indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in people aged 5 years and older.

The vaccine is a white to off white frozen solution, is administered intramuscularly in the deltoid muscle and is available in 3 presentations:

Purple cap (for 12 years of age and older)	*Grey cap (for 12 years of age and older)*	*Orange cap (for age 5 years to <12 years)*
Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
30 micrograms/dose	30 micrograms/dose	10 micrograms/dose
Requires dilution	Do not dilute	Requires dilution
PBS/Sucrose presentation	Tris/Sucrose presentation	Tris/Sucrose presentation

Individuals aged 12 years and older

The 2 formulations (purple cap and grey cap) are administered as 30 µg/dose as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose (third dose) may be administered approximately 6 months after the second dose in individuals 16 years of age and older.

Individuals aged 5 through 11 years

The Tris/Sucrose formulation (orange cap) is administered after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose may be administered at least 6 months after the second dose.

On 17 June 2022, an additional formulation was approved first in the United States (US): the paediatric Tris/Sucrose presentation - maroon cap (3 micrograms/dose) for individuals aged between 6 months and 4 years. This is a concentrate for dispersion for injection, to be administered after dilution intramuscularly in the anterolateral aspect of the thigh (or in the deltoid muscle in individuals 1 year of age and older) as a primary series of 3 doses (0.2 mL). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.

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

Rapporteur assessment comment:

Of note, after DLP of the current PSUR:

Comirnaty is currently also available as two adapted vaccines (only to be used in people aged 12 years and older who have received at least a primary vaccination course against COVID-19):

- Comirnaty Original/Omicron BA.1 contains tozinameran and riltozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2. (procedure EMEA/H/C/005735/II/0140)

- Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2. (procedure EMEA/H/C/005735/II/0143)

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

An EU procedure is ongoing concerning the extension application to add a new strength of 5/5 µg (tozinameran, famtozinameran) for children between 5 to 11 years of age. (procedure EMEA/H/C/005735/X/0147)

1.2. Worldwide marketing authorisation status

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

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020. In the European Union, conditional marketing authorisation was granted on 21 December 2021.

Overall BNT162b2 is authorised in 104 countries/regions. BNT162b2 is authorised for the following formulations:

- PBS/Sucrose – Purple cap 30 µg formulation:
    - in individuals aged 16 years and older in 103 countries including full (5), conditional (49), EUA and other type of approvals (52).
    - in individuals aged between 12 and 15 years in 81 countries including full (2), conditional (46), EUA and other type of approvals (34).
- Tris/Sucrose formulation:
    - Grey cap: at the dosage of 30 µg formulation in individuals aged 12 years and older in 73 countries including full (3), conditional (344), EUA and other type of approvals (28).
    - Orange cap: at the dosage of 10 µg formulation in individuals aged between 5 and 11 years in 79 countries including full (2), conditional (43), EUA and other type of approvals (35).
    - Maroon cap: at the dosage of 3 µg formulation in individuals aged between 6 months and 4 years in the US with EUA.
    - The booster dose has received approvals in 83 countries including full (3), conditional (46), EUA and other type of approvals

Rapporteur assessment comment:

The provided information regarding the worldwide marketing authorisation status is noted.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

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

Rapporteur assessment comment:
The provided information is noted.

1.3.2. Changes to reference safety information

The reference safety information (RSI) for this PSUR is the Core Data Sheet (CDS) version 13.0 dated 10 May 2022, which is located in Appendix 1 of the PSUR. The 4 previous CDS versions (version 9.0 dated 02 Dec 2021 , version 10.0 dated 21 Dec 2021, version 11.0 dated 14 Jan 2022 and version 12.0 dated 23 Mar 2022) were also in effect during the reporting interval.

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

Rapporteur assessment comment:
The EU SmPC of Comirnaty (version 10 Aug 2022 which is after the PSUR DLP of 18 June 2022) is in line with the CDS.

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively, 66,656 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates:

- BNT162b2: 59,260 participants of which 33,096 had received BNT162b2; 25,205 had received BNT162b2 post-unblinding and had received placebo before; 959 had received BNT162b2/placebo.
- Variant vaccines based on BNT162b2: 1836 participants of which 747 had received BNT162b2 (B.1.351); 372 had received BNT162b2 (B.1.617.2); 697 had received BNT162b2 (B.1.1.7 + B.1.617.2);20 had received BNT162b2 (B.1.1.7.
- 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: 7044 participants.
- Placebo: 5871 participants.

Of note, BNT162b2 is also being utilised in another Pfizer clinical development program (B747): 372 participants received BNT162b2 as a study vaccine or as a comparator in the clinical study B7471026.

Post-marketing exposure

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

- EMEA/H/C/005735/MEA/002.8 (9th SSR), "*The MAH should provide an estimate of the exposure of "third doses" in future PSURs separately (reporting period and cumulatively), if applicable*.", and
- EMEA/H/C/005735/MEA/002.10 (11th SSR), "*The MAH is requested to report the total number of administered Comirnaty dose 3 in the EU/EEA, per country, and by age group.*"

MAH's response: It is not possible to determine with certainty the number of subjects who received BNT162b2 during the period of this review, and this applies also to the "third doses".

The total number of the BNT162b2 third doses administered, downloaded from the HA's websites (EMA, PMDA and FDA) is provided in Table 9 through Table 13 of the PSUR (only table 9 and 13 are reproduced here). Details for the cumulative number of third doses administered by age group and during the interval period in the EU/EEA countries are shown in Table 9 and in Table 13:

Table 9. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Dose Number

Age Group	1st Dose	2nd Dose	Dose Unknown	3rd Dose[a]	4th Dose[b]
< 18 years[c]	13636393	11718536	982	1885318	1839
0 – 4 years[d]	6570	5512	0	123	0
5 – 9 years[e]	2400265	1552704	101	1101	0
10 – 14 years[e]	4509303	4075582	420	199566	107
15 – 17 years[f]	3551465	3307482	704	410503	258
18 – 24 years[g]	11371811	10563808	4035	5272098	13263
25 – 49 years[g]	51444284	49059427	36983	25414999	112807
50 – 59 years[g]	23719359	23084094	25646	14917699	115305
60 – 69 years[g]	16347236	16155340	28333	16472372	508401
70 – 79 years[g]	15638054	15485654	21790	15020989	843612
≥ 80 years[g]	12162934	11939294	9463	10747352	935314
Age Unknown[e]	80136	65263	28	18179	59
EEA – All[h]	224378211	223231140	126250	151603079	9331517

a. Indicated as Dose Additional 1 in the ECDC webpage.
b. Indicated as Dose Additional 2 in the ECDC webpage.
c. Data from 19 countries.
d. Data from 13 countries.
e. Data from 17 countries.
f. Data from 18 countries.
g. Data from 27 countries.
h. Data from 30 countries.

Cumulative period up to 2022 week 24 (up to 19 June 2022) – Downloaded on 18 June 2022
https://www.ecdc.europa.eu/en/publications-data/data-COVID-19-vaccination-eu-eea

Table 13. EU/EEA – Interval Number of BNT162b2 Administered Doses by Age Group and Dose Number

Age Group	1st Dose	2nd Dose	Dose Unknown	3rd Dose[a]	4th Dose[b]
< 18 years[c]	4421971	4233201	611	1833167	1821
0 – 4 years[d]	5374	5052	0	110	0
5 – 9 years[e]	2033874	1534791	101	1055	0
10 – 14 years[e]	1262611	1665408	257	192672	101
15 – 17 years[f]	160024	272676	290	383121	254
18 – 24 years[g]	366151	599222	785	4410546	13009
25 – 49 years[g]	1067139	1916394	3954	17464295	110482
50 – 59 years[g]	318635	580614	1763	8151219	113819
60 – 69 years[g]	262799	474033	1789	5777707	506630
70 – 79 years[g]	163055	285448	993	2887858	842320
≥ 80 years[g]	146027	229916	661	1652184	934068
Age Unknown[h]	18890	12175	11	14127	11
EEA – All[i]	5369310	10625902	9945	69607125	9310883

a. Indicated as Dose Additional 1 in the ECDC webpage.
b. Indicated as Dose Additional 2 in the ECDC webpage.
c. Data from 19 countries.
d. Data from 13 countries.
e. Data from 17 countries.
f. Data from 18 countries.
g. Data from 27 countries.
h. Data from 16 countries.
i. Data from 30 countries.

Interval reporting period including 2021, week 51 through 2022 week 24 (up to 19 June 2022) – Downloaded on 18 June 2022.
https://www.ecdc.europa.eu/en/publications-data/data-COVID-19-vaccination-eu-eea

Rapporteur assessment comment:

The MAH reported as requested the total number of administered third and fourth doses of Comirnaty, cumulatively and during the interval period, for EU-EEA, US and Japan.

Cumulatively, in the EU-EEA an estimated:

- total of 151,603,079 third doses of Comirnaty were administered and during the interval period 69,607,125 third doses of Comirnaty.

- total of 9,331,517 fourth doses of Comirnaty were administered and during the interval period 9,310,883 fourth doses of Comirnaty.

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

Issue solved

Worldwide exposure:

- approximately 3,555,998,805 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on **01 Dec 2020 through 18 Jun 2022**, corresponding to **2,693,922,584 estimated administered doses**.
- approximately 1,115,282,160 doses of BNT162b2 were shipped worldwide during the current reporting interval from **19 Dec 2021 through 18 Jun 2022**, corresponding to **843,724,061 estimated administered doses**.

- overall, through 18 Jun 2022, a total of 143,844,450 adult Tris/Sucrose doses were shipped worldwide.
- overall, through 18 Jun 2022, a total of 229,269,400 paediatric Tris/Sucrose doses were shipped worldwide.

Rapporteur assessment comment:

Cumulatively, worldwide a total of 2,693,922,584 doses of Comirnaty were administered.

During the reporting period, in the EU-EEA a total of 202,094,207 doses of Comirnaty were administered and cumulatively 647,275,250 doses.

1.3.4. Data in summary tabulations

Response to the PRAC request 1 from the 2nd PSUR (EMEA/H/C/PSUSA/00010898/202112):

> *The MAH is requested to continue to report on the number of processed cases downloaded from EudraVigilance in the PSUR.*

MAH's response: During the reporting period, 311,460 cases were downloaded from EudraVigilance and 309,455 cases (99.4% of the total downloaded cases, 93,394 serious, 216,060 non serious and 1 unknown) were included in the data tabulations presented in the PSUR.

The remaining 2005 cases downloaded from EudraVigilance in the reporting period are not included in the data tabulations of this PSUR as they have not yet completed case processing; these include reports downloaded immediately prior to the PSUR data lock point. These reports will be included in the subsequent PSURs as Pfizer applies a late condition process that retrieves from the global safety database cases not included in the previous PSURs.

Of the 2005 case reports from EudraVigilance not included in this PSUR, 940 were serious and 1065 were non serious.

The table below provides updates on the corrective actions that have been or are being initiated with progress update from the data lock point (DLP) of the PSUR # 2 (18 December 2021) through the DLP of the PSUR # 3 (18 June 2022) to manage the volume of adverse event cases received.

Description of Action	Case Type(s) within scope of action	Action status (proposed / completed / congoing)	Completion Date/Due Date	Responsible party (internal Pfizer group and/or third-party)
Route to Distribution (RTD) Phase 2 BOT enabled date entry that assigns a case to a single user and subsequent routing to distribution	Initial and follow up Health Authority (HA) Non-serious post-marketing (PM) cases for COVID-19 vaccine.	Completed	03 March 2022	Pfizer
Further expand the in-scope case type for RTD.	Initial and follow-up HA non-serious non-interventional cases where reporter causality is related or unknown.	Ongoing	11 April 2022	Pfizer
Pfizer continuously assess resource needs. Following implementation of technology and process efficiency and through continuous monitoring of the adverse event (AE) reporting rate for COVID-19 vaccine, continue to assess the need for and onboard additional resources to help manage the increased volume of AE reports received associated with the COVID-19 vaccine	N/A	Ongoing: As of 31 December, > 2700 contractor and vendor resources have been onboarded. Resources onboarded are in production as of 07 March 2022.	N/A	Pfizer

Rapporteur assessment comment:

The MAH stated that the number of processed cases downloaded from Eudravigilance in the current 3rd PSUR is 309,455 cases (99.4% of the total downloaded cases, 93,394 serious, 216,060 non serious and 1 unknown). This is considered an improvement compared to the previous update provided in the previous second PSUR (96.7% of the total downloaded cases).

After DLP, on 15 Jul 2022 the MAH responded to the inspection status update regarding deprioritised non-serious cases for Comirnaty and provided the second quarter 2022 (01 Apr – 30 Jun) update on the status of COVID-19 vaccine deprioritised cases which demonstrated completed processing of all deprioritised cases according to the committed timelines:

Figure 2: Number of Non-Serious COVID-19 Vaccine Valid Cases with AESI Open in Workflow beyond Day 30

The data reflects weekly view of the number of non-serious valid COVID-19 Vaccine cases with Adverse Event of Special Interest (AESI) over day 30 which are not yet completed starting from implementation of AESI monitoring. As of 30Jun2022, there are no COVID-19 Vaccine Valid Cases with AESI beyond day 60 open in workflow.

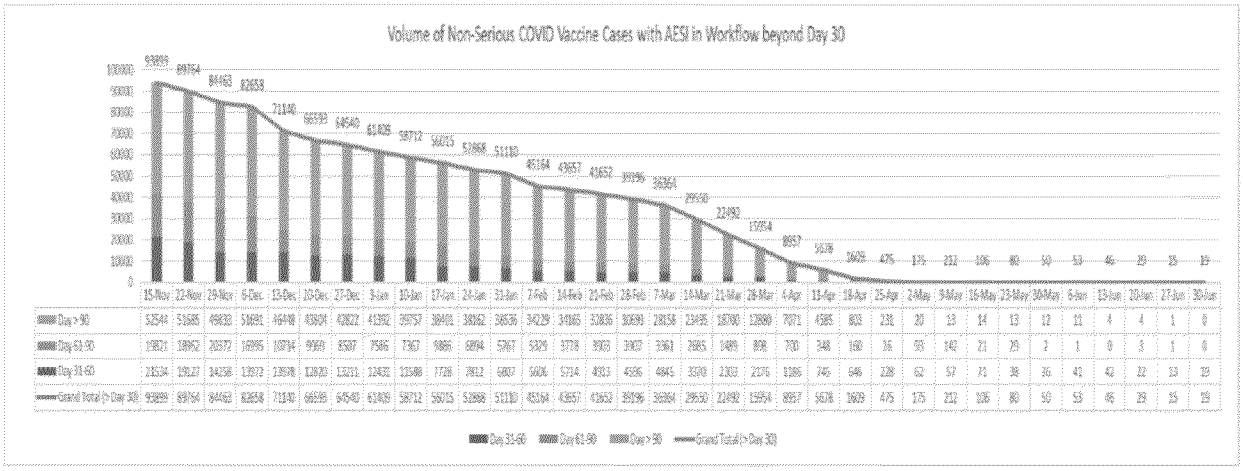
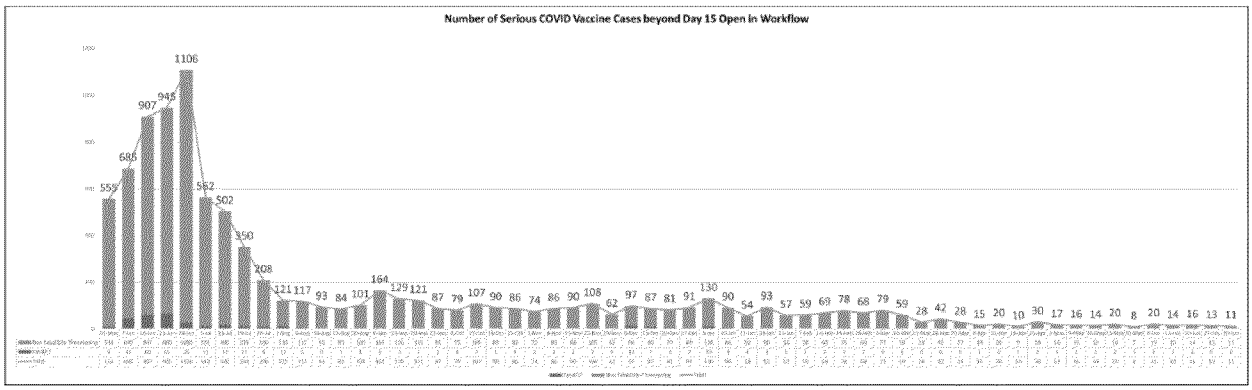


Figure 3: Number of Serious COVID Vaccine Cases beyond day 15 Open in Workflow
The data reflects weekly view of the number of serious valid COVID Vaccine cases over day 15 not yet completed for which the reportability assessment was in progress. Timeliness with expedited reporting compliance is continually monitored and remains stable. The timeline shows volume pre-CAPA implementation to current status as of 30Jun2022.



In future PSURs, the MAH should only report on the number of processed cases downloaded from EudraVigilance if the percentage processed cases of the total downloaded cases decreases below 99% as presented in the current PSUR. **Request for next PSUR**

Issue solved

During the reporting period, a total of 508,351 case reports (668 from CT and 507,683 from PM) containing 1,597,673 events were retrieved, compared to 658,249 case reports in the previous second PSUR.

Clinical trial data

During the reporting period, in the CT dataset, the number of male participants was slightly higher than female (53.9% vs 45.5%); the number of SAEs experienced by male participants is slightly higher than female (482 vs 391); in the 18 - 30 years and the 31 - 50 years age groups, the number of SAEs reported in females was higher than in males, while in the paediatric population, in 51-64 years and in the elderly (≥ 65 years) age groups, the SAEs reported in male participants was higher than in females.

A total of 879 SAEs were reported in 668 cases.

The overall safety evaluation includes a review of the most frequently reported serious events by SOC and PT for events reported in ≥2% of all clinical trial cases during the reporting interval as compared to the cumulative period through 18 June 2022 (Table 16).

Table 16. Clinical Trial Data: Serious Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 - 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases[a]	BNT162b2 / b2s01 / BT Cases	All Cases[b]	BNT162b1 / b2 / b2s01 / b3 / c2[c] / BT Cases
	(N=668) AEs (n=879)	(N=657) AEs (n=865)	(N=2426) AEs (n=3191)	(N=2284) AEs (n=3004)
	n (AERP,[d] %)	n (AERP,[d] %)	n (AERP,[d] %)	n (AERP,[d] %)
Injury, poisoning and procedural complications				
Maternal exposure during pregnancy[e]	25 (3.7)	25 (3.8)	121 (5.0)	113 (5.0)
General disorders and administration site conditions				
Condition aggravated	24 (3.6)	23 (3.5)	79 (3.3)	72 (3.2)
Infections and infestations				
Pneumonia	17 (2.5)	17 (2.6)	56 (2.3)	54 (2.4)
Gastroenteritis	15 (2.3)	15 (2.3)	22 (0.9)	21 (0.9)
Appendicitis	14 (2.1)	13 (2.0)	58 (2.4)	53 (2.3)
Cardiac disorders				
Atrial fibrillation	16 (2.4)	16 (2.4)	47 (1.9)	46 (2.0)
Nervous system disorders				
Cerebrovascular accident	13 (2.0)	13 (2.0)	40 (1.6)	39 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Prostate cancer	13 (2.0)	13 (2.0)	32 (1.3)	32 (1.4)

a. Includes BNT162b2 (b2), BNT162b2s01 (b2s01), BT, and Placebo.
b. Includes BNT162b1, b2, b2s01, b3, BNT162c2 (c2), BT and Placebo.
c. The variant vaccines b1 and c2 are study drugs in study BNT162-01, b2s01 in Study BNT162-14 and b3 in Study BNT162-04, respectively. Please refer to Section 7 for details on these studies.
d. Reporting proportion calculated as n/N (% of cases) in the current reporting period or cumulatively.
e. Reported as serious occurrence as associated to SAEs. This PT is coded in maternal cases, and in foetal cases when a foetal AE is reported. For associated SAEs, refer to Section 16.3.5.3, *Use in Pregnant/Lactating Women*.

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

There were 2 SAEs assessed as related to BNT162b2 during the reporting interval:

- Dehydration was assessed as related by both the Investigator and the Sponsor.
- Abortion spontaneous was assessed as related by the Investigator and unrelated by the Sponsor.

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

Rapporteur assessment comment:

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

Post-authorisation data

During the reporting period, in the post-marketing dataset the number of female subjects was 2.2 times the number of male subjects (63.8% vs 29.4%); across the different age groups the ratio of female/male cases ranged between 1.1 in the less than or equal to 17 years to 2.7 in the 31-50 years group.

A total of 1,596,793 AEs (of which 439,443 were serious and 1,158,240 non-serious) were reported in 507,683 PM cases.

The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (459,731), Nervous system disorders (204,185), Musculoskeletal and connective tissue disorders (148,849), Injury, poisoning and procedural complications (130,333), Infections and infestations (82,131), Gastrointestinal disorders (81,816), Reproductive system and breast disorders (77,917), Skin and subcutaneous tissue disorders (62,405), Respiratory, thoracic and mediastinal disorders (56,663), Cardiac disorders (54,208), Surgical and medical procedures (52,531), and Blood and lymphatic system disorders (38,366).

The overall safety evaluation includes a review of the most frequently reported events by SOC and by PT for events reported in ≥2% of all post-marketing cases during the interval period as compared to the cumulative period through 18 June 2022 (table 18).

Table 18. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)
Nervous system disorders				
Headache [b]	77,974 (15.4)	9451 (6.2)	297,293 (20.0)	41,338 (9.7)
Dizziness [b]	30,880 (6.1)	5418 (3.6)	93,304 (6.3)	20,903 (4.9)
Paraesthesia [g]	14,993 (3.0)	3018 (2.0)	44,666 (3.0)	10,640 (2.5)
General disorders and administration site conditions				
Fatigue [b]	67,879 (13.4)	8675 (5.7)	235,562 (15.9)	34,742 (8.2)
Pyrexia [b]	57,746 (11.4)	6642 (4.4)	228,574 (15.4)	29,973 (7.0)
Vaccination site pain [b]	49,263 (9.7)	2199 (1.5)	190,875 (12.9)	9,703 (2.3)
Chills [b]	33,542 (6.6)	2895 (1.9)	128,602 (8.7)	14,687 (3.5)
Malaise [b]	32,701 (6.4)	3337 (2.2)	142,545 (9.6)	15,085 (3.5)
Drug ineffective [h]	26,688 (5.3)	26,664 (17.6)	41,566 (2.8)	41,515 (9.8)
Vaccination failure [d]	24,419 (4.8)	24,415 (16.1)	37,933 (2.6)	37,926 (8.9)
Chest pain [i]	17,945 (3.5)	5694 (3.8)	40,839 (2.8)	15,623 (3.7)
Pain [b]	16,529 (3.3)	3618 (2.4)	80,302 (5.4)	14,660 (3.4)
Asthenia [b]	13,703 (2.7)	2793 (1.8)	59,692 (4.0)	11,424 (2.7)
Vaccination site swelling [b]	10,670 (2.1)	446 (0.3)	40,218 (2.7)	1,954 (0.5)
Infections and infestations				
COVID-19 [c]	47,988 (9.5)	47,449 (31.3)	76,044 (5.1)	72,718 (17.1)
Musculoskeletal and connective tissue disorders				
Myalgia [b]	43,916 (8.7)	4451 (2.9)	178,198 (12.0)	18,937 (4.5)
Arthralgia [b]	29,430 (5.8)	4702 (3.1)	121,898 (8.2)	18,152 (4.3)
Pain in extremity [b]	25,090 (4.9)	4584 (3.0)	93,467 (6.3)	18,828 (4.4)
Limb discomfort [b]	11,578 (2.3)	670 (0.4)	23,939 (1.6)	2,558 (0.6)
Injury, poisoning and procedural complications				
Inappropriate schedule of product administration [d]	35,318 (7.0)	466 (0.3)	57,719 (3.9)	1,020 (0.2)
Off label use [d]	29,927 (5.9)	10,293 (6.8)	54,754 (3.7)	16,400 (3.9)
Poor quality product administered [j]	17,859 (3.5)	4 (0.003)	30,830 (2.1)	14 (0.004)
Blood and lymphatic system disorders				
Lymphadenopathy [b]	31,132 (6.1)	2794 (1.9)	79,285 (5.3)	10,712 (2.5)
Gastrointestinal disorders				
Nausea [b]	30,670 (6.0)	4338 (2.9)	124,557 (8.4)	22,152 (5.2)
Vomiting [b]	11,424 (2.3)	2454 (1.6)	38,996 (2.6)	10,498 (2.5)
Diarrhoea [b]	10,211 (2.0)	1644 (1.1)	44,491 (3.0)	8,409 (2.0)
Surgical and medical procedures				
Immunisation [e]	25776 (5.1)	11,063 (7.3)	46,775 (9.6)	19,305 (4.5)
Interchange of vaccine products [e]	25,233 (5.0)	9397 (6.2)	38,522 (2.6)	14,276 (3.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea [b]	21,736 (4.3)	6947 (4.6)	56,998 (3.8)	22,516 (5.3)
Skin and subcutaneous tissue disorders				
Rash [b]	13,640 (2.7)	1802 (1.2)	41,937 (2.8)	7,742 (1.8)
Cardiac disorders				
Palpitations [b]	13,071 (2.6)	4231 (2.8)	30,535 (2.1)	10,716 (2.5)
Tachycardia [i]	10,914 (2.2)	3028 (2.0)	25,602 (1.7)	7,887 (1.9)
Reproductive system and breast disorders				
Heavy menstrual bleeding [i]	12,905 (2.5)	1711 (1.1)	30,498 (2.1)	6,381 (1.5)
Menstrual disorder [i]	12,579 (2.5)	871 (0.6)	24,442 (1.6)	2,370 (0.6)

a. Non-serious events are not included.
b. Listed or consistent with listed AEs in current RSI.
c. Listed per case processing conventions, except for fatal cases.
d. Listed per case processing conventions.
e. PTs selected per case processing conventions to indicate cases reporting third/booster doses.
f. Reporting proportion calculated as n/N (% of all incremental cases, incremental serious cases and all cumulative cases).
g. Paresthesia / Hypoesthesia were included as ADRs in the EU-SmPC Section 4.8 as per PRAC recommendation (Procedure number EMEA/H/C/005735/II/0080).
h. Drug ineffective represents efficacy-related conditions.
i. Unlisted in the current RSI.
j. Follow the listedness of the associated AE.

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

MAH's conclusion: Overall, during the reporting period, the serious cases represented 29.8% of the total PM; fatal outcomes occurred in less than 1% of the cases. About two-thirds of the cases occurred in female subjects and the age group 31-50 years was the group most frequently reporting AEs. The most frequently reported (≥2%) AEs (listed in the current RSI) are in majority non serious. Based on the review of the PM cases, no new safety issues were identified.

Rapporteur assessment comment:

During the reporting period, the safety signal procedures concerning ***Capillary leak syndrome*** (EMEA/H/C/005735/SDA/051- EPITT 19743; with outcome continue closely monitoring through routine pharmacovigilance), ***Autoimmune hepatitis*** (EMEA/H/C/005735/SDA/042- EPITT 19749; with outcome continue closely monitoring through routine pharmacovigilance), and ***Amenorrhea*** (EMEA/H/C/005735/SDA/052-EPITT 19784; with outcome follow-up requested in the PSUR) were closed.

After DLP of the current PSUR, the safety signal procedures concerning ***Heavy menstrual bleeding*** (EMEA/H/C/005735/SDA/053- EPITT 19783) and ***Vulval ulceration*** (EPITT 19840) were ongoing and the signal procedures concerning ***Corneal graft rejection*** (EMEA/H/C/005735/SDA/055- EPITT 19789; with outcome continue closely monitoring through routine pharmacovigilance), and ***Histiocytic necrotizing lymphadenitis*** (EPITT 19835; with outcome cumulative review in next PSUR) were closed.

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

Analysis by doses

Rapporteur assessment comment:

Please refer to the assessment of Local adverse reactions and Systemic adverse Reaction in section 2.3 'Evaluation of risks and new information' below.

Tris/Sucrose Formulation

The currently authorised presentations of BNT162b2 that use tromethamine (Tris) buffer are the following:

- Grey cap: multidose vial, formulated to provide, without need for dilution, 6 doses (each 0.3 mL dose containing 30 µg modRNA) for individuals 12 years of age and older. This presentation was approved first in the US on 29 October 2021 and then in other countries worldwide.
- Orange cap: multidose vial, formulated to provide, after dilution, 10 doses (each 0.2 mL dose containing 10 µg modRNA) for individuals 5 through 11 years of age. This paediatric presentation was approved first in the US on 29 October 2021 and then in other countries worldwide.
- Maroon cap: multidose vial, formulated to provide, after dilution, 10 doses (each 0.2 mL dose containing 3 µg modRNA) for individuals 6 months through 4 years of age. This paediatric presentation was approved first in the US on 17 June 2022.

A total of 19,789 case reports with Tris/Sucrose formulation containing 38,950 events (3.9% of the total PM dataset) fulfilled criteria for inclusion in this PSUR reporting period. Data presented in **Error! Reference source not found.** through **Error! Reference source not found.** (not reproduced here) refer to the paediatric 5-11 years old orange cap and ≥ 12 years grey cap presentations. Most cases (9055 cases, 45.8%) were reported in paediatric subjects (aged ≤ 17 years). There were no significant differences in the demographic data between paediatric subjects receiving Tris/Sucrose formulation and those receiving phosphate buffered saline (PBS)/Sucrose.

A higher percentage of medication error cases was reported in the Tris/Sucrose paediatric group and this may reflect initial difficulties in managing the new formulation. Routine pharmacovigilance activities to mitigate these medication errors, including label information (vial differentiation, instructions for reconstitution and administration, vaccination scheme, storage conditions for each formulation and available dosage), educational materials for healthcare providers, medical information call centers and traceability are listed in the approved version 5.0 of the EU-RMP adopted on 10 March 2022. The approved BLA US-PVP version 1.4.1 dated 29 April 2022 includes as routine pharmacovigilance activities label information on vial differentiation.

With regard to the reported medical events, the majority were reported in lower proportion in the Tris/Sucrose group compared to the PBS/Sucrose group although there were 7 events (Vaccination site pain, Vomiting, Abdominal pain, Diarrhoea, Rash, Urticaria, Pruritus) with a higher adverse event reporting proportion (AERP) (11.4%, 7.5%, 3.8%, 2.6%, 5.5%, 2.8%, and 2.6%, respectively) in the Tris/Sucrose paediatric group.

On review, few occurrences were serious (as important medical events – 97 for PT Vomiting, 49 for Abdominal pain, 42 for Rash, 41 for Urticaria, 24 for Diarrhoea, 20 for Pruritus, and 15 for Vaccination site pain). The clinical outcome of the serious occurrences was resolved/resolving (188), resolved with sequelae (5), not resolved (39), unknown (51), and fatal (5) at the time of reporting. In the 4 cases recording Abdominal pain, Vomiting (2 each), and Diarrhoea (1) as the fatal events, limited information was provided in 4 paediatric subjects. In these 4 cases, it is not clear whether the subjects had any underlying diseases or conditions, and date of death was unknown.

In the paediatric PBS/Sucrose cases, these events were assessed as serious as follows: PTs Vomiting (325), Abdominal pain (103), Rash (133), Urticaria (76), Diarrhoea (93), PT Pruritus (76), and PT Vaccination site pain (101). These serious events had the report proportion ≤ 0.5% of the total number of events among all paediatric PBS/Sucrose cases.

Rapporteur assessment comment:

Regarding the Tris/Sucrose formulation, 38,950 AEs from 19,789 cases were retrieved during the reporting period. 46% of the cases were from paediatric subjects aged ⩽17 years and 288 AEs were considered SAEs (PT Vomiting N=97, Abdominal pain N=49, Rash N=42, Urticaria N=41, Diarrhoea N=24, Pruritus N=20, and Vaccination site pain N=15). No new important safety information could be identified.

Concerning medication errors reported in the Tris/Sucrose paediatric group, these cases have been assessed in the 13th SSR (reporting period 16 Dec 2021 – 15 Feb 2022) and 14th SSR (reporting period 16 Feb 2022 – 15 Apr 2022), and no new important safety information was identified regarding medication errors.

Booster doses (third and fourth doses)

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

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

Of the relevant 490 CT cases, all participants received homologous doses schedule (primary series and booster with BNT162b2). While among the relevant 117,750 PM cases, 47,759 cases received homologous doses schedule, 23,252 cases received heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2), and 46,739 cases received booster doses of BNT162b2 administered after an unspecified primary COVID-19 vaccination series. The details of these cases are as follows:

Homologous doses schedule (primary series and booster with BNT162b2)

Clinical trial data

- Number of cases: 490 (BNT162b2 [441], blinded therapy [46] and placebo [3]) (73.4% of 668 cases, the total CT dataset).

Post-authorization data

- Number of cases: 47,759 (9.4% of 507,683 cases, the total PM dataset; 40.6% of the PM booster dataset).
- MC cases (13,848), NMC cases (33,911).
- Country of incidence (≥2%): Netherlands (15,076), UK (6998), US (4904), Austria (3222), Germany (2855), France (2377), Japan (1930), Spain (1131), Italy (1030), and Belgium (1008).
- Subjects' gender: female (33,157), male (13,463) and unknown (1139).
- Subjects' age in years (n=43,778), range: 0.5–120.0, mean: 45.2, median: 41.0.
- Case outcome: fatal (550), resolved/resolving (15,853), resolved with sequelae (480), not resolved (21,330), and unknown (9546).
- In 550 cases (reporting 1604 events with a fatal outcome), the reported causes of death (≥20 cases) were coded to the PTs COVID-19 (86), Vaccination failure (62), Cardiac arrest (52), COVID-19 pneumonia (46), Sudden death (31), Cardio-respiratory arrest (27), Cardiac failure, Myocardial infarction (21 each), Cerebral haemorrhage and Pulmonary embolism (20 each). Of note, in 99cases limited information regarding the cause of death was provided (PT Death).
- Medical history (n=16,928): the most frequently (≥2% of homologous doses schedule PM cases) reported medical conditions included Disease risk factor (2101), Hypertension (2081), Asthma (1015), Drug hypersensitivity (827), Hypothyroidism (526), Seasonal allergy (509), Food allergy (483), Diabetes mellitus (480), Hypersensitivity (478), Depression (418), and Immunodeficiency (336).
- COVID-19 Medical history (n=3615): COVID-19 (2165), Suspected COVID-19 (1437), Post-acute COVID-19 syndrome (33), Exposure to SARS-CoV-2 (20), SARS-CoV-2 test positive (11), COVID-19 pneumonia (7), Asymptomatic COVID-19, Coronavirus infection (4 each), and Occupational exposure to SARS-CoV-2 (3).
- Number of events: 190,262.
- Event seriousness: serious (63,265), non-serious (127,091).
- The most reported (≥2% of homologous doses schedule PM cases) PTs were Headache (10,390), Immunisation (9993), Fatigue (9945), Malaise (8187), Myalgia (7932), COVID-19 (7123), Pyrexia (6602), Vaccination site pain (6486), Chills (6360), Lymphadenopathy (6287), Arthralgia (5138), Vaccination failure (4891), Nausea (4672), Drug ineffective (3064),

Vaccination site swelling (2813), Pain in extremity (2459), Vaccination site inflammation (2312), Vaccination site lymphadenopathy (2099), Vaccination site warmth (1900), Pain (1887), Dyspnoea (1815), Dizziness (1794), Vaccination site erythema (1774), Chest pain (1616), Axillary pain (1385), Off label use (1171), Palpitations (1112), and Heavy menstrual bleeding (1034).

Heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2)

Post-authorization data

- Number of cases: 23,252 (4.6% of 507,683 cases, the total PM dataset; 19.7% of the PM booster dataset).
- MC cases (3665), NMC cases (19,587).
- Country of incidence (≥2%): UK (9601), Netherlands (5987), Germany (1801), France (1192), Belgium (500), and US (496).
- Subjects' gender: female (16,361), male (6296) and unknown (595).
- Subjects' age in years (n=20,855), range: 0.3 – 102.0, mean: 46.5, median: 45.0.
- Case outcome: fatal (162), resolved/resolving (7179), resolved with sequelae (322), not resolved (12,429), and unknown (3160).
- In 162 cases (reporting 781 events with a fatal outcome), the reported causes of death (≥5 cases) were coded to the PTs Interchange of vaccine products (21), Off label use (20), Cardiac arrest (14), Sudden death (12), Cerebrovascular accident, Dyspnoea, Immunisation (11 each), Pulmonary embolism (9), Malaise, Myocardial infarction (7 each), Cerebral haemorrhage, COVID-19, Drug ineffective, Myocardial ischaemia, Pneumonia, Thrombosis (6 each), Myocarditis, Oxygen saturation decreased, and Septic shock (5 each). Of note, in 32 cases limited information regarding the cause of death was provided (PT Death).
- Medical history (n=10,734): the most frequently (≥2%) reported medical conditions included Disease risk factor (1596), Hypertension (888), Interchange of vaccine products (805), Asthma (684), Immunodeficiency (502), Hypersensitivity (289), Diabetes mellitus (278), Hypothyroidism (271), Steroid therapy (253), Depression (241), Drug hypersensitivity (229) and Clinical trial participant (224).
- COVID-19 Medical history (n=2649): Suspected COVID-19 (1346), COVID-19 (1340), Post-acute COVID-19 syndrome (22), SARS CoV 2 test positive (18), COVID-19 pneumonia (6), Coronavirus infection (4), Asymptomatic COVID-19 (2) and Exposure to SARS CoV 2 (1).
- Among the 23,252 cases reporting administration of heterologous booster dose(s) of BNT162b2 following a specified non BNT162b2 COVID-19 vaccine, the previous vaccine series consisted of:
    - 9651 subjects immunised with AstraZeneca vaccine;
    - 5334 subjects immunised with Moderna vaccine;
    - 5214 subjects immunised with unknown non Pfizer-BioNTech COVID-19 vaccine;
    - 2427 subjects immunised with Johnson and Johnson vaccine;
    - 417 subjects immunised with Coronavac (Sinovac) vaccine;

- 88 subjects immunised with Sinopharm vaccine;
- 76 subjects immunised with Sputnik vaccine;
- 29 subjects immunised with Novavax vaccine;
- 9 subjects immunised with Fiocruz vaccine;
- 2 subjects each immunised with Medicago-Clinical study and Medigen vaccine;
- 1 subject each immunised with Cansino vaccine, Covaxin vaccine, and Valneva vaccine.

- Number of events: 140,835.
- Event seriousness: serious (61,291), non-serious (79,594).
- The most reported (≥2% of heterologous dose schedule PM cases) PTs were Off label use (20,437), Interchange of vaccine products (20,376), Immunisation (9982), Headache (5229), Fatigue (4854), Myalgia (3412), Malaise (3362), Pyrexia (3144), Lymphadenopathy (3139), Vaccination site pain (2926), Chills (2918), Arthralgia (2578), Nausea (2382), Pain in extremity (1848), Pain (1362), Drug ineffective (1223), COVID-19 (1192), Dizziness (1161), Vaccination site swelling (1140), Dyspnoea (1091), Chest pain (991), Axillary pain (948), Vaccination site inflammation (942), Palpitations (850), Vaccination site warmth (830), Vaccination site lymphadenopathy (815), Vaccination site erythema (751), Pruritus (630), Rash (617), Swelling (610), Heavy menstrual bleeding (608), Asthenia, Diarrhoea (565 each), Peripheral swelling (557), Paraesthesia (548), Vomiting (516), and Tachycardia (462).

Booster doses of BNT162b2 administered after an unspecified primary COVID-19 vaccination series

Post-authorization data

- Number of cases: 46,739 (9.2% of 507,683 cases, the total PM dataset; 39.7% of the PM booster dataset).
- MC cases (11,182), NMC cases (35,557).
- Country of incidence (≥2%): Germany (20,876), France (6716), Japan (2922), Austria (2833), US (2553), and UK (1924).
- Subjects' gender: female (31,045), male (13,826) and unknown (1868).
- Subjects' age in years (n=43,405), range: 1.0 – 104.0, mean: 45.3, median: 43.0.
- Case outcome: fatal (513), resolved/resolving (18,572), resolved with sequelae (1003), not resolved (18,155), and unknown (8496).
- In 513 cases (reporting 1318 events with a fatal outcome), the reported causes of death (≥15 cases) were coded to the PTs Cardiac arrest (38), Cardio respiratory arrest, Myocardial infarction (35 each), Sudden death (25), Pulmonary embolism (24), Cardiac failure (22), Dyspnoea (19), Cerebral haemorrhage (17), and Acute myocardial infarction (15). Of note, in 150 cases limited information regarding the cause of death was provided (PT Death).
- Medical history (n=11,782): the most frequently (≥2%) reported medical conditions included Hypertension (1856), Asthma (836), Drug hypersensitivity (642), Seasonal allergy (625), Hypersensitivity (456), Diabetes mellitus (426), Hypothyroidism (384), Obesity (336), Food allergy (314), Type 2 diabetes mellitus (295), Atrial fibrillation and Depression (241 each).
- COVID-19 Medical history (n=1044): COVID-19 (869), Suspected COVID-19 (153), Exposure to SARS CoV 2 (15), COVID-19 pneumonia (12), Post-acute COVID-19 syndrome (11),

Coronavirus infection, SARS CoV 2 test positive (4 each), Asymptomatic COVID-19 and Breakthrough COVID-19 (1 each).

- Number of events: 153,862.
- Event seriousness: serious (35,762), non-serious (118,147).
- The most reported (≥2%) PTs were Headache (8533), Lymphadenopathy (7016), Pyrexia (6893), Fatigue (6751), Vaccination site pain (5985), Immunisation (5675), Chills (4558), Myalgia (3979), Dizziness (3359), Malaise (3296), Nausea (3001), Limb discomfort (2798), Arthralgia (2615), Pain in extremity (2485), Dyspnoea (2173), Influenza (1877), Rash (1738), Drug ineffective (1563), Tachycardia (1557), Asthenia (1512), Pain (1499), Paraesthesia (1416), COVID-19 (1386), Chest pain (1381), Vaccination site swelling (1336), Vomiting (1325), Off label use (1286), Herpes zoster (1203), Menstrual disorder (1101), Diarrhoea (1062), Poor quality product administered (1061), Feeling hot (1017), Immunisation reaction (1016), Influenza like illness (1006), and Palpitations (985).

Analysis booster doses versus primary vaccination series

- There were 117,750 PM cases of subjects who received at least one booster dose of BNT162b2. Among the 117,750 PM cases,
    - 106,889 PM cases involved subjects who received single booster dose of BNT162b2
    - 3427 PM cases involved subjects who received >1 booster doses of COVID-19 vaccine (the latest booster dose was BNT162b2) and
    - 7434 cases involved subjects who received unknown booster dose(s) of BNT162b2.
    - The most frequently (≥2%) reported clinical AEs in PM cases of subjects who received the booster dose(s) of BNT162b2 are largely reflective of reactogenicity and events associated with the immunisation process.
    - The most frequently (≥2%) reported clinical AEs in PM cases of subjects who received booster dose(s) of BNT162b2 were consistent with those reported in subjects receiving primary vaccination series, as shown in Table 25.
    - A higher AERP rate was observed for 9 PTs (Lymphadenopathy [14.0% vs 3.8%], Malaise [12.6% vs 4.6%], Chills [11.8% vs 5.1%], Vaccination site swelling [4.5% vs 1.4%], Vaccination site erythema [2.9% vs 1.0%], Vaccination site lymphadenopathy [2.9% vs 0.2%], Vaccination site inflammation [2.8% vs 0.3%], Axillary pain [2.7% vs 0.5%], and Vaccination site warmth [2.4% vs 0.3%]) was observed in subjects who received the booster dose(s) of BNT162b2 compared to subjects receiving the primary vaccination series. This is consistent with the known BNT162b2 safety profile (as per the RSI), where higher rates of lymphadenopathy and reactogenicity reactions in booster doses versus primary doses were observed in interventional clinical studies.
    - No clinically significant differences were noted in the other events.

MAH's conclusion: Based on the review of the cases reported with the booster dose(s), no new safety issues were identified.

Rapporteur assessment comment:

The MAH reported on the safety profile of Comirnaty in a homologous doses schedule (primary series and booster with BNT162b2), in a heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and a booster with BNT162b2) and in a schedule when the third/booster

doses of BNT162b2 were administered after an unspecified primary COVID-19 vaccination series.

MAH's conclusion is endorsed, that at the moment no new important safety information was identified in the cases reported with the booster dose(s).

The number of persons receiving multiple booster doses (i.e., homologous, heterologous, different strains) is increasing whereas the impact on safety and efficacy remains uncertain. In addition the impact (including long-term) of repeatedly (e.g., yearly) receiving booster doses (with or without strain updates) also remains unknown. The MAH is requested to discuss whether 'safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)' should be considered as *Missing information* in the RMP, and proposals should be provided how to address this knowledge gap in ongoing or newly proposed PASSs, as applicable. As boosting schemes could involve multiple vaccine brands a joined approach between different MAHs would be welcomed. **Request for supplementary information**

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 interval, there was a completed clinical trial (C4591017) 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 14 ongoing sponsor-initiated clinical trials.

Safety trials:

- PASS C4591015 [A phase 2/3, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.
- PASS C4591024 [A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.
- Other trials where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.
- Other Trials that reported new significant efficacy information, 8 ongoing clinical trials:
    - 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 <12 years of age.
- C4591031, A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.
- BNT162-01, A multi-site, phase I/II, 2-Part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults.
- BNT162-03, Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects: A phase I, randomized, placebo--controlled, observer-blind study.
- BNT162-04, A multi-site, phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults.
- BNT162-06, Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy subjects: A phase II, randomized, placebo-controlled, observer-blind study.
- 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.

No clinically important information has emerged from ongoing clinical trials.

Remaining Trials, 4 ongoing clinical trials:

- C4591005, A phase 1/2, placebo-controlled, randomized, and observer-blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy Japanese adults.
- C4591020, A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT162b2 against COVID-19 in healthy adults 18 through 55 years of age.
- C4591030, A phase 3, randomized, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.
- BNT162-17, A Phase II trial to evaluate the safety and immunogenicity of a SARS-CoV-2 multivalent RNA vaccine in healthy subjects.

No clinically important 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 utilised in another Pfizer-sponsored clinical development program (B747). The study B7471026 "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" was completed during the reporting period.

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

New safety data related to fixed combination therapies

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

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

1.3.5.2. Findings from non-interventional studies

During the reporting period, there were there were 11 ongoing sponsor-initiated non-interventional studies and one non-interventional study (C4591035) was completed.

Completed non-interventional study

Other study

- Study C4591035 titled 'Coronavirus Disease 2019 (COVID-19) Vaccination and Breakthrough Infections Among Persons with Immunocompromising Conditions in the US' was completed. No new safety information emerged from this non-interventional study.

Ongoing non-interventional studies

Safety Studies:

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

Other Studies, 5 ongoing non-interventional studies:

- C4591006, General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).
- C4591014, Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.
- C4591019, Special investigation in the population with underlying diseases considered to increase the risk of severe illness of COVID-19.
- C4591025, A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.
- C4591034, Patient-reported health-related quality of life associated with COVID-19: A prospective survey study on symptomatic adults confirmed with RT-PCR from outpatient settings in the US.

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

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

1.3.5.3. Information from other clinical trials and sources

Other clinical trials

During the reporting interval, there were 11 relevant cases that originated from non-Pfizer clinical trials. In 7 of these cases, BNT162b2 was a study drug, while in the other 4 cases the administration of BNT162b2 was concomitant.

The 6 cases originated from non-Pfizer and non-BNT trials and reported the SAEs:

- COVID-19, Drug ineffective;
- Thrombophlebitis;
- Deep vein thrombosis, Pulmonary embolism;
- Myocarditis;

The SAEs reported in these 4 cases were assessed as related to the BNT162b2 by the investigators and the MAH agreed except for the case reporting Deep vein thrombosis and Pulmonary embolism, where it was considered that there was not a reasonable possibility that the events were related to vaccine administration, based on the absence of a plausible pathophysiological mechanism.

- Immunisation, Overdose (0.5 ml of Pfizer-BioNTech COVID-19 vaccine), Ventricular tachycardia;
- Condition aggravated, Endometrial thickening.

The investigator's assessment for Ventricular tachycardia was not provided; Endometrial thickening was considered unrelated to BNT162b2 by the investigator; in both cases the MAH considered the SAEs as unrelated to the vaccine.

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

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

Medication errors

Clinical trial data

During the reporting period, there were 2 serious cases (0.3% of 668 cases, the total CT dataset) indicative of medication errors (PTs: Accidental overdose and Inappropriate schedule of product administration). In the first case, the accidental overdose referred to paracetamol and not to BNT162b2 and in the remaining case reporting inappropriate schedule of product administration, the

investigator assessed the event as not related to BNT162b2. There was 1 serious case retrieved during the reporting period of the PSUR #2.

Post-authorisation data

The potentially relevant medication error cases during the reporting period were 66,764 (13.1%) reporting 87,307 events, compared to 33,834 relevant cases (5.1%) analysed in the PSUR #2.

Out of the 66,764 relevant medication error cases, there were:

- 9426 cases reporting events indicative of medication errors related to Tris/Sucrose paediatric formulation, and
- 2750 cases reporting events indicative of medication errors related to Tris/Sucrose Grey cap presentation (adult/adolescent formulation).

These numbers represent a good index of the effectiveness of the routine pharmacovigilance activities implemented, considering that in the reporting period 182,231,200 paediatric Tris/Sucrose doses and 143,844,450 adult Tris/Sucrose doses were shipped worldwide.

Overall, among the 66,764 relevant medication error PM cases, 1326 cases (0.3% of the total interval cases, 2.0% of total relevant medication error cases) were considered harmful, 70 of which (0.1% of total relevant cases) were serious and most of them originated from vaccine administration issues (50 cases of 70 serious cases with harm).

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

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

Rapporteur assessment comment:

Two serious clinical trial cases indicative of a medication error were reported and considered not related to or did not concern Comirnaty exposure.

During the reporting period, an increased number of medication errors (N=66,764 cases with an estimated 843,724,061 administered doses) was reported compared to the previous 2nd PSUR (N=10,776 cases with an estimated 635,763,682 administered doses). 9,426 of the 66,764 cases were indicative of medication errors related to Tris/Sucrose paediatric formulation, and 2,750 of the 66,764 cases to the Tris/Sucrose Grey cap presentation (adult/adolescent formulation). However, no specific trend or pattern was observed.

No new important safety information could be identified regarding reported medication 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 8 clinical trials that presented important new safety findings for BNT162b2 (table 31).

Table 31. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

Citation/Comment
a) At Risk patients
1. Majcherek M, Matkowska-Kocjan A, Szymczak D, et al. Two Doses of BNT162b2 mRNA Vaccine in Patients after Hematopoietic Stem Cell Transplantation: Humoral Response and Serological Conversion Predictors. Cancers (Basel). 2022; 14(2):325. This article described a reduced immunoresponse to BNT162b2 in patients treated with immunosuppressants. Section 4.4. Special warnings and precautions for use (Immunocompromised individuals) of the EU SmPC includes a warning regarding vaccination in immunocompromised patients, as follows, "The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals." Use in immunocompromised patients is considered missing information for BNT162b2; please refer to Section 16.4.2 *Description of Missing Information* for the description of this topic and to Section 16.3.5.5 *Use in Immunocompromised Patients* for the summary of the cases received during the reporting period.
b) Special Patients Population (Pregnancy)
2. Citu IM, Citu C, Gorun F, et al. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. J Clin Med. 2022; 11(6):1698. This article contributes to the growing evidence that risk of spontaneous abortion after COVID-19 vaccine immunisation during the first trimester of pregnancy is commensurate with the predicted risk in non-vaccinated pregnant women. Use in pregnancy and while breast feeding patients is considered missing information for BNT162b2; please refer to Section 16.4.2 *Description of Missing Information* for the description of this topic and to Section 16.3.5.3 *Use in Pregnant/Lactating Women* for the summary of the cases received during the reporting period.
c) Efficacy and Effectiveness
3. Tartof SY, Slezak JM, Puzniak L. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: a retrospective cohort study. The Lancet Regional Health – Americas 2022;9: 100198 Published on line 14 February 2022. 4. Tartof SY, Slezak JM, Puzniak L. Durability of BNT162b2 vaccine against hospital and emergency department admission due to the omicron and delta variants in a large health system in the USA: a test-negative case-control study. Lancet Respir Med 2022; 10:689-99. 5. Kliker L, Zuckerman N, Atari N et al. COVID-19 vaccination and BA.1 breakthrough infection induce neutralising antibodies which are less efficient against BA.4 and BA.5 Omicron variants, Israel, March to June 2022. www.eurosurveillance.org submitted on 12 Jul 2022 / accepted on 28 Jul 2022 / published on 28 Jul 2022.[70] 6. Hansen CH, Friis NU, Bager P et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish nation-wide population-based study. Lancet pre-print https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4165630.[70] Please refer to Section 17.2 *Newly Identified Information on Efficacy and Effectiveness* for the comments on these articles and to Section 16.3.4.5. *Lack of Therapeutic Efficacy* for the review of the cases indicative of LOE reported in the current interval period.
d) Other Safety Information
7. Yanir Y, Doweck I, Shibli R, et al. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss. JAMA Otolaryngol Head Neck Surg. 2022;148(4):299–306. This study suggests that the COVID-19 vaccine might be associated with increased risk of Sudden Sensorineural Hearing Loss; however, the effect size is very small. The study had various limitations and no causality assessment has been conducted. The MAH will continue to monitor using routine pharmacovigilance. Please refer to Appendix 6A.3 for further discussion of this article and for cumulative review of cases indicative of hearing loss.
8. Visser C, Biedermann JS, Nierman M et al. The Immediate Effect of COVID-19 Vaccination on Anticoagulation Control in Patients Using Vitamin K Antagonists. Thromb Haemost 2022; 122:377–385.

In this study, BNT162b2 was associated with an immediate negative effect on anticoagulation control in patients treated with vitamin K antagonists. The author though cannot exclude the possibility that the effect on anticoagulation control was due to dose adjustments to avoid complications and patients themselves could have decided to decrease the dosage in the days following COVID-19 vaccination as they might be afraid for bleeding complications after intramuscular injection. This could result in a higher percentage of subtherapeutic INRs after vaccination. In addition, the authors use a surrogate variable for bleeding complications (INR >5).
The possible effects of vaccines on anticoagulation control remain debated even though several prospective studies have been performed (mostly on the effect of the influenza vaccine on anticoagulation control), but overall results were conflicting. As of now, there is no biological or pharmacological plausibility for a vaccine – drug interaction. The MAH will continue to monitor using routine pharmacovigilance.

Please refer to Section 16.3.3.1.19 *Thromboembolic AESIs* for the summary of cases indicative of coagulopathy received in the reporting period.

Rapporteur assessment comment:

The MAH identified 8 clinical trials that presented important new safety findings after Comirnaty exposure and provided an overview of the retrieved 8 studies grouped as a) At risk patients (N=1); b) Special patient population/Pregnancy (N=1); c) Efficacy and effectiveness (N=4) and d) Other safety information (N=2). No new important safety information could be identified regarding literature.

Please refer regarding the study of Yanir et al. to the assessment in section 2 2.1.1. Hearing loss of this AR.

All Other Published Sources

In the final AR for PAM-MEA-002.11 - 12. SMSR (1st SBSR) received on 09 February 2022 (EMEA/H/C/005735/MEA/002.11), the MAH was requested to include in the 2nd SBSR the following article, published in the reporting interval of the PSUR # 3:

- Ouldali et al. Multisystemic inflammatory syndrome following COVID-19 mRNA vaccine in children: a national post-authorization pharmacovigilance study posted on MedRxiv on Jan 18 2022: https://www.medrxiv.org/content/10.1101/2022.01.17.22269263v1.article-metrics.

The above article was included and discussed in the SBSR no. 2 dated 04 March 2022.

In the final AR for PAM-MEA-002.12 13th SMSR (2nd SBSR) dated 05 April 2022 (EMA/PRAC/202255/2022), the MAH was requested to discuss the following publication regarding SSNHL in association with COVID-19 vaccination:

- Formeister EJ, Wu MJ, Chari DA, et al. Assessment of Sudden Sensorineural Hearing Loss After COVID-19 Vaccination [published online ahead of print, 2022 Feb 24]. JAMA Otolaryngol Head Neck Surg. 2022;e214414. doi:10.1001/jamaot+o.2021.4414

The abstract of the above article and the discussion are available in Appendix 6A.3.

Rapporteur assessment comment:

The study of Ouldali et al. was discussed in the 13th (2nd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.12). No new safety concern was identified.

Please refer regarding the study of Formeister et al. to the assessment in section 2 2.1.1. Hearing loss of this AR.

Unpublished manuscripts

In the final assessment report for PAM-MEA-002.12 13th SSR (2nd SBSR) dated 05 April 2022 (EMA/PRAC/202255/2022), the MAH was requested to include in the 3rd SBSR the following ACIP presentation, presented in the reporting interval of the PSUR # 3:

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/04-COVID-Kracalic-508.pdf

The above presentation on myocarditis outcomes following mRNA COVID-19 vaccination was included and discussed in the SBSR no. 3 dated 06 May 2022.

Rapporteur assessment comment:

The ACIP presentation was assessed in the 14th (3rd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.13) and resulted in a request for a variation to update sections 4.4 and 4.8 of the SmPC in order to update the occurrence of myocarditis because more information is available in the age group 5-11 years; and to update the statement in the SmPC section 4.4 regarding the risk of myocarditis after a third dose of Comirnaty based on real-world evidence, which was assessed in procedure EMEA/H/C/005735/II/0141.

1.3.5.6. Other periodic reports

During the reporting period, the MAH did not submit another PSUR for BNT162b2. However, the MAH was requested to prepare Summary Monthly Safety Update Reports (SMSRs), in accordance with the EMA coreRMP19 Guidance (EMA/544966/2020) and, as applicable, with ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, January 2013] considering the information for the evidence from post-EUA/conditional marketing authorisation approval data sources.

Following the proposal of discontinuation of SSR submission by PRAC included in the final PRAC AR of the 3rd SBSR (Report EMA/PRAC/577594/2022 dated 08 June 2022), the preparation of the SBSR was discontinued.

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

Rapporteur assessment comment:

After the 14th (3rd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.13), the submission of SSRs was discontinued.

1.3.5.7. Lack of efficacy in controlled clinical trials

Study C4591007 is the ongoing, randomised, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. 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 geometric mean ratio (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. 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.

The observed vaccine efficacy (VE) from at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-µg administered to children 6 months to <5 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 28.3% (2-sided 95% CI: 8.0%, 43.9%) based on 163 cases in the BNT162b2 group and 113 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomisation of vaccine:placebo). In this population, observed VE against Delta and Omicron was 70.2% (2-sided 95% CI: 27.2%, 88.5%) and 21.8% (2-sided 95% CI: -1.7%, 39.7%), respectively. Note that most of the cases across this age population that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

The observed VE from at least 7 days after Dose 3 to the cutoff date (29 April 2022) across the total population of children 6 months to <5 years of age was 80.3% (2-sided 95% CI: 13.9%, 96.7%) based on 3 cases in the BNT162b2 group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo). Note that all post-Dose 3 cases were reported in February through April 2022.

The observed VE after 3 doses in children 6 months to <5 years of age in Study C4591007 is consistent with real-world effectiveness data for older age groups, which indicate that in adolescents (12 to 17 years of age) and adults (18 years of age and older), three doses of BNT162b2 are needed to provide a high level of protection against symptomatic disease due to Omicron.

Rapporteur assessment comment: MAH's information regarding lack of efficacy is noted. Please refer to procedure EMEA/H/C/005735/X/0138 for the line extension of Comirnaty 3 µg concentrate for dispersion for injection for infants and children between 6 months to 4 years of age (procedure EMEA/H/C/005735/X/0138).

1.3.5.8. Late-breaking information

On 08 July 2022 (after the DLP of this PSUR), the MAH submitted the EU RMP version 5.1 to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received in March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087).

Rapporteur assessment comment: Please refer to section 2.1 Summary of safety concerns 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 v 4.0 adopted 26 Nov 2021:

Table 1 Ongoing Safety Concerns

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

There were no changes to the safety concerns during the reporting period.

Rapporteur assessment comment:

During the reporting period there were no changes to the list of safety concerns in the Comirnaty RMP.

Of note, after the DLP of this PSUR, the MAH submitted additional Comirnaty RMPs:

1. RMP Version 5.1 - to include the 6 months to <2 years and 2 years to <5 years phase 1 and phase 2/3 data from interventional clinical study C4591007 for the line extension of Comirnaty 3 µg concentrate for dispersion for injection for infants and children between 6 months to 4 years of age; and to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation in procedure EMEA/H/C/005735/II/0087. (Procedure EMEA/H/C/005735/X/0138)

2. RMP version 6.0 - to support the extension of the indication to ⩾12 years of age to receive an additional booster (fourth) dose of bivalent Omicron-(BA.1) modified vaccine. (procedure EMEA/H/C/005735/II/0140)

3. RMP version 7.0 - to support the extension of the indication to introduce a first or second booster dose of a bivalent Omicron variant-modified vaccine, (BNT162b2 15 µg + BNT162b2 OMI BA.4/5 15 µg, total 30 µg), given ⩾3 months after the primary series or ⩾4 months after the third dose in individuals ⩾12 years of age. (procedure EMEA/H/C/005735/II/0143)

4. RMP version 7.2 - to support the extension application to add a new strength of 5/5 µg (tozinameran, famtozinameran) for children between 5 to 11 years of age. (procedure EMEA/H/C/005735/X/0147)

2.2. *Signal evaluation*

- Tabular overview of signals: new, ongoing or closed during the reporting interval 19-12-2021 to 18-06-2022.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Hearing loss	31May22	Ongoing		Enquiry from a competent authority (EMA PRAC, Health Canada).	Signal re-opened during the current reporting period due to Health Canada (HC) request and EMA PRAC request (per 14th Summary Safety Report [3rd bimonthly] Assessment Report). HC request was to provide a cumulative review of all cases of tinnitus and hearing loss. EMA PRAC requested MAH to perform a cumulative review on the association between sudden sensorineural hearing loss and Comirnaty exposure, including a review of the relevant new literature published after the reporting period of the 14th SSR, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Evaluation ongoing at datalock date (18 Jun 2022).
Myocarditis and Pericarditis	18May22	Closed	18May 22	Other: Internal Reviews	The safety management team endorsed myocarditis and pericarditis being added as an ADR to the Core Data Sheet as data from multiple sources has consistently shown the association and increase from background, particularly in young males after the 2nd dose. The ongoing reviews of the post-authorization safety data, clinical trial data, pre-clinical trial, and O/E analysis data support the update to Section 4.8 of the CDS.	Postauthorization safety data, clinical study safety data, and preclinical data review, Literature review, and O/E analysis.	Important Identified Risk. Myocarditis and pericarditis are currently discussed in the Warnings/Precautions section 4.4 of the CDS. Now, based on the accumulating data and supported by signal management activities, myocarditis and pericarditis will be included in Section 4.8 (Undesirable effects) of the CDS.

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
Irritability	31Jan22	Closed	31Jan22	Clinical Trial C4591007 unblinded review of data in 6 months to <5-year-olds (Pfizer).	Unblinded review of the pediatric clinical trial reactogenicity data for the C4591007 6 months to <5-year-old cohort. It was determined that "irritability" will be considered an ADR specific to the 6 months to <2-year-old population.	Review of unblinded systemic reactogenicity events for doses 1 and 2 in 6 month to < 2-year-old recipients of BNT162b2 (compared to placebo).	Identified risk – considered NOT important for purposes of risk management. "Irritability" will be considered an ADR specific to the 6 months to<2-year-old population. The CDS (and, subsequently, local labeling documents as appropriate) will be updated to include "irritability" as an ADR for this population.
Appendicitis	06Apr22	Closed	11May22	Enquiry from a competent authority (Singapore BoH).	Signal re-opened during the current reporting period in response to Singapore BoH request to provide a cumulative safety analysis on the association of appendicitis with Comirnaty, in particular in adolescents aged 12-17 years old in SBSR#4. Singapore noted 18 local reports of appendicitis post vaccination with Comirnaty, with 15 assessed as possibly related.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Appendicitis. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Hemolytic anemia	03Jan22	Closed	26Jan22	Enquiry from a competent authority (Saudi Arabia SFDA).	SFDA requested a comprehensive evaluation report of potential risks of hemolytic anemia with the use of Pfizer/BioNTech COVID-19 vaccine.	Postauthorization safety data, clinical study safety data, medical literature O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Hemolytic anemia. 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
Uveitis	31Mar22	Closed	27Apr22	Enquiry from a competent authority (Health Canada).	Request from Health Canada due to a WHO publication regarding disproportionate reporting of cases of anterior uveitis following administration of COVID-19 vaccines; request was for a cumulative review of all cases of anterior uveitis including analyses with the preferred terms uveitis, iritis, and ididocyclitis.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Uveitis. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders	11Jan22	Closed	02Feb22	Enquiry from a competent authority (EMA PRAC).	EMA PRAC request to review autoimmune/inflammatory disorder exacerbations reported following vaccination with COMIRNATY including data that have become available since the data-lock period of the 10th SMSR.	Postauthorization safety data, clinical study safety data, medical literature.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Capillary Leak Syndrome (CLS)	13Jan22	Closed	02Feb22	Enquiry from a competent authority (EMA PRAC).	EMA PRAC request based on spontaneous case reports of CLS in individuals vaccinated with COVID-19 mRNA Vaccine (nucleosidemodified) Spikevax, including in patients with medical history of CLS and a latebreaking publication from the EurêClark StudyGroup. The PRAC has agreed that the MAHs for COVID-19 mRNA vaccines, Comirnaty (BioNTech Manufacturing GmbH) and Spikevax (Moderna Biotech Spain, S.L.) should comment on the evidence provided in the publication.	Postauthorization safety data, clinical study safety data, medical literature.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and CLS. 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
Corneal Graft Rejection	01Apr22	Closed	17Jun22	Enquiry from a competent authority (EMA PRAC).	EMA PRAC requested the MAH for Comirnaty to provide a cumulative review of all cases of corneal graft rejection and related terms from all available sources.	Postauthorization safety data, clinical study safety data, medical literature.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Corneal Graft Rejection. An update to product labeling is not warranted at this time. Routine monitoring will continue.
Vasculitis	22Nov21	Closed	02Feb22	Notification from a competent authority (Netherlands Lareb).	Email received from Lareb (Netherlands) with recommendation that a causal relationship for vasculitis and COVID-19 vaccination is suggested based on their review and should be further investigated.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Vasculitis. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Cerebral venous sinus thrombosis (CVST)	30Nov21	Closed	12Jan22	Enquiry from a competent authority (Switzerland Swissmedic).	Query received via email from Swissmedic, concerning the signal 'Venous sinus thrombosis' after vaccination with Comirnaty.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and CVST. An update to product labelling 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
Lymphocytic colitis	23Dec21		10Feb22	Scientific Literature.	Signal identified from new information identified in the published literature, titled "Lymphocytic colitis following mRNA vaccination for SARS-CoV2", published in the American Journal of Gastroenterology. Conference: Annual Scientific Meeting of the American College of Gastroenterology, ACG 2021. Las Vegas, NV United States. 116(SUPPL) (pp S847), 2021. (Date of Publication: October 2021. Authors Chey S.W.; Westerhoff M.; Chey W.D).	Postauthorization safety data, clinical study safety data, medical literature.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Lymphocytic colitis. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Chronic Urticaria	24May22	Closed	01Jun22	Enquiry from a competent authority (EMA PRAC)	EMA PRAC preliminary Assessment Report for PSUR #2 contained a request to analyze new onset chronic urticaria following vaccination and respond as a Request for Supplemental Information. Assessment of relapse of chronic urticaria had been included in the PSUR (#3).	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Chronic Urticaria, new onset or flares. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Polymyalgia Rheumatica (PMR)	24Jan22	Closed	10Feb22	Enquiry from a competent authority (EMA PRAC).	EMA PRAC Assessment Report to PSUR #1 requested MAH to perform a cumulative review on the association between Comirnaty and Polymyalgia Rheumatica exacerbation.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and PMR. An update to product labelling 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
Subacute Thyroiditis (SAT)	18Jan22	Closed	16Feb22	Enquiry from a competent authority (EMA PRAC).	EMA PRAC Assessment Report to PSUR #1 requested MAH to perform a cumulative review on the association between Comirnaty and subacute thyroiditis.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and SAT. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Cerebrovascular Accident (CVA)/Stroke	27Jan22	Closed	02Mar22	Enquiry from a competent authority (Australia TGA).	Australia TGA's Medicines and Vaccines Investigation and Surveillance (MaVIS) Section is reviewing the potential safety risk of cerebrovascular accident (CVA)/stroke with COVID-19 vaccines.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Cerebrovascular Accident/Stroke. An update to product labelling is not warranted at this time. Routine monitoring will continue.
Amenorrhea	14Feb22	Closed	16Mar22	Enquiry from a competent authority (EMA PRAC).	Having considered the available evidence from national reviews (post marketing and published studies), the EMA PRAC has requested that the MAH for COVID-19 mRNA Vaccine Comirnaty should perform a cumulative review of all cases of amenorrhea from all sources.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Amenorrhea. An update to product labelling is not warranted at this time. Routine monitoring will continue. Of note: on 13 June 2022, PRAC recommended that no update to the PI was required as the current evidence was insufficient to warrant an update at this time. However, PRAC requested that an updated analysis of amenorrhoea be included in the next PSUR with DLP 18Dec2022.

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
Heavy Menstrual Bleeding	14Feb22	Closed	16Mar22	Enquiry from a competent authority (EMA PRAC).	Having considered the available evidence from national reviews (post marketing and published studies), the PRAC has requested that the MAH for COVID-19 mRNA Vaccine Comirnaty should perform a cumulative review of all cases of all heavy menstrual bleeding from all sources.	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Heavy Menstrual Bleeding. An update to product labelling is not needed at this time. Routine monitoring will continue. Of note: on 13 June 2022, PRAC recommended that no update to the PI was required as the current evidence was insufficient to warrant an update at this time, however the PRAC also provided a List of Questions and the MAH is in the process of preparing a response by 24 Aug 2022.
Loss of/Altered Taste and Smell	17Mar22	Closed	13Apr22	Enquiry from a competent authority (Australia TGA).	Australia TGA requested an analysis for Comirnaty and loss of/altered taste and smell (including anosmia, ageusia, dysosmia, dysgeusia, parosmia, phantogeusia).	Postauthorization safety data, clinical study safety data, medical literature, O/E analyses.	Based on the totality of data, there is insufficient evidence to conclude a causal association between the vaccine and Loss of/Altered Taste and Smell. An update to product labelling is not warranted at this time. Routine monitoring will continue.

Other safety topics not considered signals

Dizziness

PRAC request 3 from the 2nd Comirnaty PSUSA (procedure EMEA/H/C/PSUSA/00010898/202112):

The MAH is requested to provide a cumulative review of cases reporting dizziness after Comirnaty exposure ***outside the context of anxiety/stress-related reactions*** *(as already labelled in the Comirnaty SmPC section 4.4) and a discussion on the need to add dizziness (including a proposal for the frequency of occurrence) to the ADR table of the Comirnaty SmPC section 4.8, as applicable.*

MAH's response (Appendix 6A.1 of the PSUR):

The Pfizer safety database was searched cumulatively through 18 June 2022 for all BNT162b2 cases of PT Dizziness (MedDRA v. 25.0).

All cases of dizziness

A total of 96,959 cases (with a total of 598,847 events) were retrieved from the global safety database using the search strategy above. The majority of cases (92,849, 96%) were spontaneous; there were 72,597 females, 22,435 males, and sex was not reported in 1927 cases. Most cases were nonserious (64,467; 67%). The most frequently reported age group was 31 to 50 years (40.6%).

When provided, the most frequently reported time to onset (latency) for dizziness in the 96,959 cases was Day 0 (for 32,355 relevant events) and Day 1 (24,941 events) followed by Day 2 (for 6139 events) and Day 3 (for 3201 events).

The high number of dizziness events occurring on the day of vaccination are suggestive of a large proportion of the events of dizziness occurring as a stress-related response to the vaccination process (as currently labelled). In addition, there are a large number of reports with a latency of 1 day after vaccination; this latency data and the co-reported events suggest these reports of dizziness occurred simultaneously or, potentially, as a consequence of, reactogenicity-type events.

Medically-confirmed and serious cases of dizziness

Further analysis was concentrated on the 5563 medically confirmed healthcare professional (HCP) cases (with a total of 41,777 events) in which dizziness was reported as a serious event, and the time to onset (latency) from vaccination was Day 0 (same day) to Day 21 post vaccination.

The majority of this subset of cases (5328, 96%) were spontaneous; there were 4183 females, 1316 males, and sex was not reported in 64 cases. Most of the cases were reported in adults 18-64 years of age. The mean and median ages were 44.7 and 43 years, respectively (n=5426).

Dizziness with Latency Day 0-Day 1

Out of the 5563 cases, 4113 (74 %) reported 4145 serious events of Dizziness (some cases reported the same event more than once) up to 1 day after administration of the vaccine. There were 3223 females, 839 males, and sex was not reported in 51 cases. The mean and median ages were 43.4 and 42 years, respectively (n=4003).

When dose sequence was provided, dizziness followed Dose 1 for 2015 relevant events, Dose 2 for 1207 events, Dose 3 for 223 events, and Dose 4 for 1 event.

The outcomes of dizziness at the time of reporting was resolved/resolving for 2527 events; not resolved for 702 events; resolved with sequelae for 56 events; fatal for 21 events and unknown for 839 events.

Most cases (4063/4113, 99%) had co-reported events; the most frequently co-reported PTs are presented below in Table 5. Similar to the overall dataset of 96,959 cases, these PTs are reactogenicity events and events that are reflective of symptoms of a stress-related response (e.g., to the vaccination process itself).

Table 5. Most Frequently Co-Reported Events in 4113 Cases

PT	Number of Cases
Headache	1472
Nausea	1327
Fatigue	784
Dyspnoea	764
Pyrexia	669
Malaise	617
Asthenia	587
Vomiting	531
Myalgia	481
Chills	459
Tachycardia	427
Anaphylactic reaction	408

Fifty of the 4113 cases reported dizziness as the only event. Out of these 50 cases:

- 18 described pre-existing medical conditions such as previous post-vaccination dizziness, cardiac disorders, vascular disorders, anxiety, diabetes, COVID-19 and migraine and/or use of concomitant medication such as antidepressants, antihypertensives, glucose-lowering agents, and prednisone which may cause or contribute to dizziness.
- 32 provided limited information about medical conditions or medications.

Twenty-one of the 4113 cases described a fatal outcome (15 with a latency of 1 day postvaccination and 6 on the day of vaccination). The age of the patients ranged from 27 to 94, with 11 being 65 years or older; 8 of whom had pre-existing cardiovascular disease or cancer and were on several concomitant medications.

Rapporteur assessment comment:

Out of the retrieved 96,959 cases reporting dizziness through 18 Jun 2022, the MAH focused the analysis on 4113 medically confirmed cases (4.2%) with serious dizziness and a TTO of 0-1 day after Comirnaty exposure. This is problematic because all non-serious cases reporting dizziness (which are considered useful for a non-serious AE like dizziness) are not included in the analysis. The MAH was requested to perform a cumulative review of cases reporting dizziness after Comirnaty exposure outside the context of anxiety/stress-related reactions, which seems not to be performed.

Dizziness with Latency Day 2-Day 21

Out of the 5563 cases, 1450 (26 %) reported 1471 serious events of dizziness (some cases reported the same event more than once) with latency of Day 2 through Day 21 postvaccination. There were 960 females, 477 males, and sex was unknown in 13 cases. The mean and median ages were 48.2 and 48 years, respectively (n=1423).

When dose sequence was provided, it was Dose 1 for 619 relevant events, Dose 2 for 510 events, Dose 3 for 133 events and Dose 4 for 2 events.

The outcome of Dizziness at the time of reporting was resolved/resolving for 679 events; not resolved for 454 events; resolved with sequelae for 37 events; fatal for 22 events; unknown for 279 events. The most frequently reported latency was Day 2 (376 events) followed by Day 3 (227), Day 4 (165) and Day 5 (106).

The most frequently co-reported PTs in these 1450 cases are presented below in Table 7.

Table 7. Most Frequently Reported Events in 1450 Cases

PT	Number of Cases
Headache	548
Nausea	385
Fatigue	351
Pyrexia	221
Dyspnoea	216
Vomiting	216
Asthenia	199
Chest pain	197
Malaise	188

Out of these 1450 cases, the majority (1423, 98%) co-reported additional events that were largely consistent with expected reactogenicity events.

The remaining minority of cases (27, 2%) out of 1450 cases reported dizziness as the only event. In these cases:

- 8 of 27 reported pre-existing medical histories (e.g. diabetes, infections, arthropathy, cardiac failure) and/or concomitant medications (e.g. zopiclone, alpha blockers, antihypertensives, immunosuppressants) that may cause or contribute to dizziness, and
- 21 cases provided limited details about medical conditions or concomitant medications.

There were 22 cases with fatal outcome. The most commonly co-reported PTs in these 22 cases were headache, fatigue, and syncope (5 each). The most commonly reported latency was Day 2 (for 5 Dizziness events) followed by Day 3 (for 4 events). The age of the patients ranged from 50 to 95 years with 14 cases in patients 65 years and older. More than half of these cases reported patients with pre-existing cardiovascular medical conditions on several concomitant medications.

Rapporteur assessment comment:

Out of the retrieved 96,959 cases reporting dizziness, there were 1450 medically confirmed cases (1.5%) with serious dizziness and a TTO of 2-21 days after Comirnaty exposure. Of these 1450 cases there were 1423 cases (98%) that reported co-events which are considered a symptom of a stress-related response to the vaccination process.

Clinical trial data

C4591001

In the placebo-controlled period of pivotal study C4591001 (DLP 13 MAR 2021), there were 166 participants who reported Dizziness; 74/23,037 (0.3%) were in the placebo group and 92/23,040 (0.4%) were in the BNT162b2 group. In the placebo group, 72 out of 74 events were nonserious; all events were non-serious in the BNT162b2 group. The most frequently reported latency in the placebo group were Day 0 (for 11 events) followed by Day 1 (for 8 events). Similar to this, the most frequently reported latency in BNT162b2 group were Day 0 (for 42 events) followed by Day 1 (for 35 events).

C4591031

In the placebo-controlled period of booster study C4591031 sub study A (DLP 08 FEB 2022), there were 25 participants who reported Dizziness; 6/5048 (0.1%) were in the placebo group and 19/5088

(0.4%) were in the BNT162b2 group. In both groups the events of Dizziness were nonserious. In the placebo group the latency was reported as Day 1, Day 14, and Day 31 (for 2 events each). The most frequently reported latency in BNT162b2 group were Day 1 (for 12 events) followed by Day 0 (for 5 events).

C4591007

In the placebo-controlled period of pivotal study C4591007 for the 5 to >12 age group (DLP 06 SEP 2021), there were 2 participants who reported Dizziness (1/750 in the placebo group and 1/1518 in the BNT162b2 group). The reported latency was Day 19 for the event in the placebo group and the same day (Day 0) in BNT162b2 group.

Rapporteur assessment comment:

Pooled in the three placebo-controlled studies there were 112 of the 29,646 (0.38%) participants reporting dizziness in the Comirnaty group and 81 of the 28,835 (0.28%) participants in the placebo group.

MAH's conclusion

In the large Pfizer-run clinical trials, dizziness was not commonly reported. It occurred more frequently in the vaccine groups than placebo groups, however the frequency was < 1% in both groups. Similar to the post-authorization data, the latency tended to be on the day of vaccination or the following day.

Approximately 6% of spontaneously reported BNT162b2 vaccine AE reports are cases reporting dizziness; it is the 11th most reported event for BNT162b2 in the global safety database. The characteristics of the overall number of dizziness cases in this review (96,959) are that they are mostly non-serious, occur on the day of vaccination or the following day, and are co-reported with events that are known to be systemic reactogenicity symptoms. Consistent with the overall BNT162b2 post-authorization database of AE reports, dizziness is reported more frequently in women than men and in adults up to 64 years of age more than any other age population.

Concentration on the most medically significant cases (serious and medically confirmed) shows a similar pattern, with most events occurring within a few days of vaccination and co-reported with events that are recognized reactogenicity events and stress-related responses to the vaccination process.

Based on this review of data, the MAH has determined that dizziness should be considered an adverse reaction to BNT162b2 and will update section 4.8 of the company core data sheet accordingly. Subsequent changes to local labels, including the SmPC will occur per Pfizer process.

Rapporteur assessment comment:

Although the non-serious cases reporting dizziness were excluded from the presented analysis, the MAH states that these cases showed a similar pattern as the serious and medically confirmed cases, occurrence on the day of vaccination or the following day, and are often co-reported with events that are known to be systemic reactogenicity symptoms. Dizziness is reported more frequently in women than men and in adults up to 64 years of age more than any other age population.

Of note, dizziness is stated as an ADR in the product information of Spikevax, Vaxzevria, Jcovden, and Valneva.

Overall MAH's conclusion, that dizziness should be considered an adverse drug reaction to Comirnaty and should be added to the Comirnaty SmPC section 4.8., is endorsed. The PRAC Rapporteur considers a causal relationship between Comirnaty and dizziness is at least a reasonable possibility.

Therefore, in section 4.8 of the Comirnaty SmPC the adverse drug reaction, dizziness, should be added to the ADR table under the SOC Nervous system disorders with a frequency Unknown. The package leaflet should be updated accordingly. The MAH has already submitted a variation (procedure EMEA/H/C/005735/II/0152) to update the PI in this respect.

Acquired haemophilia

PRAC request 4 from the 2nd Comirnaty PSUSA (procedure EMEA/H/C/PSUSA/00010898/202112):

The MAH is requested to provide a cumulative review of cases reporting acquired haemophilia, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccination. The MAH should also provide a comprehensive discussion of the literature, mechanism of action and a discussion on the need to update the product information of Comirnaty, if applicable.

MAH's response (Appendix 6A.2 of the PSUR):

The safety database was searched for all BNT162b2 AE reports with the Preferred Terms under the Higher-Level Term of Coagulation factor deficiencies received cumulatively to 18 June 2022.

A total of 68 cases were retrieved, 51 were spontaneous reports, 4 were from non-interventional studies and 13 were from literature reports. All the 68 cases were assessed as serious.

Gender was reported in 64 cases (32 males and 32 females), while 4 cases did not specify the gender. Sixty-three (63) cases reported an age, which ranged from 25 years to 97 years (mean: 74.59, median: 77). Consistent with known information on acquired hemophilia, the large majority of cases are in patients ≥65 years of age (79.3%).

France reported 23 cases, Italy reported 14 cases while Japan reported 5 cases. The top 10 countries reporting cases of acquired hemophilia are shown below (Table 2).

Table 2. Top 10 Countries

Country	Number	Percentage
France	23	34%
Italy	14	21 %
Japan	5	7.4 %
Switzerland	4	5.9 %
United Kingdom	4	5.9 %
Australia	3	4.4 %
Finland	3	4.4 %
Ireland	2	2.9%
Malaysia	2	2.9 %
United states	2	2.9 %

All 68 cases reported an event of Acquired Hemophilia. Other adverse event PTs co-reported in the cases included anemia (13), hematoma (11) spontaneous hematoma (6), hemorrhage (5), contusion (4), mouth hemorrhage (3), hematuria (3), ecchymosis (3), hemoglobin decreased (3), factor VIII deficiency (3), hemorrhagic shock (2).

Sixty-four (64) of the cases were medically confirmed while the remaining 4 were non medically confirmed.

Seventeen (17) of the 68 cases occurred after the first dose, 33 cases reported onset after the second dose, 8 cases reported onset after the third dose and the dose was not reported in the remaining 10 cases.

Case outcome was reported as follows: recovering/recovered (29), not recovered (25), fatal (6) and unknown (8).

Rapporteur assessment comment:
Post-marketing through 18 Jun 2022, a total of 68 cases reporting acquired hemophilia were retrieved. France and Italy reported most cases, 23 (34%) and 14 (21%) respectively.

Fatal case reports

1. A 90-year-old male received the first dose of BNT162b2 on 23 March 2021. Medical history included diabetes, stroke, obstructive arteriosclerosis of lower extremities, chronic renal failure and COVID-19. The patient's concomitant medications were not reported. Information on subsequent doses were not reported. He experienced acquired hemophilia 88 days after the first dose. Lab findings included aPTT. He was hospitalized on an unspecified date in July 2021 for hemorrhagic syndrome. Therapy included prednisone, multiple transfusions for digestive hemorrhage and discontinuation of antiaggregant and anti-vitamin K recently introduced for atrial fibrillation. The patient died on an unspecified date in 2021. Cause of death and autopsy were not reported.

MAH comment: Diabetes mellitus and chronic renal failure in this patient could be confounders for acquired hemophilia. The patient's age and history of Covid-19 could also be contributory. The latency of 88 days following dose 1 and no documentation of a 2nd dose call into question the latency feasibility. Concomitant medications were not reported.

2. A 90-year-old female patient received the first dose of BNT162b2 on 25 February 2021. Her medical history included hypertension, aortic stenosis, heart failure, gout, and chronic renal failure. Concomitant medications included zopiclone, bisoprolol, furosemide, allopurinol, and paracetamol. After 14 days the patient experienced atrial fibrillation, decreased hemoglobin, hematoma, oral mucosa bleeding, malaise, an increased tendency to bruise, acquired hemophilia and aggravated cardiac failure. Patient was hospitalized and lab showed positive Anti-factor VIII antibody. Treatment with prednisolone was initiated. On 17 April patient experienced worsening heart failure, atrial fibrillation, and kidney problem. The patient died on [redacted] 2021.

MAH comment: This patient's elderly age and paracetamol use are known risk factors for Acquired Hemophilia. Multiple comorbidities in this patient could also be contributory.

Rapporteur assessment comment:
MAH's comment is endorsed, other causes appear more likely.

3. An 84-year-old female received a second dose of BNT162b2 on 08 April 2021. The patient's medical history and concomitant medications were not reported. Two days post vaccination, the patient experienced acquired hemophilia A, with spontaneous, superficial, and deep hematomas and significant anemia reported. Relevant lab tests included partial thromboplastin time of 65.3 seconds, Factor VIII at 1%, and positive lupus like anticoagulants. Treatment was with steroids, cyclophosphamide, vitamin k and blood transfusions. The patient died on [redacted] 2021, and the cause of death was reported as acquired hemophilia, anemia, and spontaneous hematoma.

MAH comment: There is limited information on this patient's medical history and concomitant medication that may be contributing factors to the development of AH in addition to her elderly age.

Rapporteur assessment comment:

MAH's comment is endorsed, limited information for causality assessment.

4. A 67-year-old male received the second dose of BNT162b2 on 22 April 2021. Relevant medical history included rheumatoid arthritis, Crohn's disease and pulmonary legionellosis. Concomitant medications included Duragesic, prednisone, Spiriva, indacaterol and pentasa. On [redacted] 2021, patient experienced a fall at home, with diffuse hematomas. Three days later he was brought to the ER due to a deteriorating general condition and vomiting and was assessed to have hemorrhagic shock associated with acute renal failure and acquired hemophilia type A. One day after hospitalization the patient experienced sudden deterioration with onset of coma, and the following day he died from cardio-respiratory arrest.

MAH comment: Crohn's disease and rheumatoid arthritis are confounders for acquired hemophilia. In addition, this patient's traumatic fall likely contributed to his deteriorating condition.

Rapporteur assessment comment:

MAH's comment is endorsed, other causes more likely.

5. A 77-year-old man received his second dose of BNT162b2 on 28 June 2021. He reported a medical history of relapsed bladder carcinoma. He was hospitalized for hematuria, 21 days after vaccination. Hemoglobin concentration was 66 g/L, activated partial thromboplastin time was increased (3.61 ratio) and FVIII:C (Factor VIII procoagulant activity) was 0.02 IU/mL with detectable inhibitor (6.9 Bethesda Units/mL). Treatment was with methylprednisolone, recombinant activated clotting Factor VII and rituximab. However, during the hospital stay the patient developed sepsis and died from respiratory complications seven weeks after admission.

MAH comment: Bladder carcinoma in this patient could be a confounder for acquired hemophilia seen in this patient.

Rapporteur assessment comment:

MAH's comment is endorsed, other cause more likely.

6. A 97-year-old female patient received the third dose of BNT162b2 on 28 October 2021. Her medical history and concomitant medications were not reported. The patient had received the first dose on 22 February 2021 and the second dose on 15 March 2021. The patient experienced acquired hemophilia, extensive muscle hematoma, and severe anemia 18 days post vaccination. Laboratory tests revealed prolonged aPPT, Anti-factor VII antibody, Factor VIII deficiency, and Anti-factor VIII circulating inhibitor. Therapeutic measures included corticosteroids, rituximab, and concentrated red blood cell transfusion. The patient died on [redacted] 2022, with cause of death not reported.

MAH comment: Elderly age is a risk factor in this patient. There is limited information on medical history and concomitant medication which precludes a meaningful medical assessment.

Rapporteur assessment comment:

MAH's comment is endorsed, limited information for causality assessment.

Rapporteur assessment comment:

Overall in the reported total of 6 fatal cases, there were 4 cases with other causes that more likely could have caused acquired hemophilia and 2 cases with too limited information to perform a meaningful causality assessment.

The remaining 62 cases are summarized below:

- 40 cases reported one or more relevant medical history or concomitant medications that could confound the event of acquired hemophilia in these patients,
    - 13 cases reported diabetes mellitus,
    - 11 cases reported cancer/neoplasm: breast cancer, prostate cancer, unspecified cancer, renal neoplasm, diffuse large b-cell lymphoma, laryngeal carcinoma, lung adenocarcinoma,
    - 6 cases reported autoimmune diseases: Giant cell arteritis, rheumatic fever, rheumatoid arthritis, Sjogren's disease, granulomatosis with polyangiitis, sarcoidosis,
    - 3 cases reported hypothyroidism,
    - 3 cases reported asthma or broncho-pneumopathy,
    - 2 cases reported polymyalgia rheumatica,
    - 2 cases reported previous history of Acquired hemophilia,
    - 1 case reported history of myelodysplastic syndrome,
    - 1 case reported angiodysplasia,
    - 1 case reported COVID-19,
    - 14 cases reported use of concomitant medications such as acetaminophen, olanzapine, apixaban, acetylsalicylic acid, levothyroxine, risperidone, chlorpromazine and levomepromazine.
- 18 cases had limited information on medical history, concomitant medication, time to onset, dose number and schedule, and clinical information surrounding the event precluding a meaningful medical assessment.

Rapporteur assessment comment:

The MAH reports that 18 of the 62 remaining cases had limited information. However, details of these 18 cases were not presented and hampers PRAC rapporteur's assessment of these 18 cases.

Furthermore, there is no information if the cases were tested positive or negative for SARS-CoV-2 infection.

The remaining 4 cases are described below:

1. An 84-year-old male received his second dose of BNT162B2 on 06 May 2021. Medical history included transient ischemic attack, lumbago, arterial hypertension. The patient's concomitant medications were not reported. Twenty-five days after the second dose, the patient experienced acquired hemophilia with multisite hemorrhagic anemia: retroperitoneal and psoas muscle hematoma. Therapy was started with eptacog-alfa, prednisone, cyclophosphamide and suspended on 30 June 2021 due to the onset of severe isolated thrombocytopenia. Outcome was not reported.

MAH comment: This patient's age is a potential risk factor for AH. There is insufficient information on concomitant medication, confirmatory lab test and details surrounding the event.

Rapporteur assessment comment:
MAH's comment is endorsed, limited information for causality assessment.

2. A 67-year-old man received the second dose of BNT162b2 on 16 Jun 2021. His medical history was unremarkable. He was admitted to the Emergency Room for urgent otolaryngological assessment due to a large hematoma of the tongue, extending in the cervical region. Hemoglobin concentration was 125 g/L, the aPTT ratio was 2.55, FVIII:C (factor VIII procoagulant activity) was 0.06 IU/mL with detectable anti-FVIII activity (2.5 Bethesda Units/mL). Recombinant activated clotting Factor VII, cyclophosphamide and prednisone was administered. Outcome of the event was reported as recovered.

MAH comment: Although this patient did not have a prior relevant history, there is insufficient information on the time to onset, concomitant medication and clinical details preceding the event.

Rapporteur assessment comment:
MAH's comment is endorsed, limited information for causality assessment.

3. An 86-year-old female patient received the first dose of BNT162b2 on 22 June 2021. The patient's medical history included coronary artery bypass. The patient reportedly took aspirin. She experienced acquired hemophilia 11 days after the first dose, which was described as multiple subcutaneous hemorrhages and bleeding tendency. The aspirin was stopped, but it is unclear if the bleeding subsided, with bleeding stoppage described as "not good". On 13 July 2021, the patient received the second dose, and subcutaneous hemorrhage and muscle hemorrhage appeared. Fifteen days after the second dose, the patient was hospitalized and laboratory tests revealed prolonged aPTT with an inhibitor pattern in the cross-mixing test, low factor VIII activity and a diagnosis of acquired hemophilia was made. Outcome of the event was reported as not recovered.

MAH comment: Elderly age in this patient is a risk factor. Aspirin use could also be contributory to the event of Acquired hemophilia.

Rapporteur assessment comment:
Although the case reported a rechallenge of complaints after the 2nd Comirnaty dose, it is not clearly stated if there was Aspirin use. Therefore MAH's comment is endorsed, other causes could be possible.

4. A 25-year-old female patient received second dose of BNT162b2 on 18 August 2021. The patient's first dose was on 17 July 2021. Medical history included obesity treated with bariatric surgery in December 2020, cholecystectomy, appendectomy and active smoking. Familial history included phlebitis in a cousin, no autoimmune disease, no first-degree venous thromboembolism. The patient previously took lovavulo (oral contraceptive) and vitamin B12 and experienced digestive intolerance. On 28 August 2021, 10 days after vaccination the patient visited the emergency room for pain in the right leg, edema and multiples bruises, the patient has reportedly had the symptoms for one month. Lab test revealed anti-FVIII antibodies and assessment of acquired hemophilia A. Outcome was not reported.

MAH comment: Acquired hemophilia is more common in young females especially during pregnancy or post-partum period, however there is limited information on this patient's obstetric history. In addition, time of onset of acquired hemophilia is unclear.

Rapporteur assessment comment:

MAH's comment is endorsed, limited information for meaningful causality assessment.

Rapporteur assessment comment:

Overall in the remaining 62 cases:

- there were 40 cases reported one or more relevant medical history or concomitant medications that could confound the event of acquired hemophilia;
- there were 18 cases had limited information event precluding a meaningful medical assessment, however lack of details hampered the PRAC rapporteur's assessment;
- there were 4 cases with limited information for meaningful causality assessment.

No information was providied if the cases were tested positive or negative for SARS-CoV-2 infection. However, the MAH is requested to inform the PRAC rapporteur immediately if there are more supportive acquired hemophilia cases after Comirnaty exposure.

Clinical trials

There were no cases of acquired hemophilia reported in the pivotal Pfizer-led clinical trials.

Literature

There were no relevant literature articles other than literature case reports which are reviewed in the post marketing section.

Observed versus expected analysis

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 68 acquired hemophilia cases reported cumulatively through 18 June 2022 globally. The overall expected case counts were estimated using background incidence rates (IR) reported by a surveillance study of patients treated for acquired hemophilia in hematology departments covering all National Health Service hospitals in the UK during 1 May 2002 – 30 April 30 2003. This study was selected because in a literature review, the MAH found that this figure of 1.5 cases per million is widely cited for acquired hemophilia incidence and is in the low end of the range of 1 to 4 cases per million reported by a review article.

Table 3. Observed to Expected (O/E) Ration for Spontaneously Reported Cases of Acquired Hemophilia Through 18 June 2022

Stratification	Observed cases	Time at risk (PY)	Background rates per 100,000 PY	Expected cases	O/E ratio	95% CI LL	95% CI UL
21-day risk window							
US/EEA							
≤11 years	0	1,917,834	0.005	0.09	0.000	-	-
12-17 years	0	3,324,066	0.017	0.57	0.000	-	-
18-24 years	0	4,733,892	0.029	1.37	0.000	-	-
25-49 years	2	19,546,111	0.029	5.67	0.353	0.043	1.275
50-59 years	0	9,025,268	0.029	2.62	0.000	-	-
60-69 years	2	7,901,305	0.310	24.49	0.082	0.010	0.295
70+ years	18	10,962,290	1.032	113.08	0.159	0.094	0.252
Overall Global	34	127,075,389	0.150	190.61	0.178	0.124	0.249
42-day risk window							
US/EEA							
≤11 years	0	2,779,982	0.005	0.13	0.000	-	-
12-17 years	0	5,127,186	0.017	0.87	0.000	-	-
18-24 years	0	7,477,185	0.029	2.17	0.000	-	-
25-49 years	2	30,991,113	0.029	8.99	0.223	0.027	0.804
50-59 years	1	14,461,569	0.029	4.19	0.238	0.006	1.329
60-69 years	7	12,856,855	0.310	39.86	0.176	0.071	0.362
70+ years	24	17,896,776	1.032	184.61	0.130	0.083	0.193
Overall Global	50	203,986,419	0.150	305.98	0.163	0.121	0.215

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 18 June 2022, O/E ratios were well below one overall and by age for both risk windows of 21- and 42-days. This suggests that the number of observed cases is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines overall and within the queried strata.

Rapporteur assessment comment:

All O/E ratios are well below 1.

MAH's conclusion

Consistent with the rarity of the disorder, the search of the clinical trial database did not reveal any cases of acquired hemophilia. The medical literature search results were of case reports (included in the safety database analysis), but no larger, population level studies were retrieved.

The search of the safety database identified 68 cases, all reported as serious. Of the 68 reports, 40 cases included details in the medical history regarding medical conditions and diseases under treatment that could predispose to developing acquired hemophilia (cancer, rheumatoid arthritis, chronic kidney failure, nephroangiosclerosis, diabetes mellitus and hypothyroidism). Six cases reported fatal outcomes (4 of them were confounded by medical history and 2 had age-related risk factors and limited information on medical history). A further 18 cases had insufficient information on medical history and concomitant medications to conduct a thorough assessment. In the remaining 4 cases, although some clinical details were provided, 3 cases had age-related risk factors and history of aspirin use, while the remaining case, in a 67-year-old man, lacked clear information on concomitant

medication and time to onset to make a conclusive medical assessment. Fifty-four (54) (79%) of the 68 cases occurred in elderly patients greater than 65 years, who are the most predisposed to developing acquired hemophilia, with many of these patients having associated comorbidities.

The ratios of observed to expected cases were less than one overall and by age for both the 21- and 42-days risk windows.

Overall, the totality of data does not support a causal association between vaccination and acquired hemophilia and there is no need to update the product information at this time. Routine monitoring will continue.

Rapporteur assessment comment:

Post-marketing

Out of the retrieved 68 cases reporting acquired hemophilia through 18 Jun 2022:

- there were 6 fatal cases, of which 4 cases reported other causes that more likely could have caused acquired hemophilia and 2 cases with too limited information to perform a meaningful causality assessment.
- there were 40 cases reported one or more relevant medical history or concomitant medications that could confound the event of acquired hemophilia,
- there were 18 cases had limited information event precluding a meaningful medical assessment,
- there were 4 cases with limited information for meaningful causality assessment.

Clinical trials

There were no cases of acquired hemophilia in clinical trials. However, clinical trials are not designed to capture rare adverse events.

Literature

There were 13 literature cases reports, which were reviewed in the post-marketing section.

O/E analysis

Alle O/E ratios were well <1.

Overall MAH's conclusion is endorsed, that the data does not support a causal association between Comirnaty exposure and acquired hemophilia. However, the MAH is requested to inform the PRAC rapporteur immediately if there are more supportive acquired hemophilia cases after Comirnaty exposure.

MIS-C/-A

Introduction (Appendix 6A.4 of the PSUR)

In August 2021, the European Medicines Agency (EMA) issued a signal assessment report on Multisystem inflammatory syndrome in children (MIS-C) with SARS-CoV-2 vaccination and requested all Market Authorization Holders (MAH) of these vaccines perform cumulative review of MIS- C and Multisystem inflammatory syndrome in adults (MIS-A).

A cumulative review of cases reported within Pfizer's global safety database was performed with a data lock point (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 Pfizer's assessment the Pharmacovigilance Risk Assessment Committee (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 Monthly Summary Safety Report (MSSR) and Periodic safety update report (PSUR). Cases were requested to be assessed using the Brighton Collaboration (BC) case definition1 with MIS-C defined as patients age < 21 years and MIS-A those age ≥ 21 years.

Interval cases have subsequently been analyzed and discussed in the following documents:

- MSSR #11 (interval 03 September through 26 October 2021),
- Summary bimonthly safety report (SBSR) #1 (interval 27 October through 15 December 2021),
- Periodic Safety Update Report #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).

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. The following MedDRA version 25.0 Preferred Terms (PTs) were used: 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.

Methodology

The safety database was searched for all BNT162b2 cases reported in the interval 18 December 2021 through 18 June 2022.

Results

One hundred and ninety-nine (199) case reports for this reporting period were retrieved using the above method. Of these cases 49 occurred in patients aged less than 21-years-old and were classified in consideration of MIS-C, 142 occurred in patients aged greater than or equal to 21 years and were classified in consideration of MIS-A. In 8 cases no age was reported and 7 of which provided such limited information as to preclude a meaningful analysis of the case.

MIS-C

In 2 of the 49 cases considered for MIS-C limited clinical information was reported precluding an analysis of the case per the BC criteria. The remaining 47 cases were classified as per Table 1.

Table 1. BC classification of potential MIS-C cases

BC level	Number of cases
1	10
2	5
3	3
4	26
5	3

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 47 potential new MIS-C cases. Of these, 10 were classified as BC level 1, 5 as BC level 2, 3 as BC level 3, 26 as BC level 4, and 3 as BC level 5.

Of the 10 BC level 1 MIC-C cases, 4 cases were previously assessed in the 13th SSR (16 Dec 2021-15 Feb 2022) (AER numbers [redacted], and 6 cases were previously assessed in the 14th SSR (16 Feb 2022-15 Apr 2022) (AER numbers [redacted]).

The 8 cases that were classified as BC level 2 (probable MIS) and 3 (possible MIS) have not been reproduced in this AR. These were all either considered confounded by previous COVID-19 infection, no information was provided on previous COVID-19 infection or this information was incomplete.

Therefore the previous PRAC conclusion in the 14th SSR (procedure EMEA/H/C/005735/MEA/002.13) remains valid, i.e. that the data is currently insufficient to support regulatory action and therefore no update of the product information in relation to MIS-C is currently warranted. Although one additional MIS-C BC level 1 case (AER number [redacted] literature case from [redacted] that occurred in an 16-year old male) besides the Danish index case that was considered probably related with Comirnaty was identified, this is given the extensive exposure of Comirnaty (in children) not to be considered unexpected and does not present a new safety concern.

MIS-A

One hundred and forty-three (142) cases were in patients aged greater than or equal to 21 years and were classified in consideration of MIS-A. Twelve cases reported insufficient information to assess the case. Table 5 demonstrates the BC level classification of the remaining 130 cases.

Table 5. BC classification of potential MIS-A cases

BC level	Number of cases
1	1
2	1
3	0
4	34
5	94

Rapporteur assessment comment:

During the reporting period, the MAH identified a total of 130 potential new MIS-A cases. Of these, 1 was classified as BC level 1, 1 as BC level 2, 0 as BC level 3, 34 as BC level 4, and 94 as BC level 5.

The case classified as BC level 1 (AER number [redacted] is new and discussed below.

In the 14th SSR (16 Feb 2022-15 Apr 2022) (procedure EMEA/H/C/005735/MEA/002.13) there was reported another BC level 1 MIS-A (AER number [redacted] which was considered confounded and therefore unlikely to be associated with Comirnaty. However, this case seems not to be retrieved in current safety database search.

The case classified as BC level 2 was previously assessed in the 13th SSR (16 Dec 2021-15 Feb 2022) (AER number [redacted] and considered to be confounded by previous COVID-19 infection and causality is therefore considered unlikely.

BC level 1 case: AER # [redacted]

50-year-old female, case reported in the literature from [redacted].

The patient was hospitalized with fever, myalgia and shortness of breath approximately 2 weeks after dose 2 of BNT162b2 and antibiotics were administered. She was subsequently hospitalized approximately 6 weeks after dose 2 with persistent fever, widespread rash, proteinuria, and hyperferritinemia.

She developed pulmonary edema which required non-invasive mechanical ventilation. In addition to the persistent fever she developed seizures. Cerebrospinal fluid (CSF) analysis and magnetic resonance imaging of the brain were "noncontributory", and no evidence of infectious foci were observed serologically or microbiologically.

Her past medical record was significant for a childhood history of meningitis. She described no COVID-19 symptoms before presentation. Polymerase chain reaction (PCR) tests for SARS-CoV-2 were negative on multiple occasions. Physical examination showed widespread salmon-coloured rashes on her trunk and extremities.

C-reactive protein (CRP) of 286 mg/L, erythrocyte sedimentation rate (ESR) of 70 mm/h, ferritin of over 100,000 ng/ml (reference range (RR): 13-150), hemoglobin of 10.2 g/dl (RR: 11.9-14.6), aspartate aminotransferase of 594 U/L (RR: 0-33), alanine aminotransferase of 141 U/L (RR: 0-35), lactate dehydrogenase of 3,494 U/L (RR: 135-214), serum albumin of 3.0 mg/dl (RR: 3.5-5), creatinine of 1.0 mg/dl (RR: 0.4-0.98), D-dimer of 9.28 mg/l (RR: 0-0.5), fibrinogen of 289 mg/dl (RR: 170-420), proteinuria of 1.8 g/day, and serum proBNP of 10,522 pg/ml (RR: 0-125) with normal cardiac enzymes.

Echocardiography showed left ventricle systolic dysfunction and mild pericardial effusion.

Antinuclear antibody and rheumatoid factor were negative, bone marrow examination was unremarkable, and SARS-CoV-2 immunoglobulin (IgG) antibody levels were positive.

MIS - thought to be related to vaccine was considered and methylprednisolone was initiated. Persistent fever and high ferritin (>100,000) resulted in anakinra (Interleukin-1 receptor antagonist) being added to the treatment. The patient was discharged at day 21 after clinical and laboratory improvement and remains in remission on anakinra and low dose methylprednisolone.

MAH comment: The case is classified as BC level 1 based on the presence of persistent fever, mucocutaneous (rash) and neurological (seizures) clinical features, elevated inflammatory markers and 2 markers of disease activity (elevated proBNP and echocardiogram findings). The authors discount differential diagnoses of macrophage activation syndrome (discounted on normal bone marrow examination) and adult-onset Still's disease (AOSD) although they feel the pulmonary oedema and cardiac failure are atypical. Many of the features described in the report are compatible with a diagnosis of AOSD; of note pleuritis and pericarditis are commonly described, and a biological hepatitis can be seen in up to 60% of patients. Myalgias are also common, particularly associated with fever spikes. The authors also consider MIS-A secondary to COVID-19 unlikely on the basis of a full vaccination history, presence of IgG antibodies, a negative SARS-CoV-2 PCR and a lack of COVID-19 symptoms preceding the illness. Of note it is unclear if the antibodies are anti-N or anti-S. Although providing sufficient clinical detail to classify the case as BC level 1 there is a notable lack of detail regarding the patient's complete blood count.

Rapporteur assessment comment:

Although MAH's comment is acknowledged, the presented MIS-A case is considered a BC level 1 case and considered probably related with Comirnaty. However, a coincidental finding cannot be excluded either, given the extensive exposure of Comirnaty in adults.

MAH's conclusion

In summary, 199 cases were reviewed for potential MIS for the PSUR period 19 December 2021 through 18 June 2022; 18 cases were classified as BC Level 1-3 MIS-C cases and 2 as BC level 1-3 MIS-A cases. As highlighted in the individual case commentaries, in the majority of cases there are either confounding elements or important clinical detail is missing which would facilitate causality assessment.

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

Rapporteur assessment comment:

MIS-C

During the reporting period, the MAH identified a total of 47 potential new MIS-C cases. Of these, 10 were classified as BC level 1, 5 as BC level 2, 3 as BC level 3, 26 as BC level 4, and 3 as BC level 5.

The 10 BC level 1 MIC-C cases were previously assessed in the 13th SSR and the 14th SSR (procedures (procedure EMEA/H/C/005735/MEA/002.13).

Therefore the previous PRAC conclusion in the 14th SSR (procedure EMEA/H/C/005735/MEA/002.13) remains valid, i.e. that the data is currently insufficient to support regulatory action and therefore no update of the product information in relation to MIS-C is currently warranted. Although one additional MIS-C BC level 1 case (AER number [redacted], literature case from [redacted] that occurred in an 16-year old male) besides the Danish index case that was considered probably related with Comirnaty was identified, this is given the extensive exposure of Comirnaty (in children) not to be considered unexpected and does not present a new safety concern.

MIS-A

During the reporting period, the MAH identified a total of 130 potential new MIS-A cases. Of these, 1 was classified as BC level 1, 1 as BC level 2, 0 as BC level 3, 34 as BC level 4, and 94 as BC level 5.

The presented BC level 1 MIS-A case is considered probably related with Comirnaty, due to the absence of other etiologies or confounding. However, given the extensive exposure of Comirnaty in adults this is not considered unexpected and does not present a new safety concern.

Another BC level 1 MIS-A (AER number [redacted] reported by the MAH in the 14th SSR (interval period 16 Feb 2022-15 Apr 2022) was considered confounded by previous COVID-19 infection and therefore unlikely to be associated with Comirnaty. However, this case seems not to be retrieved in current safety database search. The MAH is requested to explain why the BC level 1 MIS-A case (AER number 202200572949) from the 14th SSR was not included in current MIS-A overview (interval period 19 Dec 2021 to 18 Jun 2021). **Request for supplementary information**

No new important information could be identified concerning MIS-C/-A. The MAH should continue to closely monitor this safety issue as outlined in PRAC's signal recommendation (EPITT 19732) and all new cases of MIS-C/-A should be reported in the future PSURs. **Request for next PSUR**

Autoimmune hepatitis (AIH)

PRAC request from the signal procedure concerning autoimmune hepatitis (EMEA/H/C/005735/SDA/042- EPITT 19749):

The MAH should provide in the next PSUR (submission date 27 August 2022) a cumulative review of all cases of autoimmune hepatitis, including any relevant new data, from all available sources. The cumulative review should include, but not be limited to, data from clinical trials, post-marketing cases and any relevant articles from literature, using a data lock-point as recent as possible.

MAH's response (Appendix 6A.5 of the PSUR):

The safety database was searched for all BNT162b2 AE reports reporting PT: Immune-mediated hepatic disorder, Immune-mediated hepatitis, or Autoimmune hepatitis, cumulatively to 18 June 2022 using MedDRA version 25.

Results

A total of 194 cases (and 920 events) were retrieved from the global safety database with the search criteria mentioned above. There were 124 (63.9 %) females, 67 (34.5%) males and for 3 cases sex was not reported. Age was reported as ranging from 10 to 91 years (mean: 54.3, N: 187). There were 9 cases with age below 17 years, there were 111 cases within the adult category (≥18- <65 years), 67 elderly (≥65 years) and age was not reported in 7 cases. All cases were assessed as serious. Case outcome was reported as recovered, recovering, or recovered with sequelae in 93 cases; no outcome was reported at the time of reporting in 75 cases; outcome was unknown in 23 and fatal in 3 cases. The cases were reported mostly by Germany (57, 29.4%), Japan (23, 11.9%), UK (21, 10.8%) and France (21, 10.8%).

Medical history (MH) was reported in 111 out of 194 cases. Among these 111 cases, 21 described events consistent with liver disorders (of which 9 co-reported other underlying autoimmune diseases), an additional 27 cases reported underlying autoimmune diseases (other than autoimmune hepatitis), 10 reported underlying cancer and 5 reported cholecystic disorders. A total of 169 of the 194 cases reported which vaccine dose was administered prior to the relevant adverse event (Table 2).

Table 2. Vacine dose administered

Dose	Number of cases
1	44
2	95
3	29
4	1
Unknown	25
Total	194

Time to onset was reported in 99 of the 194 cases and ranged between the same vaccination day up to 202 days post vaccination (mean: 22.8; median: 21; N: 99). Table 3 report details on the time to onset.

Table 3. Time to onset

Days	Number of cases
0-2	9
3-7	29
8-15	26
16-30	34
>30	57
Not reported	39
Total	194

A total of 60 of the 194 cases reported biopsy results, 39 cases did not report biopsy results but reported either viral markers/serum IgG or autoantibodies and 95 cases did not report any result of laboratory or diagnostic tests and therefore do not allow a proper assessment of the event.

Rapporteur assessment comment:

Post-marketing through 18 Jun 2022, 194 cases reporting autoimmune hepatitis were retrieved. A TTO of 3-30 days after Comirnaty exposure was reported in 89 of the 194 cases.

No results of laboratory or diagnostic tests was reported in 95 cases and did not allow a proper assessment of the event.

Biopsy results were reported in 60 cases and laboratory data only were reported in 39 cases.

Cases with liver biopsies and/or laboratory data

The International Scoring System for Diagnosis of Autoimmune Hepatitis and the Simplified criteria for the diagnosis of autoimmune Hepatitis were used when the data was provided.

The 99 cases reporting information (60 reporting biopsy results and 39 cases reporting laboratory examination were further analyzed based on diagnostic criteria for autoimmune hepatitis and divided in 2 groups:

1. Cases with reported liver biopsy results (n: 60)

   Medical History was not reported in 43 cases, 17 did not report medical history, 11 autoimmune diseases, 8 pre-existing liver disorders, 5 ongoing cancers, 1 reported as substance use, 1 post-partum, 1 BRCA1 gene mutation, 15 did not report relevant MH to liver issues. Please note that one subject may have reported more than 1 of the MH events described above.

   Most cases reported the event after dose 2 (Table 4).

Table 4. Number of cases by dose in subjects that had liver biopsy

Dose	Number of cases
1	15
2	30
3	9
4	1
Unknown	5
Total	60

   Time to onset ranged from the day of vaccination to 202 days after vaccination (Table 5).

Table 5. Number of cases by time to onset

Days	Number of cases
0-2	4
3-7	10
8-15	10
16-30	9
>30 (from 31 to 202)	20
Not reported	7
Total	60

   None of the cases provided sufficient information to use the International AutoImmune Hepatitis Group (IAIHG) revised scoring system for diagnosis of autoimmune hepatitis. However, 7 cases reported this score in the narrative. (Table 6, not reproduced here):

   - These 7 cases had IAIHG-revised scores that ranged from 12 to 20. Six of the 7 cases are females, who are at increased risk of developing autoimmune disorders

such as AIH. Two of the 7 reports describe times to onset that suggest an unlikely association with vaccination (58 and 61 days). Of the remaining 5 cases, 2 had at least one other autoimmune disorder, suggesting a propensity for the development of AIH, and the remaining 3 did not provide any information about past medical history or concomitant medication use.

Although none of the remaining 53 cases with liver biopsies provided sufficient information for the IAIHG-revised scoring system, they were assessed using the IAIHG 4 simplified diagnostic criteria (1. positivity for autoantibodies, 2. elevated IgG levels, 3. Histological evidence of interface hepatitis and 4. the exclusion of viral hepatitis) by Hennes EM et al 2008. With this simplified criterion, a score of 7 is considered definite AIH and 6 is probably AIH (Table 7, not reproduced here):

- In these 9 cases assessed as having an IAIHG-simplified score of ≥6, 4 described a time to onset inconsistent with temporality to vaccination (31 days to 202 days). Three of the remaining 5 cases do not provide medical history or concomitant medication details. One of the remaining 2 cases describes the presence of EBV which is an alternative etiology for hepatitis.

The remaining 44 cases were assessed as having an IAIHG-simplified score <6 and are described below (subjects may have 1 or more of the following characteristics):

- In 15 cases, time to onset was not suggestive of a temporal relationship with vaccination (13 cases reported the time to onset between 31 to 90 days post vaccination (mean: 51 days); 11 of these 15 cases also lacked medical history or concomitant medication information, hampering a proper medical assessment,
- In 8 cases, an underlying autoimmune disorder was reported in medical history suggesting a predisposition to autoimmunity (e.g. thyroiditis, multiple sclerosis, pericarditis, coeliac disease and diabetes mellitus),
- In 6 cases, evidence of an underlying infection was described (e.g., EBV, CMV, herpes, tick bite on antibiotic treatment) suggesting an alternate etiology of hepatitis,
- In 4 cases, subjects had a pre-existing hepatic disorder (e.g. Autoimmune hepatitis, hepatitis C, chronic cholangitis),
- 4 subjects were undergoing treatment for cancer raising the possibility of drug-induced liver injury,
- In 3 cases, the reported time to onset was too close to vaccination (same vaccination day or the day after) for reasonable attribution,
- 1 case described illicit drug use which can cause hepatic dysfunction,
- 1 case was reported as post-partum raising the possibility of post-partum autoimmune hepatitis,
- 1 case was reported as hepatitis secondary to use of the immune checkpoint inhibitors.

One case reported a fatal outcome, the case is summarized below:

[redacted]: 74-year-old female patient received BNT162b2 (COMIRNATY), dose 2 on 14 May 2021. Medical history included ongoing obesity, cholecystectomy, nephrectomy, bypass

surgery, ongoing non-alcoholic steatohepatitis. Concomitant medications included calcium, colecalciferol, atorvastatin, paracetamol, oral acetylsalicylic acid. The same vaccination day the subject experienced fatigue and 3.5 months later was hospitalized for pneumonia, autoimmune hepatitis, circulatory collapse, respiratory failure, hepatotoxicity (all with onset 75 days after vaccination). The patient was found to have liver enzyme elevation. An abdominal ultrasound showed steatosis and minimal ascites. A liver biopsy showed acute and chronic inflammation with bridging necrosis and newly gracil fibrosis and non-steatotic liver disease. Drug/immunological reaction, AIH or viral hepatitis were suspected as was cirrhosis. Hepatitis B, C, E virus tests were negative; Hepatitis A antibody: IgG positive, IgM negative; Immunoglobulins: Normal; Smooth muscle antibody, Anti-cyclic citrullinated peptide antibody: Positive; Mitochondria antibody: Negative. The patient date of death was [redacted] 2021 and was reported to be due to pneumonia, circulatory collapse, respiratory failure, autoimmune hepatitis. An autopsy was not performed.

Rapporteur assessment comment:

Of the 60 cases reporting biopsy results there were:

- 7 cases with an IAIHG-revised scores that ranged from 12 to 20:
  - 2 cases had a TTO > 30 days (unlikely association with vaccination),
  - 2 cases had at least one confounding by underlying conditions,
  - 3 cases had no information on medical history or concomitant medication use.
- 9 cases with an IAIHG-simplified score of ≥6:
  - 4 cases had a TTO > 30 days (unlikely association with vaccination),
  - 5 cases had no information on medical history or concomitant medication use.
- 44 cases with an IAIHG-simplified score <6:
  - 15 cases had a TTO > 30 days (unlikely association with vaccination),
  - 3 cases had a TTO < 3 days (unlikely association with vaccination),
  - 17 cases at least one confounding by underlying conditions,
  - 6 cases had evidence of an underlying infection,
  - 2 cases had drug induced autoimmune hepatitis,
  - 1 fatal case - TTO >30 days, underlying confounding conditions and concomitant medications.

The MAH did not perform a causality assessment for each of the autoimmune hepatitis cases.

Based on review of these 60 cases reporting biopsy results, the PRAC Rapporteur considers that a causal relation between Comirnaty and autoimmune hepatitis is:

- Unlikely in 52 cases due to non-plausible TTO, underlying conditions and/or concomitant confounding medication.
- Unassessable in 8 cases, due to limited information.

2. Cases where the diagnosis was based on laboratory data only (n: 39)

   In 39 cases, only laboratory data was provided as a basis for the diagnosis of AIH. None of the cases had sufficient information to score ≥ 6 using the IAIHG-simplified score.

   Characteristics of the 39 cases are described below (subjects may have 1 or more of the following characteristics):

   - 13 cases did not report either MH or concomitant medication hampering a proper medical assessment,
   - 9 cases that reported previous underlying hepatic issues and report the event as
   - recurrence (1 case in the context of recurrent AIH in liver transplant),
   - 8 cases reported a time to onset not suggestive of a temporal relationship with vaccination (ranging from 35 to 128 days post vaccination; mean: 77 days),
   - 6 cases did not report time to onset precluding a proper causality assessment,
   - 8 cases were concomitantly diagnosed with infection (3 Covid-19, 2 hepatitis viral, 1 viral meningitis, 1 EBV and 1 Pneumonia), that are known to be possibly associated with liver issues,
   - 4 cases were reported in the context of cancer under treatment (few cases reported that the treatment had also triggered previously other autoimmune diseases) suggesting an alternative aetiology for AIH (mostly reported as nivolumab or pembrolizumab),
   - 3 subjects had concomitant autoimmunity diseases (such as thyroiditis, diabetes and Sjogren's syndrome), suggesting an increased risk for the development of AIH
   - 2 cases were reported as suspected drug induced liver dysfunction,
   - 1 case reported alcohol use which is a potential alternative explanation for the hepatic lab abnormalities
   - 1 case unspecified illicit drug dependance (even if the drug is not specified most illicit drug are known to cause liver issues)
   - 1 case was diagnosed with variable immunodeficiency syndrome (pre-existing). This immune disorder is characterized by recurrent infections and low antibody levels,
   - Autoimmune diseases are present in about 50% of the affected people and liver issues are common.

   One case reported a fatal outcome and is summarized below:

   [redacted] A 76-year-old male patient received BNT162b2 on 04 Jan 2022 as dose 3. The vaccine for primary COVID-19 immunization was not known. The patient's relevant medical history included: Arterial hypertension, Steatosis hepatic, Coronary heart disease, Autoimmune hepatitis, Polyneuropathy. The patient's concomitant medications were not reported. Ten days post dose 3 he presented with abdominal pain and fulminant hepatitis and steroids were started. His general condition deteriorated, and he was diagnosed with hepatocellular carcinoma less than 2 months later; he received supportive care and passed away on an unspecified date.

Rapporteur assessment comment:

There were 39 cases reporting laboratory data only. The MAH did not perform a causality assessment for each of the autoimmune hepatitis cases.

Based on review of these 39 cases with diagnosis based on laboratory data only, the PRAC Rapporteur considers that a causal relation between Comirnaty and AIH is:

- Unlikely in 26 cases due to non-plausible TTO, underlying conditions and/or concomitant confounding medication.
- Unassessable in 13 cases, due to limited information.

Cases without liver biopsy or laboratory data (95 cases)

A total of 95 cases did not report any biopsy or laboratory data to confirm the diagnosis of AIH. These cases did not provide sufficient information to perform a medical assessment. Given the lack of information reported to assess the diagnosis the diagnostic criteria for autoimmune hepatitis could not be applied. Lack of information hampers a full assessment.

One case reported a fatal outcome and is summarized below:

AER# [redacted] an 88-year-old male patient received second dose of BNT162b2 20Mar2021. Patient concurrent conditions included hypertension, hypercholesterolemia, diabetes, and pruritus. Concomitant medications included insulin glargine; metformin; amlodipine; lansoprazole. The patient experienced autoimmune hepatitis and jaundice 31 days following the second vaccination and aggravation of already known pruritic condition, severe rash, hepatic cirrhosis and kidney and liver failure on an unknown date in 2021. The patient was treated with an unspecified Adrenal cortical hormone. CT-scan on an unknown date in 2021 was normal. Blood test on an unknown date in 2021 showed high liver enzymes. Gastroscopy and ultrasounds scan on an unknown date in 2021 showed minor infection and minor gallstones. The patient died more than 100 days after vaccination. Reported causes of death: Autoimmune hepatitis, Hepatic cirrhosis, Liver failure and Kidney failure, Jaundice, Pruritus aggravated.

Rapporteur assessment comment:

It is agreed that causality cannot be established in these 95 cases in absence of data to support autoimmune hepatitis diagnosis.

The fatal case [redacted] was previously assessed in the closed signal procedure concerning autoimmune hepatitis (EMEA/H/C/005735/SDA/042- EPITT 19749): The underlying confounding condition(s) e.g. diabetes mellitus and extensive concomitant mediation (amlodipine, lansoprazole, metformin, of which the SmPC already labels increased liver enzymes and liver disorders such as hepatitis and jaundice) hampers causality assessment.

Clinical trial data

There were no reports of autoimmune hepatitis in the Pfizer-run, placebo-controlled Phase 2/3 Study C4591001 in participants 16 years and older from dose 1 to 1 month after dose 2 (data cut-off date 13 March 2021); the safety population consisted of 21926 participants in the BNT162b2 group and 21921 participants in the placebo group.

Rapporteur assessment comment:

There were no reports of autoimmune hepatitis in clinical trial C4591001.

Observed versus expected analyses

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 194 autoimmune hepatitis cases reported cumulatively through 18 June 2022 globally (Table 10). The overall expected case counts of autoimmune hepatitis were estimated using background incidence rates (IR) reported by a population-based study of the Clinical Practice Research Datalink (CPRD) in England during 1997-2015. The overall incidence rate was 2.08 (95% CI 1.94-2.22) per 100,000 population per year, with incidence peaking at approximately 70 years of age for both men and women. This background incidence rate is the middle of a range reported by a systematic review of 17 studies worldwide of 0.42 (United Kingdom, 1971-1987) to 3.00 (West Suffolk, England, 2003-2004) per 100,000 population (Jepsen P et al 2015, Tanner AR et al 1989, Whalley S et al 2007). The CPRD study was selected because it reported recent incidence rates by age, covering a large population.

Table 10. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Autoimmune Hepatitis Through 18 June 2022

Stratification	Observed cases	Time at risk (PY)	Background rates per 100,000 PY	Expected cases	O/E ratio	95% CI LL	95% CI UL
21-day risk window							
US/EEA							
≤11 years	3	1,917,834	0.51	10	0.307	0.063	0.896
12-17 years	1	3,324,066	1.06	35	0.028	0.001	0.158
18-24 years	3	4,733,892	0.84	40	0.075	0.016	0.220
25-49 years	19	19,546,111	1.24	242	0.078	0.047	0.122
50-59 years	14	9,025,268	3.29	297	0.047	0.026	0.079
60-69 years	11	7,901,305	4.19	331	0.033	0.017	0.059
70+ years	13	10,962,290	3.3	362	0.036	0.019	0.061
Overall, any dose	64	57,410,765	2.08	1194	0.054	0.041	0.068
Overall, dose 1	17	22,917,286	2.08	477	0.036	0.021	0.057
Overall, dose 2	35	21,280,003	2.08	443	0.079	0.055	0.110
Overall, dose 3	12	13,213,476	2.08	275	0.044	0.023	0.076
Overall Global	94	127,075,389	2.08	2643	0.036	0.029	0.044
42-day risk window							
US/EEA							
≤11 years	3	2,779,982	0.51	14	0.212	0.044	0.618
12-17 years	3	5,127,186	1.06	54	0.055	0.011	0.161
18-24 years	4	7,477,186	0.84	63	0.064	0.017	0.163
25-49 years	31	30,991,113	1.24	384	0.081	0.055	0.115
50-59 years	20	14,461,569	3.29	476	0.042	0.026	0.065
60-69 years	20	12,856,855	4.19	539	0.037	0.023	0.057
70+ years	22	17,896,776	3.3	591	0.037	0.023	0.056
Overall, any dose	103	91,590,667	2.08	1905	0.054	0.044	0.066
Overall, dose 1	30	22,917,286	2.08	477	0.063	0.042	0.090
Overall, dose 2	56	42,494,750	2.08	884	0.063	0.048	0.082
Overall, dose 3	17	26,178,631	2.08	545	0.031	0.018	0.050
Overall Global	149	203,986,419	2.08	4243	0.035	0.030	0.041

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

Note: The background rate source is Grønbaek L, 2020. Age <=11: Average of 0-4, 5-9, 10-14 in the source study; age 12-17: Average of 10-14, 15-19; Age 18-24: average of 15-19, 20-24; 25-49: average of 25-29, 30-34, 35-39, 40-44, 45-49; Age 50-59: Average of 50-54, 55-59; Age 60-69: 60-64, 65-69; Age 70+: 70-74, 75-79, 80-84, 85-89, and 90+

Based on the selected background rates and the estimated number of exposure person-years through 18 June 2022, O/E ratios were well below one overall, by age, and by dose for both risk windows of 21- and 42-days. This suggests that the number of observed cases of autoimmune hepatitis is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines overall and within the queried strata.

Rapporteur assessment comment:

All O/E ratios were well below 1.

Literature

The following database were searched: BIOSIS Previews <1969 to 2022 Week 31>, Embase <1974 to 2022 June 24>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 24, 2022>.

A total of 64 articles were retrieved. Relevant articles that are new compared to the previous review (previous PRAC request) where the literature was up to 2022 January 7th are discussed below:

Chow K W et al performed a systematic review to analyze every published case of AIH reported following COVID-19 vaccination and reviewed their characteristic findings, treatment, and outcomes. The data were retrieved using PubMed, Embase, and Web of Science from December 1, 2019, to November 1, 2021. The authors identified and analyzed a total of 32 cases. Although they concede that causality "cannot be proven" by this review, the authors refer to the cases as "vaccine-induced AIH" and hypothesize that molecular mimicry may be the mechanism leading to autoimmune tissue damage in susceptible individuals. They then conclude the article by stating that their findings should "under no circumstances deter individuals from getting vaccinated" as the benefits of vaccination outweigh the risks. (Chow KW et al 2022).

Roy A et al also performed a systematic review collating the available literature on potential Immune-mediated liver injury (ILI) following COVID-19 vaccination. Their final study selection included 23 patients with histopathological data in 13 studies. Reports included the AstraZeneca (n=3), Moderna (n=11) and Pfizer/BNT COVID-19 (n=9) vaccines and time to onset ranged from 11.2-23.4 days. The authors note that 62.5% of the patients were female and ¼ of the patients had background autoimmune diseases; they describe jaundice as the most typical presenting symptom. IAIHG-simplified and IAIHG-revised scores were provided for 7 of the 23 cases and the authors calculated IAIHG-simplified scores for 11 cases (4 were probable, and 7 were definite AIH). Only one of the 23 patients reported a challenge-rechallenge. They conclude that most of the cases with ILI resembled AIH, that taking into consideration the limitations of the data, the crude incidence of ILI reported after vaccination seems to be far below the reported global incidence of AIH in the general population and that it is unclear whether COVID-19 vaccines are a trigger, causation or mere association with ILI.

Interestingly, Bril F wrote a letter stating that, while the resemblance cases reporting autoimmune hepatitis after Covid-19 vaccination suggests a potential causal link between the vaccine and AIH, this cannot be taken as proof that this link really exists. He further explains that considering an annual incidence of 1 case per 100,000 inhabitants as previously reported, and assuming an even distribution during the 12 months, we can estimate 1 monthly case per 1,200,000 inhabitants. Based on CDC data, during the first month of the US COVID-19 vaccination program, approximately 13,000,000 people received at least 1 dose of the vaccine (available at https://covid.cdc.gov/covid-data-tracker/#vaccinations). Based on AIH incidence, we can therefore roughly estimate that ~10 people from this vaccinated cohort would have developed AIH within a month of getting the vaccine. Thus, it should not be surprising that we will all continue to see these cases as we continue with our vaccination efforts. Epidemiological studies assessing changes in AIH incidence may be able to shed some light on this uncertainty. Only if we observe a true increment of AIH incidence after COVID-19 vaccination, can we make the case for a potential relationship. Until then, primary care providers and hepatologists are encouraged to keep their eyes open and maximize adverse event reporting to the appropriate authorities (BrilF 2021). The same concept has been stated also very efficiently by other literature articles (Shroff H et al 2022, Lleo A et al 2022).

Bril F et al in another article state that while it is important to further explore the potential link between COVID-19 vaccines and autoimmunity, this should not discourage patients and physicians

from prescribing and/or receiving these vaccines. Even if confirmed in the future, cases of vaccine-induced autoimmunity appear to be uncommon as evidenced by only a handful of reports despite massive vaccination worldwide. Furthermore, it is likely that SARS-CoV-2 infection can trigger the same autoimmune processes as its vaccines do, leaving unvaccinated people not only at risk of developing the autoimmune process, but also the other complications associated with COVID-19 (Bril F et al 2021).

Overall, the literature at this time consists of case reports and case series which cannot confirm that COVID-19 vaccines cause autoimmune hepatitis due to confounding/triggering factors (as for example the post-partum state for the case reported from Bril et al, the underlying autoimmune disease (sarcoidosis) for the case described by Palla et al, and the use of liver toxic drugs in the cases described by Mc Shane et al and Clayton-Chubb et al.).

The European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and British Association for the Study of Liver currently recommend the available SARS-CoV-2 vaccines for patients with chronic liver disease and liver transplant recipients (Nasa P et al 2021 and Sharma A et al 2021).

Rapporteur assessment comment:
MAH's overall statement regarding literature is accepted, the available case reports and case series cannot confirm that Comirnaty causes autoimmune hepatitis due to confounding/triggering factors.

MAH's conclusion

Overall, most of the potential AIH cases in the safety database do not provide sufficient information for a proper assessment, while cases that report information are mostly confounded by underlying comorbidities or concomitant drugs that represent an increased propensity for the development of AIH or potential alternative etiologies. Many cases reported the event with a time to onset that is not plausible for the vaccine to be causative (as for example the same vaccination day/1-2 days post vaccination or more than 30 days after vaccination).

The upper limit of the 95% confidence interval for the observed to expected ratio did not exceed 1; therefore, a signal was not identified.

In, C4591001, a large Pfizer-run double-blind placebo-controlled study of the vaccine there were no reports of Autoimmune hepatitis in either the vaccine or placebo groups, however, given the rarity of AIH, this is not unexpected.

Literature information consists of case reports and case series. Large population-based observational studies may eventually provide more useful information than cases series about the incidence of AIH in unvaccinated populations compared to those vaccinated with Pfizer/Biontech COVID-19 vaccine.

In addition, the pandemic has been associated with increased alcohol consumption, unhealthy eating habits, and interruptions to hepatology services, which might lead to an upward trend in liver disease incidence and severity that has been unnoticed until resumption of usual health care can return after the COVID-19 pandemic period.

Overall, given the totality of the available information, a causal association between Comirnaty and AIH cannot be concluded. Changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored.

Rapporteur assessment comment:

Post-marketing

Through 18 Jun 2022, 194 cases reporting autoimmune hepatitis were retrieved:

- Biopsy results were reported in 60 cases, a causal relation between Comirnaty and autoimmune hepatitis is considered Unlikely in 52 cases (due to non-plausible TTO, underlying conditions and/or concomitant confounding medication) and Unassessable in 8 cases (due to limited information).
- Laboratory data only were reported in 39 cases, a causal relation between Comirnaty and AIH is considered Unlikely in 26 cases (due to non-plausible TTO, underlying conditions and/or concomitant confounding medication) and Unassessable in 13 cases (due to limited information).
- Causality cannot be established in these 95 cases in absence of data to support autoimmune hepatitis diagnosis.

Clinical trial

No reports of autoimmune hepatitis in clinical trial C4591001.

Observed versus expected analyses

All O/E ratios for autoimmune hepatitis were well below 1.

Literature

The available case reports and case series cannot confirm that Comirnaty causes autoimmune hepatitis due to confounding/triggering factors.

Therefore, MAH's conclusion is accepted that a causal association between Comirnaty and autoimmune hepatitis cannot be concluded based on the available information. No new important information could be identified concerning autoimmune hepatitis. The MAH should closely monitor any new cases, patterns, or trends of reporting autoimmune hepatitis through routine pharmacovigilance.

Issue solved

Glomerulonephritis/nephrotic syndrome

Rapporteur assessment comment:

Here we refer to section 'Evaluation of Other Risks (not categorised as important), Adverse events of special interest (AESIs)' below in this AR and the overview of immunoglobulin A (IgA) nephropathy hereafter.

IgA nephropathy (IgAN)

Response to the PRAC request 5 from the 2nd PSUR (procedure EMEA/H/C/PSUSA/00010898/202112):

The MAH is requested to provide a cumulative review of cases reporting IgA nephropathy, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccination. The MAH should also provide a comprehensive discussion of the literature, mechanism of action and a discussion on the need to update the product information of Comirnaty, if applicable.

MAH's response:

Background

In August 2021, the European Medicines Agency (EMA) issued a signal assessment report on glomerulonephritis and nephrotic syndrome and Comirnaty (EPITT no:19722). A cumulative review of the association of Comirnaty with glomerulonephritis and nephrotic syndrome using all sources (cases in the Market Authorisation Holder's (MAH) safety database, clinical trial data, literature review and observed to expected analysis) was performed. This cumulative review covered the Preferred Terms (PTs) under the MedDRA v24.0 high level term (HLT) Glomerulonephritis and Nephrotic Syndrome, encompassing a broad range of renal pathologies, including IgA nephropathy (IgAN). The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the MAH closely monitor the issue of 'glomerulonephritis/nephrotic syndrome' and present a cumulative review of cases from all sources and relevant literature in upcoming periodic safety update report (PSUR) submissions. PRAC subsequently requested a focused review of IgAN.

IgA nephropathy

IgAN is the most prevalent primary idiopathic glomerulonephritis globally, with an overall incidence of at least 2.5 per 100,000. Significant geographical variations are noted with lowest incidences in North America and Europe and highest in East Asian countries.

It has been proposed that geographical variations apparent in disease prevalence may represent regional differences in screening for renal disease and threshold for renal biopsy. Notably in Japan, all primary and secondary school students undergo urinalysis annually as part of a routine health check program under the supervision of the national government. Further testing of university students and routine health checks by employers mean that increased incidence noted in this population.

IgAN is characterised by persistent microscopic haematuria and/or proteinuria or recurrent episode of macroscopic haematuria concurrent with upper respiratory tract infections. It is often asymptomatic, identified on incidental urine analysis and diagnosed by renal biopsy with demonstration of diffuse mesangial IgA deposits in glomeruli.

Although patients can present at any age there is a peak incidence in the second and third decades of life. This is particularly pertinent given 20-40% of patients develop kidney failure within 10-20 years of diagnosis. A 2:1 male preponderance exists in North American and Western European populations, but IgAN is equally distributed between the sexes in Asian populations.

The pathogenesis of IgAN is widely accepted to follow a "multi-hit hypothesis", involving confluence of genetic and environmental influences that modulate immune function and lead to IgAN.

Patients with IgAN have increased circulating levels of galactose-deficient IgA1 (Gd-IgA1), although this disordered glycosylation is heritable it is not sufficient in itself to cause disease. The triggers for the formation of Gd-IgA1 are not entirely understood, however exposure to environmental and infective factors may play a role. The abnormal IgA1 acts as an epitope for the formation of anti-glycan IgG antibodies. Circulating IgA immune complexes are identified in patients with IgAN, although IgA does not often activate complement the complexes contain Gd-IgA1, anti-glycan autoantibodies and complement C3. The circulating Gd-IgA1-anti-glycan IgG immune complexes deposit in the mesangium activating inflammatory and cellular proliferative signaling cascades.

The resultant local inflammation, mesangial matrix production and mesangial cell proliferation can lead to glomerular and interstitial fibrosis.

The pathognomonic finding of IgAN is the presence of mesangial IgA deposits identified by immunofluorescence-microscopy.

Clinical presentation varies from asymptomatic microscopic haematuria and or proteinuria to acute rapidly progressive glomerulonephritis. Approximately 40-50% present with gross haematuria, sometimes provoked by bacterial tonsillitis or viral upper respiratory tract infections. In these patients this first presentation is presumed to be the onset of disease although this is not proven. The concurrent "synpharyngitic" presentation differentiates this from post-streptococcal glomerulonephritis which has a usual 2-3-week latency from infection.

30-40% of cases are identified due to microscopic haematuria or proteinuria on incidental testing or during the investigation of chronic kidney disease; in these patients the disease duration is unknown.

Less than 10% of patients present with nephrotic syndrome or rapidly progressive glomerulonephritis; it is often presumed in these patients that the disease has been present for longer but not previously identified on routine urinalysis/or they have not had any prior episodes of macroscopic haematuria.

Clinical management focusses on supportive therapy; blood pressure control, reducing proteinuria with renin-angiotensin system blockage and lifestyle modifications to slow the rate of renal function decline. Immunosuppressive therapies are reserved for the highest risk patients.

IgAN can also be associated with other systemic conditions; chronic liver disease, coeliac disease, inflammatory bowel disease, Henoch-Schoenlein purpura and ankylosing spondylitis often termed "secondary IgAN".

IgA nephropathy, COVID-19 & Vaccines

Farooq et al systematically reviewed literature reports of IgAN and IgA vasculitis following COVID-19. They describe early seroconversion to IgA in COVID-19 patients and that mucosal infections are believed to enhance IL-6 production which stimulates poor galactosylation of IgA1, forming Gd-IgA1 and contributing to the disease process suggesting COVID-19 infection may trigger IgAN or flare via such mechanisms.

IgAN has not frequently been reported following preventative vaccinations (Wu et al.). Excessive production of IgA1 monomers in IgAN patients in response to influenza vaccine has been previously seen although the clinical significance is not reported (van den Wall Bake eta al.).

Literature

A search of OVID MEDLINE (R) (1946)-present, OVID MEDLINE (R) In-Process & Epub Ahead of Print and Embase (1974 to 14 July 2022) was conducted with the following search strategy: BNT162B2 or Tozinameran or Comirnaty and the PT "IgA nephropathy" through 30 June 2022.

Of the 49 results retrieved, 28 reflected case reports or case series reported in association with COVID-19 vaccinations, of these, 22 reported cases relating to IgA nephropathy. 5 were not deemed valid individual case safety reports in the MAH safety database.

Eight (8) cases are represented in the cumulative dataset described below.

Nine (9) additional literature case reports are registered in the MAH safety database, identified after the DLP. They do not provide sufficient clinical detail, consistency, specificity or strength of association to alter the conclusion on IgAN and Comirnaty after consideration of the totality of data.

Wu et al conducted a qualitative systematic review of new-onset and relapsed kidney histopathology cases reported in association with COVID-19 vaccination. The review includes 46 cases from 36 articles. 14 cases of IgAN were included; 6 new-onset, 6 previously known cases and 2 patients who

presented with macroscopic haematuria who did not have kidney biopsy and were presumed to have IgAN. 6 new onset cases were reported with a median time to onset of just one day (interquartile range (IQR) 1-2 days); 5 reported following Dose 2 of Moderna vaccine and 1 following Dose 2 of Comirnaty. Macroscopic haematuria was also reported in 6 patients with a previous histopathological diagnosis of IgAN with a similarly short median time to onset of 2 days (IQR 1-2 days). Onset was after Comirnaty in 3 cases (1 after dose 1, 2 after dose 2) and 3 after Dose 2 of Moderna COVID-19 vaccine. Further, 2 patients were included with presumed IgAN, given their presentation of macroscopic haematuria and mild proteinuria; both following Moderna COVID-19 Dose 2 vaccination. 1 of the patients had previously received episodic steroid therapy for IgA vasculitis as a child. The authors suggest that scenarios where subclinical IgAN becomes clinically apparent following COVID-19 vaccination are a possibility. They also suggest that the short latency from vaccination is similar to the concurrent onset of haematuria seen in synpharyngitic IgAN in clinical practice. (*Wu HHL, Kalra PA, Chinnadurai R. New-Onset and Relapsed Kidney Histopathology Following COVID-19 Vaccination: A Systematic Review. Vaccines (Basel). 2021;9(11):1252.*)

Racenis et al investigated the impact of COVID-19 vaccination on the clinical course of IgAN in an adult Latvian patient population. 54 adult patients with a morphological diagnosis of primary IgAN at a single centre were enrolled. Clinical and laboratory parameters were evaluated at an inclusion visit and at a second visit 6 months later. Thirty-six patients were unvaccinated and 18 vaccinated; baseline proteinuria was the only significantly different parameter at baseline (lower 24-hour proteinuria in the vaccinated population). Fourteen patients were vaccinated with mRNA vaccines; 13 with Comirnaty and 1 with Spikevax. Four patients were vaccinated with Vaxzevria vector vaccine. Baseline renal function; estimated glomerular filtration rate (eGFR), haematuria, 24-hour proteinuria and disease activity markers; IgA, C3c were compared to the results at the 6-month follow-up visit with no significant difference noted in the vaccinated group compared to the non-vaccinated group. The authors concluded that COVID-19 vaccination did not affect the clinical course of IgAN, in this small prospective study.(*Rācenis K, Saulīte AJ, Popova, et al. MO213: Sars-COV-2 Vaccination DID Not Affect the Clinical Course of IGA Nephropathy in Latvian Adult Cohort, Nephrology Dialysis Transplantation 2022;37(3):1145.*)

Musetti et al conducted a retrospective study at a single centre in Italy from late December 2020 to 31 December 2021. Thirty-eight patients with immune-mediated nephropathies (either on or off immunosuppressive therapies), excluding those with end-stage renal disease or kidney transplant recipients were included. Seven IgAN patients were included. Five (5) male and 2 female patients, with an average age of 40.4±12.0 years. 42.9% were on immunosuppressants at the time of vaccination and 28.6% had prior relapses and the authors calculated a relapse rate prior to vaccination of 9.6 per 100 person-years. One IgAN patient had a relapse 5 days following vaccination and a post-vaccination relapse rate calculated at 34.8 per 100 person-years. The authors report a slightly higher rate of relapse post vaccination however conclude that relapses of immune-mediated nephropathies are uncommon after COVID-19 vaccination.(*Musetti C, Fornara L, Cantaluppi V. MO239: Clinical Evaluation of Immunological and Clinical Recurrence of Immune-Mediated Nephropathies after SARS-COV-2 Vaccine, Nephrology Dialysis Transplantation, 2022;37(3).*)

The MAH states that in summary there is a paucity of large-scale epidemiological data in the literature, however a single-centre prospective study reported that SARS-CoV-2 vaccination did not affect the clinical course of IgAN. Limited data in the literature case reports precludes meaningful assessments of case causality.

Rapporteur assessment comment:

Of the 49 results retrieved from the literature search through 30 Jun 2022, there were 22 reported cases relating to IgA nephropathy. 8 of the 22 case reports are presented in the cumulative safety

database case review below. Five cases reports were not considered valid reports by the MAH. Nine cases were retrieved after the DLP of current PSUR, however did not provide sufficient information to alter the conclusion on IgA nephropathy and Comirnaty.

In the retrieved literature, no new important information could be identified concerning IgA nephropathy.

Clinical trial data

In the blinded, placebo-controlled period of pivotal study C4591001 (data cut-off date 13 March 2021) 1131 adolescents 12-15 years of age had received primary vaccination with BNT162b2 and 1129 had received placebo. The median duration of follow-up for adolescents 12-15 years of age was >2 months after Dose 2. No participants reported IgA nephropathy. Of note, there were no participants in the BNT162b2 or placebo groups who had a medical history of IgA nephropathy.

Of participants 16 years of age and older, 22,026 participants had received primary vaccination with BNT162b2 and 22,021 participants had received placebo. During the blinded placebo-controlled follow-up period (up to the earlier of the time of unblinding or data cut off), 51.1% of participants in the BNT162b2 group and 51.4% of participants in the placebo group had a follow-up time between ≥4 months to <6 months after Dose 2. No participants 16 and older were reported to have IgA nephropathy. Of 22,026 participants 16 years of age and older who received primary BNT162b2, 1 had a medical history of IgA nephropathy; of the 22,021 placebo recipients, 1 had a history of IgA nephropathy.

There were no AE reports of IgA nephropathy in Study C4591007 in participants 5 to < 12 years of age (data cut-off 06 Sep 2021). Of the 1518 participants who received BNT162b2 10 mcg as a primary vaccine and of the 750 participants who received placebo, none had medical histories of IgA nephropathy.

Rapporteur assessment comment:

There were no reports of IgA nephropathy in the clinical trials.

Cumulative safety database case review

The safety database was searched for all cases of BNT162b2 reporting the MedDRA v 25.0 PT IgA nephropathy, and for cases with a medical history of IgA nephropathy coded with the PT Condition aggravated through 30 June 2022.

A total of 103 cases were retrieved. A majority (80) of the cases were spontaneous, 21 were from literature non-study while 2 were from clinical studies. A total of 100 cases were serious while 3 were non-serious. Table 1 provides the distribution of cases by age. The mean age was 33.5 years (103 cases).

Table 1. Case Distribution by Age

Age Range	Number of Cases	Percentage of Cases
Less than or equal to 17 years	19	18.4 %
18 - 30 years	26	25.2 %
31 - 50 years	35	34.0 %
51 - 64 years	12	11.7 %
65 - 74 years	2	1.9 %
Greater than or equal to 75 years	1	1.0 %
Unknown	8	7.8 %

Regarding sex distribution, a majority (64) of cases were reported in female patients while 36 were in males and gender data was not provided for 3 remaining cases.

Concerning the countries of origin, of the 103 cases, most cases were received from Japan (36) and France (18). The top reporting countries are shown below in Table 2.

Table 2. Reporting Country (n=103)

Country	Number of Cases	Percentage of Cases
Japan	36	35.0%
France	18	17.5 %
United States	10	9.7 %
Australia	7	6.8 %
Germany	7	6.8 %
United Kingdom	5	4.9 %
Netherlands	4	3.9 %
Spain	3	2.9 %
Italy	2	1.9 %

The case outcome was recovered in 17 cases, recovering in 22 cases, recovered with sequel in 3 cases and not recovered in 42 cases while outcome was unknown in 19 cases. None of the cases had a fatal outcome.

Of these 103 cases, 2 were excluded from further analysis as PT "condition aggravation" in these cases was not in context of IgA nephropathy.

Of the remaining 101 cases, 75 were medically confirmed while 26 were non-medically confirmed cases. A total of 37 cases reported an aggravation of IgA nephropathy in context of medical history of the same while 64 reported new onset IgA nephropathy. However, 6 of these 64 cases reported a history of haematuria which could indicate that renal disease was present at baseline.

Latency from last dose was provided in 80/101 cases. Latency varied from 0 to 263 days. The latency from time of the vaccination until the development of the relevant event was reported as: the same day of vaccination to 3 days post vaccination for 53 relevant events, from day 4 to day 10 for 12 events, from day 11 to day 24 for 4 events, and post day 24 for 11 events.

Dosing information was provided in 95 of the 101 cases. Of these 95 cases, 62 reported IgA nephropathy following dose 2, 23 reported following dose 1 while 10 reported events following dose 3.

Of the 101 cases, 3 were excluded from further analysis as in these cases COVID-19 vaccine manufacturer was unknown.

Of the remaining 98 cases, 3 cases reported an implausible latency of 170-263 days. 52 of the remaining 95 cases had insufficient information regarding either latency, medical history, concomitant medications, relevant investigations, clinical course and/or event details thus, precluding a meaningful assessment of these cases both in terms of confirming the diagnosis of IgA nephropathy and/or assessing a relationship to vaccination. Of these 52 cases, 25 were medically unconfirmed cases.

The remaining 43 cases are presented below based on new onset (Table 3, N=24) or condition aggravated in cases with pre-existing history of IgA nephropathy (Table 4, N=19, not reproduced here).

Table 3: Cases pertaining to IgA Nephropathy, new onset (n=24)

AER Number **Age/Gender** **Country**	**Medical history** **Co-suspect/** **concomitant**	**Relevant PT(s)** **Other PTs** **Latency (from**	**Case summary**	**MAH comment**

Dose Source Medically confirmed (Y/N)	**medications**	**last dose, for IgA nephropathy) Seriousness Outcome**		
[redacted] 41 Y/F [redacted] Dose 2 Literature Y	Gestational diabetes Not reported	IgA nephropathy Haematuria 1 day Serious Unknown	The patient presented with subnephrotic range proteinuria, hypertension, and elevated serum creatinine 1 day after Dose 2 of Comirnaty. The patient received Dose 1 of Comirnaty 23 days before. A renal biopsy showed IgA nephropathy with fibrocellular and fibrous crescents. The chronic features on histopathology were reported to be suggestive of pre-existing undiagnosed IgA nephropathy that might have been unmasked after vaccination. Relevant investigations: Serum creatinine 153 mol/L (normal range unknown), Urine dysmorphic red blood cells/microliter: above 200, Urine protein-to-creatinine ratio 2.03 g/g (normal range not provided), Serum IgG 12.9 g/L (normal range: 5.49- 17.11 g/l), Serum IgA 6.4 g/L (normal range: 0.47-3.59 g/l), Serum IgM, 1.1 g/L (normal range: 0.15- 2.59 g/l), Complement C3 0.83 g/L (normal range: 0.90-1.80 g/l), C4 0.2 g/L (normal range: 0.10-0.40 g/l), Anti-nuclear antibody: 1:320, homogeneous, anti-GBM antibody (Enzyme-linked immunosorbent assay [ELISA]): below 1.5. Patient treated with pulse methylprednisolone, followed by oral prednisolone and IV cyclophosphamide.	Personal or family history of IgA nephropathy is not reported nor is a precedent infection or autoimmune disorder. The biopsy report indicates that the nephropathy is chronic raising the possibility that the onset may have preceded any vaccination. The patient also suffered from gestational diabetes.
Rapporteur assessment comment (1): Medically confirmed literature case reporting biopsy with pre-existing undiagnosed IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

[redacted] 13 Y/F [redacted] Dose 1 Literature Y	Salmonella test positive/ Tobacco user/ Viral pharyngitis Not reported	IgA nephropathy Acute kidney injury, Anuria, Pyrexia, Haematuria, Influenza, Proteinuria 1 day Serious Recovering	Patient developed de novo IgA nephropathy within 24 hours following Dose 1 of Comirnaty manifesting as fever, asthenia, muscle pain and macroscopic haematuria. On examination, she had mild streptococcus-negative pharyngitis. 3 days later, a renal biopsy showed IgA nephropathy, Oxford score M1E1S0T0. Other labs: Blood creatinine: 5 mg/dl, blood urea nitrogen 96 mg/dl (normal ranges not reported), infectious testing negative, immunological test negative, urine protein 3.88 g/l, SARS-CoV-2 Serology negative. Kidney function rapidly deteriorated, and the patient became oliguric; subsequently, haemodialysis was started. Treatment consisted of IV methylprednisolone pulses, followed by oral prednisone. Kidney function improved progressively; at 30 days postvaccination, serum creatinine had returned to almost normal values.	The reported co-infection is a potential and more likely aetiology of the nephropathy in this case; the latency of <24 hours after the first exposure to vaccination is less biologically plausible.
Rapporteur assessment comment (2): Medically confirmed literature case reporting a TTO of 1 day after dose 1 and a co-infection. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

[redacted] 74 Y/M [redacted] Dose 2 Spontaneous Y	Atrial fibrillation/Urinary occult blood Edoxaban	IgA nephropathy Glomerulonephritis rapidly progressive, Haematuria, Headache, Oedema peripheral, Urinary occult blood positive, Decreased appetite, Malaise 4 days Serious Recovering	On 04 Jul 2021, 4 days after the Dose 2 of Comirnaty, the patient experienced haematuria aggravated, general malaise, lower leg oedema and inappetence. Patient received Dose 1 of Comirnaty 3 weeks before. 9 days later, the patient was diagnosed with IgA nephropathy based on a renal biopsy which showed IgA nephropathy with crescents. Labs: creatinine 3.51 mg/dl (normal range not reported), Protein urine 1.91 g/gCr (3+), urinary occult blood (3+), antinuclear antibody and ANCA were negative. In Dec 2020, creatinine 1.09 mg/dl, Protein urine (negative), urinary occult blood (2+). The patient was treated with steroids. The reporter stated, "The base was probably undiagnosed stable IgA nephropathy. It was suspected to be exacerbated by immune activation because of COVID-19 vaccination".	The past medical history of occult blood in the urine and the reporter note that this may be an exacerbation raises the likelihood of underlying nephrology that evolved in accordance with the disease natural progression.
Rapporteur assessment comment (3): Medically confirmed literature case reporting pre-existing undiagnosed IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 40 Y/F [redacted] Dose 2 Spontaneous	Dermatitis atopic Dupilimab	IgA nephropathy 2 days Serious Not recovered	The patient was diagnosed with mesangial IgA nephropathy based on renal biopsy 2 days after receiving Dose 2 of Comirnaty. No information provided regarding first dose of COVID-19 vaccine. Evidence of isolated C3 consumption associated with a low positive level of anti-deoxyribonucleic acid antibodies at 33 IU. No additional information.	Limited information has been provided including why the patient had a renal biopsy.
Rapporteur assessment comment (4): Spontaneous case with limited information which is considered unassessable.				

[redacted] 20 Y/F [redacted] Dose 2 Spontaneous N	Not reported Not reported	IgA nephropathy, Haematuria 1 day Serious Unknown	1 day after receiving Dose 2 of Comirnaty, the patient experienced massive macrohaematuria. No information on first dose of COVID- 19 vaccine. IgA nephropathy diagnosed based on renal biopsy on an unknown date (details unspecified). Reportedly, the patient already had persistent microhaematuria (onset unknown). No additional information.	Limited information regarding timing between 2 doses of COVID-19 vaccine. Details are lacking regarding labs, clinical course, concomitant medications and medical history precludes an adequate assessment.
Rapporteur assessment comment (5): Spontaneous case with limited information which is considered unassessable.				
[redacted] 40 Y/F [redacted] Dose Unknown Spontaneous Y	None Not reported	IgA nephropathy Nephrotic syndrome, Proteinuria, Hypoproteinaemia, Hyperlipidaemia 7 days Serious Unknown	1 week after receiving Comirnaty (dose unknown), the patient experienced generalized oedema and weight increased. Examination revealed marked proteinuria (14 g/day), hypoproteinaemia, and hyperlipidaemia (values unknown) and was diagnosed with nephrotic syndrome. A renal biopsy showed mild mesangial proliferation and adhesion. On immunofluorescence, IgA, IgM, IgG, and C3c presented with the positive image of mesangial pattern and electron microscopy showed disappearing image of foot processes. Steroid pulse therapy led to complete remission within 10 days. Based on renal biopsy, the possibility of IgA nephropathy was considered. However, a possibility of minimal lesion nephrotic syndrome was also considered as there was no haematuria and immediate remission was observed.	No information on dose number of covid vaccine, medical history and concomitant medications precludes an adequate assessment. Further, the clinical presentation (no haematuria and immediate remission) raised the possibility that another nephropathy was present.
Rapporteur assessment comment (6): Spontaneous medically confirmed case with limited information which is considered unassessable.				

[redacted] 12 Y/M [redacted] Dose 2 Spontaneous Y	None Not reported	IgA nephropathy Haematuria, Pyrexia, Proteinuria 0 day Serious Unknown	The same day as receiving Dose 2 of Comirnaty, the patient experienced frank haematuria (3+), pyrexia and proteinuria (2+). History of frank haematuria an unspecified duration after receiving first dose of Comirnaty 23 days earlier. After that, only urinary occult blood continued. No other details provided.	Although rechallenge positive for haematuria, no information regarding concomitant medications, confirmatory diagnostic tests including biopsy and labs precluded an adequate assessment.
Rapporteur assessment comment (7): Spontaneous medically confirmed case with limited information which is considered unassessable.				
[redacted] 63 Y/F [redacted] Dose 2 Literature spontaneous Y	Hypertension / Psoriatic arthropathy Not reported	IgA nephropathy 3 days Serious Unknown	The patient presented with gross haematuria for 6 weeks, 3 days after the Dose 2 of Comirnaty. Labs: creatinine 10 mg/dl (baseline 0.5; normal range unknown) and urine protein: creatinine ratio of 7.3 gm/gm (normal range unknown). Renal imaging including CT urogram was normal. Renal biopsy showed IgA nephropathy with a fibrocellular crescent and acute tubular necrosis likely secondary to lysed red cells in setting of multiple RBC casts in the tubules. The patient was treated with steroids and creatinine decreased to 4.5 in 15 days. As per the authors "SARS- COV2 vaccines use nucleoside modified purified mRNA which does elicit higher neutralizing antibody titer and strong cluster of differentiation response leading to production of several proinflammatory cytokines. Thus, there is a concern that vaccines might exacerbate immune mediated glomerular diseases. IgA1 is involved in the pathogenesis of IgA nephropathy and patients	History of autoimmune disease (psoriatic arthritis) is a possible risk factor for IgA nephropathy in this case. No information on concomitant medications and first dose of covid vaccine.

			with IgA nephropathy have higher than normal IgA1 response to other vaccines like influenza. Also, while studying the antibody response to covid-19 illness, patients with IgA nephropathy are known to express higher IgA response compared to IgG and IgM along with reports of concurrent worsening of the glomerulonephritis".	
Rapporteur assessment comment (8): Spontaneous medically confirmed case reporting a history of psoriatic arthritis. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 50 Y/F [redacted] Dose 2 Spontaneous Y	Appendicitis / Obesity / Peritonitis / Pregnancy Not reported	IgA nephropathy, Acute kidney injury, Haematuria, Pyrexia, General physical health deterioration 1 day Serious Recovering	1 day after receiving Dose 2 of Comirnaty, the patient presented with macroscopic haematuria. No details provided regarding the first dose of covid vaccine. Labs: creatinine: 220 µmol/l (normal range unknown); blood immunoglobulin A: 2.82; GFR 27, blood urea 11.5 (unit and normal range unknown). A biopsy 9 days after vaccination revealed glomerulonephritis with mesangial IgA deposits. Extensive vascular lesions were noted. Protein urine: (unspecified date) 0.9 g/l, rheumatoid factor: (unspecified date) 5.3 IU/ml (normal range unknown).	No information regarding timing between two doses of covid vaccines and concomitant medications.
Rapporteur assessment comment (9): Spontaneous medically confirmed case reporting no information regarding concomitant medications and timing of dose 1, and therefore considered unassessable.				

[redacted] 5 decade/F [redacted] Dose 2 Literature spontaneous Y	Haematuria / Proteinuria Not reported	IgA nephropathy, Haematuria, Pyrexia, Protein urine present, Urinary occult blood positive 0 day Serious Unknown	The same day of receiving Dose 2 of Comirnaty, the patient presented with pyrexia and frank haematuria. No details provided regarding the first dose of covid vaccine. A kidney biopsy confirmed the diagnosis of IgA nephropathy. Urinary protein 1.45 g/gCr, serum creatinine 0.65 mg/dL (normal range unknown), urinary occult blood: 3+. Urine occult blood was 3+ at a routine annual check-up as well. It was reported that the patient was scheduled to undergo tonsillectomy combined with steroid pulse therapy. Haematuria recovered spontaneously.	No information regarding timing between the two doses of covid vaccines. In addition, the patient had occult blood 3+ at routine health check-up before vaccination suggesting a pre-existing nephropathy which may have evolved in accordance with the natural disease progression. That patient was scheduled to undergo tonsillectomy raises question of tonsillitis as a cause of IgA nephropathy.
Rapporteur assessment comment (10): A medically confirmed case reporting confounding factors for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 29 Y/F [redacted] Dose 1 Spontaneous Y	Abortion/ Anti-antibody/ COVID-19/ Cystitis / Hypothyroidism/ Lymphoma/ Suicide attempt/ Uterine cancer Not reported	IgA nephropathy, Acute kidney injury, Nephritis, Asthenia, Oedema peripheral, Myalgia, Decreased appetite, Weight decreased, Oropharyngeal candidiasis, Rash erythematous, Arthralgia, Cystitis, Oral candidiasis, Normocytic Anaemia 21 days Serious Not recovered	1 week after Dose 2 of Comirnaty, the patient developed asthenia, oedema of the lower limbs, myalgia then secondarily anorexia and weight loss, oropharyngeal candidiasis. A blood test 2 weeks later revealed acute renal failure with creatinine at 18 mg/l (baseline 7.8 mg/l; normal range not reported). A urine strip test showed proteinuria 3+ and haematuria 3+. The urine test revealed proteinuria at 0.85 g/24 hours, including 50% albumin, albuminuria at 0.4 g/day; associated microscopic haematuria at more than 1000/mm3, associated hypoalbuminemia at 32 g/l (normal range unknown).	Antithyroid antibodies are suggestive of an underlying autoimmune disorder. No information provided regarding concomitant medications.

			Serum protein electrophoresis showed hypo-serum albuminemia, hyper alpha-1, hyper alpha-2, restriction of heterogeneity in the area of beta globulins and gamma globulins, immunofixation qualitatively normal. A renal biopsy showed nephropathy with mesangial deposits of immunoglobulin. Immunological assessment: Negative anti-neutrophil cytoplasm antibodies 1/20 of homogeneous appearance, myeloperoxidase or proteinase 3 negative, rheumatoid factor negative, positive anti-nuclear antibodies of homogeneous appearance 1/320 (threshold 1/80), antideoxyribonucleic acid negative, no specificity identified, viral serology was negative for Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV).	
Rapporteur assessment comment (11): Spontaneous medically confirmed case reporting confounding factors for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 46 Y/F [redacted] Dose 3 Spontaneous Y	None Not reported	IgA nephropathy, Urinary retention, Haematuria, Pollakiuria, Immunisation 1 day Serious Not recovered	The patient experienced pollakiuria, feeling of residual urine, and haematuria 1 day after receiving Dose 3 of Comirnaty. No information on primary immunization for COVID-19. A urine analysis showed protein urine 1+, occult blood 3+, RBC more than 100/HPF, WBC more than 100/HPF.	A latency of 1 day after dose 3 but no Information regarding supporting labs/investigations (including biopsy), medical history and concomitant medications.
Rapporteur assessment comment (12): Spontaneous medically confirmed case with limited information which is considered unassessable.				

[redacted] 20 Y/M [redacted] Dose 2 Spontaneous Y	COVID-19 / Haematuria / Mite allergy / Seasonal allergy Not reported	IgA nephropathy, Off label use, Interchange of vaccine products, Renal failure, Fatigue 7 days Serious Not recovered	1 week after receiving Dose 2 of Comirnaty, the patient was diagnosed with IgA nephropathy. The patient received first dose of other manufacturer's Covid vaccine 6 months earlier. A kidney biopsy showed IgA nephropathy with crescentic glomerulonephritis, GFR 17 ml/min (normal range unknown). Family history of kidney transplant (unspecified diagnosis). No additional information.	Interchange of vaccines reported. The patient had a family history of kidney transplant (unspecified diagnosis). Additionally, the patient had a history of macroscopic haematuria once, a few years ago suggesting a pre-existing condition, possibly genetic. Baseline labs not reported.
Rapporteur assessment comment (13): Spontaneous medically confirmed case reporting confounding information in the medical history for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 34 Y/F [redacted] Dose 1 Spontaneous Y	COVID-19 pneumonia / Cholangitis / Colitis / Endoscopic retrograde cholangiopancreatography / Pregnancy / Tooth extraction Metronidazole, Spiramycin	IgA nephropathy, Nephropathy, Urine odour abnormal, Nephroangiosclerosis, Tubulointerstitial nephritis, Glomerulonephritis, Urine abnormality, Proteinuria, Haematuria, Creactive protein increased, Inflammation 3 months Serious Recovered	Approximately 3 months after the Dose 1 of Comirnaty, the patient was diagnosed with IgA nephropathy based on a kidney biopsy. Immunofluorescence results were suggestive of active subacute and chronic mesangial nephropathy. Serum creatinine 86 µmol/l (normal range not reported), haematuria at 1,000,000/ml. The patient also experienced an inflammatory syndrome with CRP at 14 mg/L and a sedimentation rate of 51 mm; normal ranges unspecified. Spontaneously favourable outcome.	Long latency of 3 months suggests a biologically less plausible causal association. In addition, immunofluorescence results were suggestive of active subacute and chronic mesangial nephropathy thus, indicating a pre-existing disease. Besides, an inflammatory syndrome is suggestive of concurrent infection potentially having a role in the nephropathy.
Rapporteur assessment comment (14): Spontaneous medically confirmed case reporting a TTO of 3 months after 1st dose and confounding factors for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

[redacted] 16 Y/M [redacted] Dose 2 Spontaneous Y	Haematuria Not reported	Renal impairment, IgA nephropathy, Haematuria, Pyrexia 1 day Serious Not recovered	The patient presented with pyrexia and frank haematuria the following day of receiving Dose 2 of Comirnaty. Family history (mother) of IgA nephropathy. Details of first dose of covid vaccine unknown. Serum creatinine level increased from 0.87 to 1.26 mg/dL and urine protein to creatine ratio was 0.35 g/gCr; normal ranges unknown. On the 24th day of vaccination, a renal biopsy revealed crescent formation and mild mesangium proliferation, leading to a diagnosis of IgA nephropathy. The patient was treated with steroids and immunosuppressants.	Family history of IgA nephropathy confounds the assessment as does pre-existing haematuria. No information on first dose of covid vaccine and concomitant medications.
Rapporteur assessment comment (15): Spontaneous medically confirmed case reporting confounding factors for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

[redacted] 34 Y/F [redacted] Dose 2 Spontaneous Y	Arthralgia / Gestational diabetes / Migraine / Psoriasis / Synovial cyst removal Not reported	IgA nephropathy, Maternal exposure during pregnancy 47 days Serious Not recovered	The patient received 2 doses of Comirnaty at an interval of 22 days. 47 days after second dose, proteinuria and haematuria was detected on urine strip test. Approximately 2 months later, the patient had her first nephrology consultation: renal function was normal with creatinine at 49 µmol/L, urea at 4 mmol/L (normal ranges not reported), micro haematuria at 386/mm3, proteinuria at 1.07 g/L, HBV positive. A renal biopsy revealed 36 permeable glomeruli optically with a sclerohyalin glomerulus, permeable glomeruli represented the mesangial axes that were frequently enlarged with an increase in cellularity. Discrete lesions with inability to make a formal diagnosis in the absence of a direct immunofluorescence study.	History of autoimmune disease (psoriasis) is a risk factor for IgA nephropathy as is chronic liver disease from HBV although it is not clear if the patient has active liver disease. In addition, the long latency from vaccination is suggestive of a less likely biological association to vaccination. Finally, renal parameters were normal, and biopsy was not confirmatory, lacking immunofluorescence to confirm the deposition of IgA.
Rapporteur assessment comment (16): Spontaneous medically confirmed case reporting a TTO of 47 days and confounding factors in medical history for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				
[redacted] 15 Y/M [redacted] Dose 2 Literature spontaneous Y	Haematuria / Protein urine present / Urinary occult blood positive Not reported	IgA nephropathy, Mesangioproliferative Glomerulonephritis, Pyrexia 1 day Serious Unknown	The following day of receiving Dose 2 of Comirnaty, the patient experienced pyrexia and frank haematuria. 1 week later, a renal biopsy showed mild mesangioproliferative nephritis. In one glomerulus, cellular crescents were observed. Fluorescence antibody technique revealed IgA deposition in the mesangial region leading to a diagnosis of IgA nephropathy. No information regarding first dose of covid vaccine.	No information on first dose of covid vaccine and concomitant medications. The patient already had history of occult blood in urine and haematuria suggesting disease at baseline with natural progression should be considered.
Rapporteur assessment comment (17): Medically confirmed literature case reporting confouding factors in medical history for the casuse of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

[redacted] 49 Y/F [redacted] Dose 2 Spontaneous Y	Endometriosis / Rhinitis allergic Dienogest	IgA nephropathy, Haematuria, Proteinuria Unknown Serious Recovering	The patient received Dose 2 of Comirnaty on 21 May 2021. On an unspecified date in June 21, the patient developed haematuria, proteinuria and IgA nephropathy. Vaccination history included: Comirnaty (1st dose) and DPT (dates unspecified). The patient also had a history of urinary occult blood 2+ 3 years before. She was hospitalized 6 months later, and a kidney biopsy confirmed the diagnosis of IgA nephropathy. The patient was treated with steroids.	Limited information provided in this case regarding exact latency, time for other vaccinations, baseline and current labs. Patient had a history of occult blood, but no other details provided. Biopsy performed 6 months after the event, no details provided.
Rapporteur assessment comment (18): Spontaneous medically confirmed case with limited information which is considered unassessable.				
[redacted] 12 Y/M Dose 1 [redacted] Literature spontaneous Y	None None	IgA nephropathy 1 day Serious Recovering	The patient presented with new-onset gross haematuria, proteinuria, and acute kidney injury < 24 h following the Dose 1 of Comirnaty. The patient had no family history of autoimmune diseases. A kidney biopsy was consistent with IgA nephropathy. Microscopic examination of the biopsy sections revealed 11 glomeruli in the submitted cores, all of which showed mild increase of mesangial cells and matrix; no thickening of capillary loops, segmental sclerosis, crescent formation or necrosis were seen. Many of the tubules showed red cell casts with mild tubular injury and flattening of epithelial cells. The immunofluorescence studies showed 5 glomeruli revealing granular mesangial deposits of IgA (+1) and C3 (+1), and absence of IgG, IgM, C4 and fibrinogen. Other labs: Serum Creatinine 1.77 mg/dl (normal range: 0.53-0.79 mg/dl), Serum Urea 61 mg/dl (normal range: 15-36 mg/dl),	The latency of <24 hours after the first exposure to vaccination is less biologically plausible. Besides, lack of information regarding medical history and concomitant medications precludes an adequate assessment.

			complement factor C3: 137 mg/dl, C4: 21 mg/dl, CRP 51.23 mg /dl (0.1- 2.8). Urine analysis: proteinuria at 1.7 g/l, RBCs 1920/ul. The event improved after treatment with methylprednisolone.	
Rapporteur assessment comment (19): Medically confirmed case with limited information which is considered unassessable.				
[redacted] 18 Y/F [redacted] Dose 3 Spontaneous Y	Seasonal allergy Bepotastine Besilate	IgA nephropathy, Haematuria, Cystitis, Urinary occult blood, Protein urine, Pyrexia, Fatigue, Malaise 2 days Serious Not recovered	2 days after receiving Dose 3 of Comirnaty, the patient presented with proteinuria (2+) and haematuria (50- 99, urinary occult blood 3+). Primary immunization was completed with Comirnaty 8 months earlier. A urine culture was positive for Escherichia coli and Klebsiella pneumoniae. Suspected IgA nephropathy.	The diagnosis of IgA nephropathy was not confirmed. No confirmatory diagnostics (including biopsy) provided. Concurrent urinary tract infection confounds the assessment.
Rapporteur assessment comment (20): Spontaneous case with no confirmed diagnosis of IgA nephropathy which is considered unassessable.				
[redacted] 24 Y/M [redacted] Dose 2 Spontaneous Y	Allergy to animal / Asthma / Colour blindness / Deafness unilateral / Dust allergy / Mite allergy Not reported	IgA nephropathy, Acute kidney injury, Pyrexia, Chills, Odynophagia, Haematuria, Pharyngitis streptococcal 79 days Serious Not Recovered	The patient presented with fever, chills, odynophagia, haematuria and streptococcal pharyngitis approximately 2.5 months after receiving Dose 2 of Comirnaty. No information regarding first dose of covid vaccine. A kidney biopsy confirmed IgA nephropathy. Serum creatine 102 µmol/l.	Long latency of 79 days suggests a biologically implausible latency. Additionally, concurrent streptococcal pharyngitis is a potential and more likely etiology of nephropathy.
Rapporteur assessment comment (21): Spontaneous medically confirmed case reporting a TTO of 79 days and a co-infection for the cause of IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure				

[redacted] 42 Y/F [redacted] Dose 2 Spontaneous Y	Not reported Influenza vaccine	IgA nephropathy, Haematuria, Protein urine, Renal disorder 2 days Serious Not recovered	The same day as receiving the second dose of Comirnaty, the patient developed haematuria and proteinuria and was diagnosed with IgA nephropathy. The patient received first dose of Comirnaty on an unspecified date. A renal biopsy was consistent with IgA nephropathy (details unspecified). The patient was treated with methylprednisolone.	Medical history and timing between 2 doses of Comirnaty unknown. Further, concomitant influenza vaccine (date of administration unknown) confounds the assessment.
Rapporteur assessment comment (22): Spontaneous medically confirmed case with limited information which is considered unassessable.				
[redacted] 14 Y/F [redacted] Dose 2 Literature spontaneous Y	Haematuria / Urine analysis abnormal Not reported	IgA Nephropathy 1 day Serious Unknown	On the following day of the Dose 2 of Comirnaty, the patient developed high fever and frank haematuria. The patient received Dose 1 of Comirnaty on an unspecified date. On the 7th day, urine albumin/Cr ratio increased to 1.99 g/gCr. On the 12th day, the serum albumin level decreased to 3.6 g/dL (serum creatinine: 0.54 mg/dL); normal ranges not reported. Based on the renal biopsy results, a diagnosis of IgA nephropathy was made. Reportedly, it was considered that latent IgA nephropathy became prominent because there was a strong temporal relationship with vaccine.	History of haematuria and abnormal urine analysis however, no diagnostic details are provided. Besides, details of biopsy results and concomitant medications are not provided.
Rapporteur assessment comment (23): Medically confirmed case with limited information which is considered unassessable.				

[redacted] 13 Y/F [redacted] Dose 3 Spontaneous Y	Not reported Not reported	IgA nephropathy, Cystitis, Pyrexia, Haematuria, Proteinuria 2 days Serious Recovering	2 days after receiving Dose 3 of Comirnaty, the patient developed pyrexia, frank haematuria and proteinuria. Primary immunization completed with Comirnaty 7 months earlier. Cystitis was suspected. A blood test demonstrated that an inflammatory response was alleviated, however haematuria and proteinuria persisted and deformed erythrocytes were observed in the urine. Reportedly, the patient had undiagnosed IgA nephropathy, which was possibly "exteriorized" owing to pyrexia (infection). Renal biopsy was not performed.	The reporter indicated suspected undiagnosed nephropathy possibly unmasked due to concurrent infection raises the likelihood of underlying nephropathy. Further, no confirmatory biopsy was performed.
Rapporteur assessment comment (24): Spontaneous confirmed literature case reporting pre-existing undiagnosed IgA nephropathy. Therefore the cause of IgA nephropathy in this case is considered unlikely related to Comirnaty exposure.				

MAH's summary of the 43 cases

A total of 7/43 cases reported IgA nephropathy/ condition aggravated after dose 1 of Pfizer/BioNTech COVID-19 vaccine. Four of these cases reported a short latency of 1-2 days thus, making a biological association less likely. Besides, 2 of these 4 cases had additional confounders including concurrent infection and concomitant medications including mycophenolate mofetil and tacrolimus. The remaining 2/4 cases had limited information regarding medical history, concomitant medications and / or relevant investigations thus, precluding an adequate assessment. The remaining 3/7 cases were confounded by a long latency of 3 months, underlying autoimmune disease, suspected concurrent infection and chronic nephropathy.

Of the remaining 36 cases, 32 reported IgA nephropathy/condition aggravated after dose 2. Of these 32 cases, 23 reported 1 or more confounders like concurrent infection (e.g.: influenza), concomitant medications (enalapril, lisinopril), pre-existing haematuria, underlying autoimmune conditions, already aggravated renal dysfunction or poorly controlled IgA nephropathy, probable natural disease progression, or the biopsy was not confirmatory, long latency of more than 6 weeks and or family history.

The remaining 9 cases had insufficient information regarding medical history, concomitant medications, baseline labs or relevant investigations thus, precluding an adequate assessment. Of the remaining 4 cases, 3 reported IgA nephropathy after dose 3. All these 3 cases lacked information regarding medical history, concomitant medications and/or relevant investigations thus, precluding an adequate assessment.

In the remaining case, dosing information was not provided. In this case, medical history and concomitant medications were not reported. Further, the clinical presentation raised the possibility that another nephropathy was present.

Biopsy at the time of event occurrence was reported in 28/43 cases, biopsy was not done in 4 cases while 11 cases did not have information regarding biopsy. Outcome was recovered/recovering in 20/43 cases, not recovered in 12 cases while outcome was not reported in 11 cases. The patients received treatment with steroids/immunosuppressants in 12/43 cases. No treatment was provided in 6 cases of which 5 were recovering/recovered. Treatment information was not provided in the 25 remaining cases.

Rapporteur assessment comment:

A total of 103 cases of IgA nephropathy were retrieved from MAH's safety database, 8 cases were excluded because no IgA nephropathy, unknown COVID-19 vaccine, or implausible latency, and 52 cases reported limited information precluding a meaningful assessment. Of the remaining 43 cases:

- 24 cases reported new onset of IgA nephropathy, of which the PRAC Rapporteur considered that in 13 cases confounding factors seem to provide a more likely explanation for the event and that causality with Comirnaty cannot be established in these cases and that 11 cases are unassessable for a meaningful causality assessment.
- 19 cases reported condition aggravated in pre-existing history of IgA nephropathy, of which the PRAC Rapporteur considered 15 cases unassessable and 4 cases reported confounding factors seem to provide a more likely explanation for the event and that causality with Comirnaty cannot be established in these cases (AER numbers [redacted] and [redacted].

In conclusion, based on the information provided in the cases reporting new onset of IgA nephropathy or condition aggravated in pre-existing history of IgA nephropathy, there is no a causal association between Comirnaty exposure and occurrence of IgA nephropathy or exacerbation of IgA nephropathy.

Observed versus expected analyses

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 101 immunoglobulin A (IgA) nephropathy cases reported cumulatively through 18 June 2022 globally (table 5).

The overall expected case counts of IgA nephropathy were estimated using background incidence rates (IR) reported by a retrospective cohort study in population older than 15 years of age residing in a north-western region of Italy. Between January 1, 1970, and December 31, 1994, 1,926 cases of biopsy-proven primary glomerulonephritis were diagnosed, and IgA nephropathy was the most frequent type with an overall incidence rate 1.47 per 100,000 population per year and a predominance in males (males, 2.27 versus females, 0.67 per 100,000 population per year). These rates provided a low range of background rates for IgA nephropathy, and therefore, low expected case counts to conservatively estimate O/E results. 2 reviews reported overall incidence rate of IgA nephropathy ranged from 2.5 to 4.5 per 100,000 population per year with higher rates in Asia.

Table 5. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of IgA Nephropathy Through 18 June 2022

Stratification	Observed cases	Time at risk (PY)	Background rates per 100,000 PY	Expected cases	O/E ratio	95% CI LL	95% CI UL
7-day risk window							
US/EEA							
Sex							
Males	12	9,010,462	2.27	204.54	0.059	0.030	0.102
Females	22	10,160,733	0.67	68.08	0.323	0.203	0.489
Overall							
Any dose	34	19,171,195	1.47	281.82	0.121	0.084	0.169
Dose 1	7	7,645,271	1.47	112.39	0.062	0.025	0.128
Dose 2	21	7,099,445	1.47	104.36	0.201	0.125	0.308
Additional/booster dose(s)*	6	4,426,479	1.47	65.07	0.092	0.034	0.201
Global overall	77	42,516,664	1.47	624.99	0.123	0.097	0.154
14-day risk window							
US/EEA							
Sex							
Males	12	18,006,074	2.27	408.74	0.029	0.015	0.051
Females	23	20,304,722	0.67	136.04	0.169	0.107	0.254
Overall							
Any dose	35	38,310,796	1.47	563.17	0.062	0.043	0.086
Dose 1	7	15,284,506	1.47	224.68	0.031	0.013	0.064
Dose 2	22	14,192,990	1.47	208.64	0.105	0.066	0.160
Additional/booster dose(s)*	6	8,833,300	1.47	129.85	0.046	0.017	0.101
Global overall	83	84,874,815	1.47	1247.66	0.067	0.053	0.082
21-day risk window							
US/EEA							
Sex							
Males	12	26,983,060	2.27	612.52	0.020	0.010	0.034
Females	25	30,427,706	0.67	203.87	0.123	0.079	0.181
Overall	37	57,410,765	1.47	843.94	0.044	0.031	0.060
Any dose							
Dose 1	8	22,917,286	1.47	336.88	0.024	0.010	0.047
Dose 2	22	21,280,003	1.47	312.82	0.070	0.044	0.106
Additional/booster dose(s)*	7	13,213,476	1.47	194.24	0.036	0.014	0.074
Global overall	86	127,075,389	1.47	1868.01	0.046	0.037	0.057

CI = confidence interval; EEA=European Economic Area; LL = lower limit; PY = person-years; UL= upper limit; US=United State.
*Additional /booster dose(s) denote first booster (or additional) or second booster dose from data sources that supply vaccine doses administered for this analysis.

Rapporteur assessment comment:

All O/E ratios for were well below 1.

MAH's conclusion

The 103 cases of IgAN retrieved from the global safety database is a relatively small number of cases when considering the number of doses (estimated 1-2 billion) administered worldwide since authorization and the number of AE reports (>1.6 million) for BNT162b2 in the safety database. Concentration on cases that appeared to have sufficient information still revealed some with scant detail, lack of support of IgAN diagnosis, or plausible alternative explanations for IgAN. Cases without confounders have temporality as the main link to vaccination. Trends observed were that most cases occurred following dose 2 and many cases were from Japan. The higher number of cases describing females versus males and the fact that most cases were reported in adults 18-50 years of age is consistent with the overall dataset of spontaneous AE reports for the vaccine. It is notable that Japan was the highest reporting country (35% of cases of IgAN) because the Japanese healthcare system is recognized as being proactive in renal disorder screening.

No adverse events of IgA nephropathy were reported in the pivotal clinical trials for BNT162b2 and there were a very small number of participants with a medical history of IgAN.

There has been no statistical signal of disproportionate reporting in the MAH safety database for the PT IgA nephropathy.

The published literature mostly comprises clinical case reports and a systematic review qualitatively analysing 14 such cases. Although small, a prospective study of COVID-19 vaccination in patients with existing IgAN suggested no impact of vaccination on the clinical course of the disease.

O/E ratios were below one suggesting that the number of observed cases of IgA nephropathy is not higher than expected in the absence of Pfizer/BioNTech COVID-19 vaccines overall and within the queried strata.

Overall, a causal association of Comirnaty with IgA nephropathy cannot not be concluded based on this review of available clinical, literature and post-marketing data. The MAH will continue to monitor the subject using routine Pharmacovigilance.

Rapporteur assessment comment:

Literature

Of the 49 results retrieved from the literature search through 30 Jun 2022, no new important information could be identified concerning IgA nephropathy.

Clinical trial data

There were no reports of IgA nephropathy in the clinical trials.

Post-marketing

A total of 95 valid cases of IgA nephropathy were retrieved from MAH's safety database, of which 24 cases reported new onset of IgA nephropathy (13 cases reported confounding factors seem to provide a more likely explanation for the event and that causality with Comirnaty cannot be established in these cases and 11 cases are considered unassessable) and 19 cases reported condition aggravated in pre-existing history of IgA nephropathy (15 cases are considered unassessable and 4 cases reported confounding factors seem to provide a more likely explanation for the event and that causality with Comirnaty cannot be established in these cases). The remaining 52 cases reported limited information precluding a meaningful assessment.

In conclusion, based on the information provided in the cases reporting new onset of IgA nephropathy or condition aggravated in pre-existing history of IgA nephropathy, there is not a causal association between Comirnaty exposure and occurrence of IgA nephropathy or exacerbation of IgA nephropathy.

Observed versus expected analyses

All O/E ratios for were well below 1.

Overall, MAH's conclusion is endorsed that based on provided data no causal association of Comirnaty with IgA nephropathy can be concluded. No new important information could be identified concerning IgA nephropathy. The MAH should closely monitor any new cases, patterns, or trends of reporting IgA nephropathy through routine pharmacovigilance.

Issue solved

2.2.1. Post-approval regulatory requests

2.2.1.1. Hearing loss

Response to the PRAC request 2 from the 14th (3rd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.13):

> *The MAH is requested to perform a cumulative review on the association between sudden sensorineural hearing loss and Comirnaty exposure, including a review of the relevant new literature published after the reporting period of the 14th SSR, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.*

MAH's response (Appendix 6A.3. of the PSUR):

Reference is also made to the 08 Jun 2022 request from Health Canada for a cumulative review of cases of tinnitus and hearing loss and provision of an observed to expected analysis.

The MAH provided a cumulative review of hearing loss and tinnitus.

Literature

A cumulative search of literature was conducted through 18 June 2022, retrieved four relevant literature articles:

1. Formeister EJ, Wu MJ, Chari DA, et al. Assessment of Sudden Sensorineural Hearing Loss After COVID-19 Vaccination. JAMA Otolaryngol Head Neck Surg. 2022;148(4):307–315. doi:10.1001/jamaoto.2021.4414.

   This cross-sectional study and case series involved an up-to-date population-based analysis of 555 incident reports of probable Sensorineural Hearing Loss (SSNHL) in the US Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System (VAERS) over the first 7 months of the US vaccination campaign (December 14, 2020, through July 16, 2021). In addition, data from a multi-institutional retrospective case series of 21 patients who developed SSNHL after COVID-19 vaccination were analyzed. The study included all adults experiencing SSNHL within 3 weeks of COVID-19 vaccination who submitted reports to VAERS and consecutive adult patients presenting to 2 tertiary care centers and 1 community practice in the US who were diagnosed with SSNHL within 3 weeks of COVID- 19 vaccination. Results: A total of 555 incident reports in VAERS (mean patient age, 54 years [range, 15-93 years]; 305 women [55.0%]; data on race and ethnicity not available in VAERS) met the definition of probable SSNHL (mean time to onset, 6 days [range, 0-21 days]) over the period investigated, representing an annualized incidence estimate of 0.6 to 28.0 cases of SSNHL per 100 000 people per year. The rate of incident reports of SSNHL was similar across all 3 vaccine manufacturers (0.16 cases per 100 000 doses for both Pfizer-BioNTech and Moderna vaccines, and 0.22 cases per 100 000 doses for Janssen/Johnson & Johnson vaccine). The case series included 21 patients (mean age, 61 years [range, 23-92 years]; 13 women [61.9%]) with SSNHL, with a mean time to onset of 6 days (range, 0-15 days). Patients were heterogeneous with respect to clinical and demographic characteristics. Preexisting autoimmune disease was present in 6 patients (28.6%). Of the 14 patients with posttreatment audiometric data, 8 (57.1%) experienced improvement after receiving treatment. One patient experienced SSNHL 14 days after receiving each dose of the Pfizer-BioNTech vaccine. Study Conclusions: In this cross-sectional study, findings from an updated analysis of VAERS data and a case series of patients who experienced SSNHL after COVID-19 vaccination did not suggest an association

between COVID-19 vaccination or an increased incidence of hearing loss compared with the expected incidence in the general population (the annual incidence of idiopathic SSNHL was estimated to be 11 to 77 cases per 100 000 people per year).

MAH comment: The MAH agrees with the study authors that the reporting rate of hearing loss compared with the expected incidence in the general population suggests no association with COVID-19 vaccination. Strengths of the study include population-based setting with large sample size. One of the major limitations in the study is a lack of concurrent comparison group. Formeister et al compared the incidence of SSNHL after vaccination to a historical incidence of idiopathic SSNHL that was reported during 2006-2007 in the US, therefore changes in the demographics and in the diagnostic criteria of SSNHL and the fact that the historical rate was estimated from claims data (and not self-reported data) may influence the comparison.

2. Yanir Y, Doweck I, Shibli R, Najjar-Debbiny R, Saliba W. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss. JAMA Otolaryngol Head Neck Surg. 2022;148(4):299–306. doi:10.1001/jamaoto.2021.4278.

   Yanir performed a retrospective, observational study on data from the Clalit Health Services (CHS), which provides inclusive healthcare for more than half of the Israeli population. This database, designed for administrative and clinical management is available for clinical studies. They identified cases of SSNHL by using the (International Classification of Diseases, Ninth Revision) ICD-9 diagnosis codes for sensorineural hearing loss (SNHL) and included only those patients with concurrent prednisone treatment (defined as purchasing a prescription from start date of diagnosis of SNHL up to 30 days after). Observed cases of SSNHL appearing after COVID-19 vaccination were compared with the expected cases of SSNHL based on experience of the CHS population in 2018 and 2019 (before the COVID-19 pandemic and vaccine introduction in Israel). CHS members aged > 16 years who received the first Pfizer-BioNTech vaccine dose from 20 December 2020 (the start date of mass COVID-19 vaccination in Israel) until 30 April 2021 were included. Those not diagnosed with SSNHL after dose 1, who received dose 2 before 30 April 2021 made the population for estimation of the standardized incidence ratios (SIR) after second vaccine dose. Retrospective follow-up of cases through 31 May 2021 was performed. Observed cases occurring within 21 days of the first and second Pfizer-BioNTech vaccine dose were compared with expected cases estimated from the historic comparator group. During the data collection period, 2.6 million CHS members received first Pfizer-BioNTech vaccine dose; of these 2.4 million received the second dose before 30 April 2021. SSNHL was detected within 21 days in 91 patients after the first vaccine dose and in 79 patients after the second vaccine dose. When using the 2018 comparator group for reference, the age- and sex- weighted SIRs were 1.35 (95% CI, 1.09-1.65) for the first vaccine dose and 1.23 (95% CI, 0.98- 1.53) for the second dose. Higher SIRs were observed in female patients aged 16 to 44 years (SIR, 1.92; 95% CI, 0.98-3.43) and patients ≥ 65 years old (SIR, 1.68; 95% CI, 1.15-2.37) after the first dose and in male patients 16 to 44 years (SIR, 2.45; 95% CI, 1.36- 4.07) after the second dose. The authors concluded that the Pfizer-BioNTech vaccine might be associated with an increased risk of SSNHL; however, the effect size is very small and the benefit of COVID-19 vaccines outweighs its potential association with SSNHL.

   MAH comment: Strengths of the study include population-based setting with large sample size. One of the limitations in the study is a lack of concurrent comparison group. The study utilized recent historical data (2018 and 2019) before the COVID-19 pandemic; therefore, no major temporal differences are expected. However, confounding and detection bias could have been introduced. Although Yanir et al have controlled for age and sex through standardization, age

was controlled in wide age ranges (i.e., 16-44, 45-64, and ≥65 years). Given that age is a strong risk factor for SSNHL and vaccinated people were older (and may be sicker), especially during the early phase vaccination program, there could be residual confounding by age which contributed to the increased occurrence of SSNHL. There could also be confounding by other unmeasured factors (e.g., cardiovascular and coagulation disorders, which are risk factors for SSNHL) that might differ between the vaccinated group and the general population. Last but not least, the observed association could be susceptible to detection bias during the COVID-19 pandemic period when patients may be more likely to be alert to any adverse events after vaccination and seek medical care for hearing loss (or other adverse events) after vaccination and thus have SSNHL diagnosed. The weak association in the study could be an artifact of confounding and detection bias.

3. Wichova H, Miller ME, Derebery MJ. Otologic Manifestations After COVID-19 Vaccination: The House Ear Clinic Experience. Otol Neurotol. 2021 Oct 1;42(9):e1213-e1218. doi: 10.1097/MAO.0000000000003275. PMID: 34267103; PMCID:PMC8443418.

   The authors conducted a retrospective chart review in recently vaccinated patients over a 30-day time frame in a tertiary otology ambulatory practice. Results: Within the same 30-day time period in 2019, 2020, and 2021, 1.6, 2.4, and 3.8% respectively, of all office visits were for patients with the diagnosis of new onset idiopathic sensorineural hearing loss (SSNHL) without other underlying otologic diagnoses. In this time frame in 2021, 30 patients out of the 1,325 clinical visits had new or significantly exacerbated otologic symptoms that began shortly after COVID-19 vaccination. Specifically, 18 patients received Moderna and 12 patients received Pfizer vaccine. Their mean age was 60.9±13.8 years old; 11 were women and 19 men. The mean onset of symptoms was 10.18 ± 9 days post-vaccination. Symptoms included 25 patients (83.3%) with hearing loss, 15 (50%) with tinnitus, eight (26.7%) with dizziness, and five (16.7%) with vertigo. Eleven patients had previous otologic diagnoses, including six patients with Menière's disease, two with autoimmune inner ear disease (AIED), and three having both. Authors' Conclusions: There are no definite correlations to the COVID-19 pandemic or vaccination and new or worsened otologic symptoms. Vaccinated patients with new or exacerbated otologic symptoms should be promptly referred for evaluation.

   MAH comment: The MAH agrees with the authors that no definite correlation between vaccination and new or worsened otologic symptoms could be concluded. The sample size of this retrospective chart review is very small and the clinical data regarding vaccination is limited to the intake questionnaire and details that were documented during a clinic visit.

4. Woodcock R, Bartels L. Preliminary Evidence of a Link between COVID-19 Vaccines and Otologic Symptoms. medRxiv 2022.02.23.22271144; doi: https://doi.org/10.1101/2022.02.23.22271144.

   This non peer-reviewed article in preprint investigates whether U.S. Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System (VAERS) data suggest an association between vertigo, tinnitus, hearing loss, Bell's palsy and the COVID-19 vaccines administered in the United States. VAERS reports of these events were compared with published rates for the general population. Of note, the author Ramsi A. Woodcock suffers from otologic symptoms that he believes to have been caused by COVID-19 vaccination; he is the patient of the 2nd author, Loren J. Bartels. Results: The COVID-19 vaccines were associated with statistically significant increases in the reporting of vertigo, tinnitus, hearing loss, and Bell's palsy (1877, 50, 12, and 14 cases per 100,000, respectively). In relation to the mRNA-1273 or BNT162b2 vaccines, the Ad26.COV2.S vaccine was associated with a statistically significant excess incidence of vertigo, tinnitus, and hearing loss of at least 723, 57, and 55

cases per 100,000, respectively. Authors' Conclusion: These results suggest an association between the COVID-19 vaccines and vertigo, tinnitus, hearing loss, and Bell's palsy. They also suggest that the association is relatively strong for the Ad26.COV2.S vaccine.

MAH comment: This article is not weighed heavily in consideration of this signal for these reasons: it is a pre-published and non-peer reviewed article, the author states a clear bias (experienced an AE they believe was caused by COVID-19 vaccination) and the author, while using a well-known database, does not explain their methodology for obtaining or assessing the VAERS data or the background rates. Their use of the term "incidence" as opposed to "reporting rates" with respect to the VAERS data and focus on the initial part of the observation period as a way to account for underreporting is questionable. Further, all COVID-19 vaccines were included in the assessment.

MAH's overall conclusion: The literature articles retrieved in the search do not present any new significant safety information or conclude a causal relationship.

Rapporteur assessment comment:

The study of Formeister et al. and the study of Yanir et al. were already assessed in the 14th (3rd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.13):

- Formeister et al. did not suggest an association between COVID-19 vaccination and an increased incidence of SSNHL compared with the expected incidence in the general population, based on the cross-sectional analysis of VAERS data and review of SSNHL cases.
- Yanir et al. concluded that the Pfizer-BioNTech vaccine might be associated with an increased risk of SSNHL; however, the effect size is very small. However, the strength of the study includes population-based setting with a large sample size of which the results could be considered a signal for a potential association between SSNHL and Comirnaty exposure.

As a result the MAH was requested to perform a cumulative review on the association between sudden sensorineural hearing loss and Comirnaty exposure.

In the two additional retrieved articles:

- Wichova et al. stated that no definite correlation between vaccination and new or worsened otologic symptoms could be concluded.
- The study of Woodcock et al., a publication not-peer reviewed and published on medRxiv, is not considered relevant due to missing information regarding used methodology for the comparison of the rates of vertigo, tinnitus, hearing loss, Bell's palsy between the VAERS database (after COVID-19 vaccination) and the published rates for the general population.

No new important safety information could be identified from literature concerning hearing loss and tinnitus.

Safety database review

The Pfizer safety database was searched cumulatively through 18 June 2022 for all BNT162b2; BNT162b2S01 cases reported using MedDRA v 25.0 PTs of Conductive deafness, Deafness, Deafness bilateral, Deafness neurosensory, Deafness occupational, Deafness permanent, Deafness transitory, Deafness unilateral, Hypoacusis, Mixed deafness, Neurosensory hypoacusis, Sudden hearing loss, Tinnitus, and/or Tinnitus retraining therapy.

Result

Cases with both Hearing loss and Tinnitus events

A total of 2009 cases (with a total of 10,592 events) reporting both tinnitus and hearing loss events were retrieved.

The majority of cases (1998) were spontaneous; 1601 cases were serious, 408 were nonserious. There were 1177 females, 795 males, and sex was not reported in 37 cases. When provided, the ages ranged as shown in Table 2 below. The mean and median ages were 49 years (n=1921).

Table 2. Reported Age in 2009 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	27	1.30%
18 - 30 years	176	8.80%
31 - 50 years	840	41.80%
51 - 64 years	561	27.90%
65 - 74 years	238	11.80%
Greater than or equal to 75 years	82	4.10%
Unknown	85	4.20%

Further analysis was concentrated on 1491 cases reporting relevant events with time to onset (latency) of 0 to 21 days post vaccination.

Out of these 1491 cases, 431 cases reported a pre-existing medical condition that represents a reasonable alternative cause of the relevant events. Examples of the conditions include: deafness, tinnitus, COVID-19, autoimmune disorders, anxiety and panic disorders, balance and vestibular disorders, diabetes, chronic sinusitis, and auditory conditions. Of these 431 cases, 166 reported pre-existing deafness and/or tinnitus, 22 of which reported an aggravation or exacerbation/worsening of the condition after vaccination.

An additional 72 cases reported use of co-suspect or concomitant medications that represent a potential alternative cause of the events. Examples of the medications include: Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), beta blockers, tricyclic antidepressants, aspirin, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), benzodiazepines, loop diuretics, isotretinoin, immunosuppressants and other vaccines.

Out of the remaining 988 cases in this dataset, 27 cases lacked details on medical history, concomitant medications, outcome, and dose number precluding a thorough assessment.

Of the remaining 961 cases, further analysis was concentrated on the 212 reports that were healthcare professional confirmed (HCP) cases. Of these 212 cases (459 serious relevant events), 104 cases co-reported PTs unlikely to be caused by vaccination that suggested the possibility of concomitant conditions (e.g., ear infection, vestibular disorder, vertigo, syncope, tympanic membrane disorder, COVID-19, nasal congestion, middle ear effusion, ear hemorrhage, ear canal stenosis, inner ear infarction, etc.) contributing to the cause of the hearing loss/tinnitus events.

In the remaining 108 HCP cases (159 relevant events), when dose sequence was provided, it was Dose 1 for 60 relevant events, Dose 2 for 63 events and Dose 3 for 11 events (there were no events reported post Dose 4). The outcome of the relevant events at the time of reporting was resolved/resolving for 54 events; not resolved for 84 events; resolved with sequelae for 6 events; unknown for 15 events. The most frequently reported latency was Day 1 (for 24 events) followed by Day 0 (for 17 events), Day 5 (for 16 events), and Day 2 (for 15 events).

Medically confirmed cases with no co-reported events

Out of these 108 cases, 71 cases reported relevant events of hearing loss and/or tinnitus only (no other events were reported in these cases).

In 50 of these 71 cases, no information on diagnostic procedures or tests supporting the diagnosis were provided, therefore the causality assessment for these 50 cases is Unassessable per the WHO-UMC causality assessment categories8.

In 21 of the 71 cases, diagnostic tests and/or procedures such as Acoustic stimulation test, Audiogram, Ear, nose and throat examination, and Otic examination were reported. Of note, none of these cases reported confirmatory Computerized Tomography (CT) scan and/or Magnetic Resonance Imaging (MRI) results. Twenty (20) out of 21 cases occurred in adults 24 to 67 years old. One of the cases reported a patient with pre-existing alopecia areata and psoriasis. Two other cases reported pre-existing medical history and concomitant medications for hypothyroidism and benign prostatic hyperplasia, respectively, and another 17 remaining adult cases did not report any additional details. The last of these cases describes a possible rechallenge in a child:

- A 14-year-old female with no relevant medical or family history and no concomitant medications or vaccines experienced tinnitus and deafness (the patient had difficulty in talking with family members) 5 days following dose 1 of Comirnaty. There were no complaints of giddiness. The following day, the patient's tinnitus was slightly alleviated compared to the previous day, however she sought medical attention and her audiometry test showed worsening compared to testing in May (reason for pre-vaccination hearing test was not explained). A head MRI approximately 1 month later showed "no significant change." The reason for a previous MRI of the head was not explained. The patient had dose 2 of Comirnaty and reported that her tinnitus was aggravated, she underwent another head MRI (no change) and further audiometry testing. The audiometry tests show progressive worsening of hearing loss from May to 10 Dec 2021.

Date	Test or Vaccine
May 2021	Pure tone audiometry: 21.3 dB R, 17.5 dB L
28 Aug 2021	Dose 1 vaccine
03 Sep 2021	Pure tone audiometry: 26.3 dB R, 27.5 dB L
03 Oct 2021	Head MRI "no significant change"
18 Sep 2021	Dose 2 vaccine
03 Oct 2021	Head MRI "no significant change"
12 Nov 2021	Pure tone audiometry: 37.5 dB R, 42.5 dB L
10 Dec 2021	Pure tone audiometry: 45.0 dB R, 36.3 dB L

The causality assessment of these 21 cases is Possible.

Medically confirmed cases with co-reported adverse events

Out of the remaining 108 cases, 37 had co-reported events along with the hearing and tinnitus events. In 25 of these 37 cases, either no diagnostic procedures or tests supporting the diagnosis were reported, test results were reported as normal, or test results were not available at the time of reporting. The causality assessment for these 25 cases is Unassessable per the WHO-UMC causality assessment categories.

In 12 of the 37 cases diagnostic procedures/tests such as Acoustic Stimulation, Audiogram, ENT exam, Investigation, Otic exam, and/or Weber tuning were reported, supporting the diagnosis. Upon detailed review of the narratives of these 12 cases, the following factors were noted in 6 of the cases making an individual causal association Unlikely:

- One report was in a 54-year-old woman and was associated with left-sided facial numbness (head CT normal),
- One report in a 34-year-old man was associated with actual swelling of the ear on the affected side, suggesting the possibility of a contributing outer-ear etiology,
- Two cases reported a pre-existing medical history of malignancy introducing the possibility of exposure to ototoxic chemotherapeutics,
- One report in a 34-year-old woman with 2 years of seasonal allergies and intranasal steroid use introducing the possibility of eustachian tube dysfunction,
- One report in a 15-year-old girl who underwent a tympanoscopy and was found to have a probable polylymphatic fistula.

The remaining 6 reports, while lacking details, did not provide alternative explanations for the tinnitus or deafness making a causal association Possible.

Rapporteur assessment comment:

Through 18 Jun 2022, there were a total of 2,009 cases reporting hearing loss and tinnitus. Of these 2,009 cases a TTO of >21 days was reported in 518 cases, pre-existing medical condition in 431 cases, concomitant medications in 72 cases and lack of information in 27 cases. Of the remaining 961 cases further analysis was concentrated on the 212 cases (22%) that were HCP confirmed:

- 104 cases co-reported PTs unlikely to be caused by vaccination.
- 71 cases had hearing loss and/or tinnitus only, of which 50 cases were considered unassessable and 21 cases were considered possibly related to Comirnaty exposure (including a possible rechallenge in a 14 year old female).
- 37 cases had co-reported events, of which 25 cases were considered unassessable, 6 cases were considered unlikely related to Comirnaty exposure, and 6 cases were considered possible related to Comirnaty exposure.

Cases of Tinnitus events only

A total of 13943 cases (with a total of 66922 events) reporting tinnitus were retrieved.

Similar to the dataset described above, the majority of cases (13781) were spontaneous; 4581 cases were serious, 9362 were nonserious. There were 8606 females, 4581 males, and sex was not reported in 356 cases. When provided, the ages ranged as shown in Table 4 below. The mean and median ages were 47.7 and 48 years, respectively (n=12756).

Table 4. Reported Age in 13943 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	162	1.20%
18 - 30 years	1423	10.20%
31 - 50 years	5712	41.00%
51 - 64 years	3783	27.10%
65 - 74 years	1335	9.60%
Greater than or equal to 75 years	399	2.90%
Unknown	1129	8.10%

Further analysis was concentrated on 10063 cases reporting tinnitus with latency of 0 to 21 days post vaccination,

Out of these 10063 cases, 2261 cases reported a pre-existing medical condition suggesting a reasonable alternative explanation for tinnitus. Examples of the conditions included deafness, tinnitus,

COVID-19, autoimmune disorders, and chronic sinusitis. Of these 2261 cases, 738 reported pre-existing tinnitus; 128 of these 738 cases reported "aggravation, exacerbation, or worsening of the pre-existing tinnitus. An additional 399 cases reported use of co-suspect/concomitant medication representing a reasonable alternative cause of the relevant event. Examples included ACEIs, ARBs, tricyclic antidepressants, aspirin, NSAIDs, benzodiazepines, loop diuretics, immunosuppressants, and other vaccines.

Out of the remaining 7403 of the 10063 cases, further analysis was concentrated on 295 HCP-reported cases (containing 295 serious tinnitus events). In these 295 cases, when dose sequence was provided, it was Dose 1 for 151 tinnitus events, Dose 2 for 85 events, Dose 3 for 26 events, and Dose 4 for 1 event. Outcome of tinnitus at the time of reporting was resolved/resolving for 90 events; not resolved for 165 events; resolved with sequelae for 6 events; and unknown for 34 events. The most frequently reported latency was Days 0 and 1 for 81 events each followed by Day 2 for 34 events and Day 3 for 22 events.

Medically confirmed cases with no co-reported events

Out of 7403 cases, 295 were HCP confirmed. Of these 295 cases, 55 cases reported tinnitus only (no other events were reported in these cases). In 53 of these 55 cases no information on diagnostic procedures or tests supporting the diagnosis was provided; therefore, causality assessment for these 53 cases is Unassessable.

Of the remaining 2 cases, a 53-year-old man with an unreported medical history had a Neurology visit and negative MRI (with and without contrast), and a 30-year-old woman with an unreported medical history was seen by a specialist who found no abnormalities on clinical examination and diagnosed probable vestibular neuritis (unilateral). The causality assessment in these 2 cases is Unlikely.

Medically confirmed cases with co-reported adverse events

Of these 295 cases, 240 cases reported tinnitus and other events. Of these 240 cases, 159 co-reported PTs suggesting the possibility of other conditions (e.g., syncope, vertigo, anaphylactic reaction, hypertension, gait disturbance, vestibular disorder, amaurosis, autoimmune disorder and panic attack) Out of the remaining 81 cases, 79 did not provide information on diagnostic procedures or tests supporting the diagnosis, therefore causality assessment for these 79 cases is Unassessable. Two remaining cases described:

- A 62-year-old male (medical history and concomitant medications were not reported) experienced malaise and pyrexia on the same day of administration of Dose 2 of the vaccine (these symptoms disappeared 3 days later) and bilateral amaurosis and tinnitus on Day 3 post vaccination. The Audiometry test suggested mild to moderate grade high frequency sensorineural hearing loss (this PT was not captured as AE); case is assessed as Possible.
- A 43-year-old male physician who complained of squeaks in the left ear following dose 2 without ENT abnormalities and with an unspecified hearing test that confirmed the "abnormalities about squeaks;" case is assessed as Possible.

Rapporteur assessment comment:

Through 18 Jun 2022, there were a total of 13,943 cases reporting tinnitus. Of these 13,943 cases a TTO of >21 days was reported in 3,880 cases, pre-existing medical condition in 2,261 cases, and concomitant medications in 399 cases. Of the remaining 7,403 cases further analysis was concentrated on the 295 cases (4%) that were HCP confirmed:

- 55 cases had tinnitus only, of which 53 cases were considered unassessable and 2 cases were considered unlikely related to Comirnaty.

- 240 cases had co-reported events, of which 159 cases co-reported PTs suggesting the possibility of other conditions causing tinnitus, 79 cases were considered unassessable, and 2 cases were considered possible related to Comirnaty exposure.

Cases of Hearing loss events only

A total of 3177 cases (with a total of 15668 events) were retrieved.

Similar to the datasets described above, the majority of cases (3117) were spontaneously reported; 2542 cases were serious, 635 were nonserious. There were 1922 females, 1147 males, and sex was not reported in 108 cases. When provided, the ages ranged as shown in Table 7 below. The mean and median ages were 50.2 and 50 years, respectively (n=2915).

Table 7. Reported Age in 3177 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	97	3.10%
18 - 30 years	408	12.80%
31 - 50 years	980	30.80%
51 - 64 years	720	22.70%
65 - 74 years	363	11.40%
Greater than or equal to 75 years	355	11.20%
Unknown	254	8.00%

Further analysis was concentrated on 2039 cases reporting hearing loss events with a latency of 0 to 21 days post vaccination. Out of these 2039 cases, 433 cases reported pre-existing medical conditions (e.g., deafness, COVID-19, anxiety, hearing aid use, autoimmune disorders, diabetes, Meniere's disease, acoustic neuroma, cerebrovascular disorders) representing potential alternative causes of the events; 76 of the 433 cases reported pre-existing hearing loss and 13 of these 76 cases reported "aggravation, exacerbation, or worsening of" the pre-existing relevant condition. Additional 88 of the 2039 cases reported the use of co-suspect/concomitant medications (e.g., ACE-Is, ARBs, beta blockers, tricyclic antidepressants, loop diuretics, immunosuppressants, and other vaccines) potentially accounting for the hearing loss events.

Out of the remaining 1518 of the 2039 cases with a latency of 0 to 21 days, further analysis was concentrated on 352 HCP-reported cases (containing 387 serious hearing loss events). In these 352 cases, when dose sequence was provided, it was Dose 1 for 175 relevant events, Dose 2 for 131 events, Dose 3 for 33 events, and Dose 4 for 2 events. The outcome of the relevant events at the time of reporting was resolved/resolving for 148 events; not resolved for 143 events; resolved with sequelae for 21 events; and outcome was unknown for 77 events. The most frequently reported latencies were Day 1 for 96 events, Day 0 for 66 events followed by Day 2 for 52 events and Day 3 for 24 events.

Medically confirmed cases with no co-reported events

Of the 352 HCP cases, 140 reported events of hearing loss only (no other events were reported in these cases). Out of these 140 cases, 116 cases did not report information on diagnostic procedures or tests to support the diagnoses; therefore, the causality assessment of these 116 cases is Unassessable.

Twenty-four (24) out of the 140 cases reported diagnostic tests or procedures such as acoustic stimulation test, audiogram, ENT examination, Investigation, MRI, otoacoustic emissions test, and otoscopy. All 24 cases reported adults, with 5 being patients 74 to 90 years old. Of these 5 reports of elderly patients, 1 reported a pre-existing hearing disability making the case Unassessable while the remaining 4 had limited information reported including any information that posed a possible

alternative cause of the hearing loss (apart from age); therefore, the causality assessment in these 4 cases reporting elderly patients is Possible.

Of the remaining 19 cases, 6 of the narratives described pre-existing medical histories confounding causality assessment (allergic rhinitis, alcoholism and hypersensitivity, otitis externa, traumatic deafness, and throat cancer) leading to their assessment of Unlikely.

The last 13 out of 24 cases did not report any additional details (e.g., medical history, concomitant medications, additional tests) and based on the lack of information on alternative contributions, the causality assessment in these 13 cases is Unassessable.

Medically confirmed cases with co-reported adverse events

Of the 352 HCP cases, 212 reported hearing loss and other events; 146 of these 112 cases co-reported PTs suggesting the possibility of an alternative explanation for the hearing loss (e.g., ear infection, meningitis, cerebellar condition, syncope, loss of consciousness, chronic rhinitis/sinusitis, Meniere's disease, etc.) contributing to hearing loss and making causality assessment Unlikely.

Out of the remaining 66 cases, in 63 cases the diagnostic procedures/tests were not reported, results of these tests were reported as normal, or results were not available at the time of reporting, therefore the causality assessment for these 63 cases is Unassessable. The last 3 cases reported diagnostic procedures/tests such as acoustic stimulation and audiogram. One case described ear edema (assessment is Unlikely) and assessment for the other 2 cases was Possible.

Rapporteur assessment comment:

Through 18 Jun 2022, there were a total of 3,177 cases reporting hearing loss. Of these 3,177 cases a TTO of >21 days was reported in 1,183 cases, pre-existing medical condition in 433 cases, and concomitant medications in 88 cases. Of the remaining 1,518 cases further analysis was concentrated on the 352 cases (23%) that were HCP confirmed:

- 140 cases had hearing loss only, of which 130 cases were considered unassessable.6 cases were considered unlikely related to Comirnaty, and 4 cases were considered possible related to Comirnaty exposure.
- 212 cases had co-reported events, of which 146 cases co-reported PTs suggesting the possibility of other conditions causing hearing loss, 63 cases were considered unassessable, 1 case was considered unlikely related to Comirnaty, and 2 cases were considered possibly related to Comirnaty exposure.

Observed to expected analyses

Hearing loss

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for 5805 hearing loss cases reported cumulatively through 18 June 2022 globally (Table 9).

The overall expected case counts of hearing loss were estimated using background incidence rates (IR) reported by a population-based cross-sectional study in the US IMS Lifelink Health Plan Claims Database, as requested by the Pharmacovigilance Risk Assessment Committee (PRAC). This study included on average 66,594 new sudden sensorineural hearing loss (SSHL) cases per year identified in inpatient and outpatient healthcare settings via the International Classification of Diseases, 9th Revision (ICD-9) code (388.2) in 2006 and 2007 with an overall annual incidence of 27 per 100,000 population. Age- and sexspecific incidence rates were also reported in this study and used as the basis for the age and sex-stratified O/E analyses.

Table 9. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Hearing Loss Through 18 June 2022

Stratification	Observed cases	Time at risk (PY)	Background rates per 100,000 PY	Expected cases	O/E ratio	95% CI LL	95% CI UL
21-day risk window							
US/EEA							
Males							
≤11 years	2	901,382	9.0	81.12	0.025	0.003	0.089
12-17 years	22	1,562,311	9.0	140.61	0.156	0.098	0.237
18-24 years	41	2,224,929	12.0	266.99	0.154	0.110	0.208
25-49 years	518	9,186,672	20.3	1867.96	0.277	0.254	0.302
50-59 years	279	4,241,876	41.5	1760.38	0.158	0.140	0.178
60-69 years	182	3,713,614	67.0	2488.12	0.073	0.063	0.085
70+ years	195	5,152,276	81.0	4173.34	0.047	0.040	0.054
Females							
≤11 years	2	1,016,452	7.0	71.15	0.028	0.003	0.102
12-17 years	42	1,761,755	7.0	123.32	0.341	0.245	0.460
18-24 years	92	2,508,963	13.0	326.17	0.282	0.227	0.346
25-49 years	804	10,359,439	21.0	2175.48	0.370	0.344	0.396
50-59 years	419	4,783,392	36.5	1745.94	0.240	0.218	0.264
60-69 years	283	4,187,692	52.0	2177.60	0.130	0.115	0.146
70+ years	265	5,810,014	62.0	3602.21	0.074	0.065	0.083
Overall							
Any dose	3,146	57,410,765	27.0	15500.91	0.203	0.196	0.210
Dose 1	1,513	22,917,286	27.0	6187.67	0.245	0.232	0.257
Dose 2	1,255	21,280,003	27.0	5745.60	0.218	0.207	0.231
Dose 3	378	13,213,476	27.0	3567.64	0.106	0.096	0.117
Overall Global	4424	127,075,389	27.0	34310.35	0.129	0.125	0.133
42-day risk window							
US/EEA							
Males							
≤11 years	2	1,306,591	9.0	117.59	0.017	0.002	0.061
12-17 years	25	2,409,778	9.0	216.88	0.115	0.075	0.170
18-24 years	44	3,514,277	12.0	421.71	0.104	0.076	0.140
25-49 years	562	14,565,823	20.3	2961.72	0.190	0.174	0.206
50-59 years	307	6,796,938	41.5	2820.73	0.109	0.097	0.122
60-69 years	203	6,042,722	67.0	4048.62	0.050	0.043	0.058
70+ years	214	8,411,485	81.0	6813.30	0.031	0.027	0.036
Females							
≤11 years	2	1,473,390	7.0	103.14	0.019	0.002	0.070
12-17 years	45	2,717,409	7.0	190.22	0.237	0.173	0.317
18-24 years	98	3,962,908	13.0	515.18	0.190	0.154	0.232
25-49 years	864	16,425,290	21.0	3449.31	0.250	0.234	0.268
50-59 years	462	7,664,632	36.5	2797.59	0.165	0.150	0.181
60-69 years	306	6,814,133	52.0	3543.35	0.086	0.077	0.097
70+ years	293	9,485,291	62.0	5880.88	0.050	0.044	0.056
Overall							
Any dose	3,427	91,590,667	27.0	24729.48	0.139	0.134	0.143
Dose 1	1,637	22,917,286	27.0	6187.67	0.265	0.252	0.278
Dose 2	1,388	42,494,750	27.0	11473.58	0.121	0.115	0.128
Dose 3	402	26,178,631	27.0	7068.23	0.057	0.051	0.063
Overall Global	4,814	203,986,419	27.0	55076.33	0.087	0.085	0.090

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

Note: The background rate by Alexander TH et al[9]. for age group of <18 years were used for ≤11 and 12-17 years, the average for age groups of 18-34, 35-44 and 45-54 years were used for 25-49 years, the average for age groups of 45-54 and 55-64 years were used for 50-59 years, and the average for age group 55-64 and 65+ years were used for 60–69 years, respectively.

Based on the selected background rates and the estimated number of exposure person-years through 18 June 2022, O/E ratios were well below one overall, by dose, and within strata of age groups and sex for both risk windows of 21- and 42-days. This suggests that the number of observed cases of

hearing loss is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines overall and within the queried strata.

Rapporteur assessment comment:
All O/E ratios were below 1 for hearing loss.

Tinnitus

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for 16671 tinnitus cases reported cumulatively through 18 June 2022 globally.

The overall expected case counts of tinnitus were estimated using background incidence rates (IR) reported by a retrospective cohort study in the UK Clinical Practice Research Datalink (CPRD) with linkage to the Hospital Episode Statistics. This study included 14,303 incident clinically significant tinnitus during 01 January 2002 to 31 December 2011, defined by a discharge from the hospital with a primary diagnosis of tinnitus or a primary care recording of tinnitus with subsequent related medical follow-up within 28 days. The overall incidence rate was 54 per 100,000 person-years (95% confidence interval [CI]=53, 55). Age- and sex specific incidence rates were also reported in this study. These rates provided a low range of background rates for tinnitus, and therefore, low expected case counts to conservatively estimate O/E results. Another retrospective cohort using CPRD identified 109,783 adults with a first-time diagnosis of tinnitus between 2000 and 2016 and reported an overall incidence rate of 250 per 100,000 person years (95%CI=246, 255).

Table 10. Observed to Expected (O/E) Ratio for Spontaneously Reported Cases of Tinnitus Through 18 June 2022

Stratification	Observed cases	Time at risk (PY)	Background rates per 100,000 PY	Expected cases	O/E ratio	95% CI LL	95% CI UL
21-day risk window							
US/EEA							
Males							
≤11 years	4	901,382	5.5	49.58	0.081	0.022	0.207
12-17 years	34	1,562,311	9.0	140.61	0.242	0.167	0.338
18-24 years	106	2,224,929	16.0	355.99	0.298	0.244	0.360
25-49 years	1,872	9,186,672	42.3	3889.02	0.481	0.460	0.504
50-59 years	1,002	4,241,876	106.0	4496.39	0.223	0.209	0.237
60-69 years	552	3,713,614	122.0	4530.61	0.122	0.112	0.132
70+ years	259	5,152,276	73.0	3761.16	0.069	0.061	0.078
Females							
≤11 years	3	1,016,452	4.5	45.74	0.066	0.014	0.192
12-17 years	58	1,761,755	7.0	123.32	0.470	0.357	0.608
18-24 years	235	2,508,963	13.5	338.71	0.694	0.608	0.788
25-49 years	3,095	10,359,439	39.3	4074.71	0.760	0.733	0.787
50-59 years	1,614	4,783,392	100.0	4783.39	0.337	0.321	0.354
60-69 years	935	4,187,692	107.0	4480.83	0.209	0.196	0.222
70+ years	462	5,810,014	81.0	4706.11	0.098	0.089	0.108
Overall							
Any dose	10,231	57,410,765	54.0	31001.81	0.330	0.324	0.336
Dose 1	5,040	22,917,286	54.0	12375.33	0.407	0.396	0.419
Dose 2	4,008	21,280,003	54.0	11491.20	0.349	0.338	0.360
Dose 3	1,183	13,213,476	54.0	7135.28	0.166	0.156	0.176
Overall Global	14,347	127,075,389	54.0	68620.71	0.209	0.206	0.213
42-day risk window							
US/EEA							
Males							
≤11 years	4	1,306,591	5.5	71.86	0.056	0.015	0.143
12-17 years	38	2,409,778	9.0	216.88	0.175	0.124	0.240
18-24 years	113	3,514,277	16.0	562.28	0.201	0.166	0.242
25-49 years	1,985	14,565,823	42.3	6166.20	0.322	0.308	0.336
50-59 years	1,075	6,796,938	106.0	7204.75	0.149	0.140	0.158
60-69 years	592	6,042,722	122.0	7372.12	0.080	0.074	0.087
70+ years	284	8,411,485	73.0	6140.38	0.046	0.041	0.052
Females							
≤11 years	4	1,473,390	4.5	66.30	0.060	0.016	0.154
12-17 years	60	2,717,409	7.0	190.22	0.315	0.241	0.406
18-24 years	244	3,962,908	13.5	534.99	0.456	0.401	0.517
25-49 years	3,237	16,425,290	39.3	6460.61	0.501	0.484	0.519
50-59 years	1,728	7,664,632	100.0	7664.63	0.225	0.215	0.236
60-69 years	991	6,814,133	107.0	7291.12	0.136	0.128	0.145
70+ years	506	9,485,291	81.0	7683.09	0.066	0.060	0.072
Overall							
Any dose	10,861	91,590,667	54.0	49458.96	0.220	0.215	0.224
Dose 1	5,286	22,917,286	54.0	12375.33	0.427	0.416	0.439
Dose 2	4,331	42,494,750	54.0	22947.17	0.189	0.183	0.194
Dose 3	1,244	26,178,631	54.0	14136.46	0.088	0.083	0.093
Overall Global	15,199	203,986,419	54.0	110152.67	0.138	0.136	0.140

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

Note: The average of background rate by Martinez C et al[12]. for age group of <10 and 10-19 years were used for ≤11 years, the average for age groups of 10-19 and 20-29 years were used for 18-24 years, the average for age groups of 20-29, 30-39, and 40-49 years were used for 25-49 years, and the average for age group 70-70 and 80-84 years were used for 70+ years, respectively.

Based on the select background rates and the estimated number of exposure person-years through 18 June 2022, O/E ratios were below one overall, by dose, and within strata of age groups and sex for both risk windows of 21- and 42-days. This suggests that the number of observed cases of tinnitus is not higher than expected in the absence of Pfizer-BioNTechCOVID-19 vaccines overall and within the queried strata.

Rapporteur assessment comment:

All O/E ratios were below 1 for tinnitus.

Clinical trial data

Hearing loss

In the placebo-controlled period of pivotal clinical trial C4591001 (DLP 13MAR2021), there were 12 participants who reported hearing loss events; 9/23,037 (0.04%) were in the placebo group and 3/23,040 (0.01%) were in the BNT162b2 group. In both groups the events of hearing loss were nonserious; the reported latency in the placebo group varied from Day 2 to Day 111; the latency in BNT162b2 group were Day 1, Day 3, and Day 19, respectively.

In the placebo-controlled period of clinical trial C4591031 (DLP 08FEB2022), there was 1 of 5048 participants in the placebo group who reported a hearing loss event; there were none reported in BNT162b2 group (5088 participants). The reported event was nonserious and occurred within the same day of vaccination.

In the placebo-controlled period of clinical trial C4591007 (DLP 06SEP2021), there were 3/750 participants who reported hearing loss events in the placebo group; there were none reported in the BNT162b2 group (1518 participants). The reported event were nonserious; the reported latencies were unknown (1 event), 65 days (1 event), and 135 days (1 event).

Rapporteur assessment comment:

Pooled in the three placebo-controlled studies there were 3 of the 29,646 (0.01%) participants reporting hearing loss in the Comirnaty group and 14 of the 28,835 (0.05%) participants in the placebo group.

Tinnitus

In the placebo-controlled period of pivotal clinical trial C4591001 (DLP 13MAR2021), there were 24 participants who reported tinnitus events; 23/23,037 (0.1%) were in the placebo group and 1/23,040 (0.004%) was in the BNT162b2 group. In both groups the events of tinnitus were nonserious. The most frequently reported latencies in the placebo group were Day 0 and Day 3 (for 3 events each); the latency for the event in the BNT162b2 group was 26 days.

In the placebo-controlled period of clinical trial C4591031 (DLP 08FEB2022), there was 1 of 5048 participants in the placebo group who reported an event of tinnitus; none were reported in the BNT162b2 group (5088 participants). The reported event was nonserious and occurred 42 days post vaccination.

There were no events of Tinnitus reported in the placebo-controlled period of clinical trial C4591007.

Rapporteur assessment comment:

Pooled in the three placebo-controlled studies there was 1 of the 29,646 (0.003%) participants reporting tinnitus in the Comirnaty group and 25 of the 28,835 (0.09%) participants in the placebo group.

MAH's conclusion

Reports of recovery of SARS-CoV-2 RNA in the middle ear of individuals who died of COVID-19 and recent findings of the ability of SARS-CoV-2 to directly infect human vestibular hair and Schwann cells provide plausible biological mechanisms for COVID-19– associated hearing loss and may open avenues of investigation into immune mechanisms in the inner ear.

There is no documented mode of action of how vaccination with COVID-19 vaccines can cause hearing loss or tinnitus.

Participants in the placebo-controlled, blinded periods of the large Pfizer-run clinical trials reported very low number of tinnitus or hearing loss in either group with the placebo group having a higher number of tinnitus and hearing loss events compared to the vaccine group.

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 spontaneously reported cases are of variable quality. While there are individual cases that provide detailed information without alternative causes of hearing loss and tinnitus, the nature of these events (their myriad etiologies) and the reports do not exclude that the events may be coincidental to vaccination.

The O/E analyses provides reassurance that the reports of hearing loss and tinnitus in the stratified populations and doses are not greater than would be expected as background occurrences.

The observational studies in the medical literature retrieved in the search do not allow a conclusion one way or the other about a causal relationship between hearing loss or tinnitus and Comirnaty at a population level. Further observational studies that include data from patients vaccinated over time (not just in the initial months of mass vaccination) will be helpful to further characterize any association.

Observational studies from healthcare networks that can combine information from vaccination records and healthcare system diagnoses may provide a more accurate picture of real-world events than passive surveillance systems (e.g., spontaneous databases). While the general expectation is that spontaneous reporting will be highest immediately following post-authorization product availability, the COVID-19 vaccines are subject to unusual reporting practices due to the global nature of the pandemic (worldwide population is affected, not a subsegment of patients), the multi-dose regimen with different mass vaccination practices in different regions, the unprecedented scrutiny on adverse events occurring in temporal relation with vaccination and the vigorous encouragement to report adverse events.

Taking into account the totality of the data available, a causal association between Comirnaty and hearing loss or tinnitus cannot be concluded at this time. Routine pharmacovigilance will continue.

Rapporteur assessment comment:

Literature

From the four retrieved relevant articles no new important safety information could be identified concerning hearing loss and tinnitus.

Post-marketing

Through 18 Jun 2022 were retrieved:

- 2009 cases reporting hearing loss and tinnitus; analysis was concentrated on the 212 HCP confirmed cases: 27 cases were considered possible related to Comirnaty exposure (including a possible

rechallenge in a 14 year old female), 110 cases were considered unlikely related to Comirnaty exposure, and 75 cases were considered unassessable.

- 13,943 cases reporting tinnitus; analysis was concentrated on the 295 HCP confirmed cases: 2 cases were considered possible related to Comirnaty exposure, 161 were considered unlikely related to Comirnaty, and 132 cases were considered unassessable.

- 3177 cases reporting hearing loss; analysis was concentrated on the 352 HCP confirmed cases: 6 cases were considered possible related to Comirnaty exposure, 153 cases were considered unlikely related to Comirnaty exposure, and 193 cases were considered unassessable.

In conclusion, despite the 27 cases reporting hearing loss and tinnitus and the 2 cases reporting tinnitus and the 6 cases reporting hearing loss that were considered possible related to Comirnaty exposure, there seems to be no causal association between Comirnaty exposure and occurrence of hearing loss and/or tinnitus in the post-marketing cases. However, a detailed MAH's case by case assessment of the cases considered possible related to Comirnaty exposure is not presented in the PSUR, which hampers PRAC Rapporteur's assessment.

Observed to expected analyses

Through 18 June 2022, for hearing loss and tinnitus, all O/E ratios were >1 overall, by dose, and within strata of age groups and sex for both risk windows of 21- and 42-days.

Clinical trial data

In the clinical trial there were more reports of hearing loss and of tinnitus in the placebo group compared to the Comirnaty group, 14 and 25 versus 3 and 1, respectively.

Overall, MAH's conclusion is endorsed that a causal association between Comirnaty and hearing loss or tinnitus cannot be concluded at this time. No new important information could be identified concerning hearing loss or tinnitus. The MAH should continue monitor any new cases, patterns, or trends of reporting hearing loss and/or tinnitus through routine pharmacovigilance.

Issue solved

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

2.2.2. Evaluation of closed signals

Rapporteur assessment comment:

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

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

Signals determined to not be risks	
Appendicitis	Appendicitis was identified as a signal during the reporting period based on a competent authority (Singapore BoH) inquiry following 18 local reports. The Pfizer safety database search through 01 April 2022 revealed 690 cases and those with sufficient information provided did not show any trends considered inconsistent with the underlying epidemiology and/or natural course of the condition. Placebo-controlled clinical trial data from the pivotal Pfizer-run studies did not reveal any clinically meaningful difference between the BNT162b2 and placebo groups. Of 3 large population-based studies from the US, Israel and Sweden, 2 showed no increase in appendicitis after vaccination while 1 showed a slightly increased risk ratio in the vaccinated group compared to the unvaccinated group. Observed to expected analyses conducted were well below 1. A plausible mechanism by which BNT162b2 could case appendicitis is unknown. The totality of the information was not supportive of a causal association between BNT162b2 and appendicitis signal was closed by the MAH.
Rapporteur assessment comment: Through 01 Apr 2022, the MAH retrieved 690 cases reporting appendicitis and did not show any trends supportive of a causal association with Comirnaty exposure. Clinical trial data showed no clinically meaningful difference between the Comirnaty and placebo groups. O/E ratios were <1. The MAH stated that there is no causal association between Comirnaty exposure and appendicitis. Therefore, the signal was closed.	
Hemolytic anemia	Haemolytic anaemia was identified as a signal during the reporting period based on a competent authority (Saudi FDA) request for an evaluation. The Pfizer safety database search through 13 January 2022 yielded 176 cases, most of which were confounded or contained insufficient information. Among the cases with no obvious confounder or trigger, a definitive causal association could not be concluded. There were no events of haemolytic anaemia reported in the pivotal clinical trial C4591001. The medical literature yielded one case report and one prospective study of 108 patients with autoimmune cytopenias (56 with autoimmune haemolytic anaemia [AIHI]) who were vaccinated with Pfizer/BNT, Moderna or Astra-Zeneca COVID-19 vaccines. Four elderly patients with AIHI had a clinically significant haemoglobin reduction requiring treatment adjustment (2 had received Pfizer/BNT vaccine). Notably, autoimmune cytopenia recrudescences were not predictable, since they occurred in both patients on active treatment and off therapy, independently from AIHA type, after either the first or the second dose, and regardless of vaccine type. Observed to expected analyses conducted were below 1. Based on the totality of available information, a

	causal association between BNT162b2 and haemolytic anaemia could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: MAH's response to the inquiry received from the Saudi Food and Drug Authority concerning hemolytic anemia was assessed in the 13th (2nd bi-monthly) SSR (reporting period 16 Dec 2021 – 15 Feb 2022; EMEA/H/C/005735/MEA/002.12). MAH's conclusion was endorsed that there is insufficient evidence to establish causality between the development of hemolytic anemia events and Comirnaty exposure. Closure of the signal hemolytic anemia was accepted.	
Uveitis	Uveitis was identified as a signal during the reporting period based on a competent authority (Health Canada) request for a cumulative review. The Pfizer safety database search through 04 April 2022 yielded 538 cases, 121 of which were medically confirmed and did not report confounding factors or an implausible time to onset. Of these, 9 were determined to have a possible causality based on individual assessment. During the placebo-controlled period in the pivotal clinical trial C4591001, one case was reported in the placebo group and no cases were reported in the BNT162b2 group from Dose 1 to 1 month after Dose 2. The medical literature consisted of case reports and case series descriptions with one population-based study estimating the prevalence rates of uveitis coincident with COVID-19 vaccination as 0.9 cases per million doses or less. Observed to expected analyses conducted using both a low and high range of background rates were well below 1 overall, by dose and within age and sex strata. Based on the totality of available information, a causal association between BNT162b2 could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: MAH's response to the inquiry received from the Canadian Health Authority concerning uveitis was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13). MAH's conclusion was endorsed that there is insufficient evidence to establish causality between uveitis events and Comirnaty exposure. Closure of the signal uveitis was accepted.	
Exacerbation and/ or flare of underlying autoimmune disease or inflammatory disorders	A cumulative review of autoimmune and inflammatory disorder exacerbations was requested in an updated PSUR Assessment Report received from EMA/PRAC during the reporting period (30 December 2021). The search of the safety database used SMQ Immune-mediated/autoimmune disorders (narrow terms), HLGT Autoimmune disorders, HLGT Immune disorders NEC and HLT Neuromuscular junction dysfunction. There were 2223 cases describing a medical history and adverse event of an autoimmune disease (indicating a potential exacerbation). Overall, cases lacked information to ascertain baseline disease status, treatment and other factors which may affect underlying

	disease activity, despite most reporting exacerbations or potential relapses within 2 days of vaccination. In the placebo-controlled portion of pivotal clinical trial C4591001, 2955/21926 BNT162b2 participants and 2977/21921 placebo participants had underlying autoimmune conditions. Of these, 7 (0.2%) and 4 (0.1%) of BNT and placebo participants, respectively, reported potential aggravations of their autoimmune disorder from Dose 1 to 1 month post Dose 2. From Dose 1 to unblinding, 8 participants in each group (IR/100 person years = 0.7) reported potential aggravations. The medical literature search yielded many studies of COVID-19 vaccination in patients with underlying autoimmune disorders. The findings consistently showed that reported post-vaccination adverse events were similar to those of healthy vaccinees. Most studies did not have control groups of participants with autoimmune disorders who did not receive COVID-19 vaccination, although those that did, did not report that vaccinees had more exacerbations than non-vaccinees. Based on the totality of the available information, a causal association between BNT162b2 and autoimmune disorder exacerbations could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: MAH's response on the PRAC request for a cumulative review of exacerbation (flare-up) of pre-existing AI/Inflammatory disorders was assessed in the 2nd Comirnaty PSUSA (reporting period 19 Jun 2021 – 18 Dec 2021; EMEA/H/C/PSUSA/00010898/202112). MAH's conclusion was supported and that no new important safety information could be identified. Closure of the signal was accepted.	
Capillary leak syndrome (CLS)	Capillary leak syndrome, or Systemic capillary leak syndrome (SCLS), was identified as a signal by PRAC on 13 January 2022. The safety database search yielded 44 cases, 2 of which were literature case reports, which occurred in individuals from 20 to 101 years of age. Four cases described a medical history of CLS. The majority of cases lacked clinical details or provided evidence of an alternative aetiology other than vaccination. There were no reported events of CLS in the placebo (21921) or BNT162b2 group (21926) in the placebo-controlled portion of C4591001 in participants 16 years and older from dose 1 to 1 month after dose 2. The medical literature has described cases of CLS occurring after COVID-19 infection and there were only individual case reports of CLS occurring after COVID-19 vaccination. Based on the totality of the available information, a causal association between BNT162b2 and CLS/SCLS could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: Please refer to the separate signal procedure concerning capillary leak syndrome (EMEA/H/C/005735/SDA/051- EPITT 19743) in which PRAC concluded to continue closely monitoring through routine pharmacovigilance. The signal capillary leak syndrome was closed.	

Corneal graft rejection	Corneal graft rejection was identified as a signal by PRAC on 07 April 2022. The safety database search through 14 April 2022 yielded 42 potential cases describing 40 unique individuals, all adults or elderly. There was no distinguishing trend in the cases with regard to sex, age, dose number, age of graft or time to onset. Of 12 cases with a plausible temporal relationship to vaccination, only 2 did not have reported risk factors for rejection (e.g., increased age of transplant, possible infection, graft surgery complications). Data from large clinical studies C4591001 (snapshot date of 11 April 2022), C4591031 (cut-off date of 08 February 2022) and C4591007 (cut-off dates of 08 October 2021 and 22 March 2022) were searched for PTs, corneal graft rejection and corneal graft failure. Neither of these PTs were reported in the unblinded data from the placebo-controlled portions of the studies. There were 32 clinical trial participants, all ≥16 years of age, who reported a history of corneal transplant or keratoplasty in either Study C4591001 and/or Study C4591031. There were no participants in C4591007 who reported a history of corneal transplant or keratoplasty. The medical literature consisted of case reports which were included in the safety database. There were no mechanistic studies, rather various hypotheses were theorized such as increased vascular permeability, immune responses and immune system deregulation. Based on the totality of the available information, a causal association between BNT162b2 and corneal graft rejection could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: Please refer to the separate signal procedure concerning corneal graft rejection (EMEA/H/C/005735/SDA/055- EPITT 19789). After DLP of the current PSUR, PRAC concluded to continue closely monitoring through routine pharmacovigilance. The signal corneal graft rejection was closed.	
Vasculitis	During the reporting period, vasculitis was reviewed initially following a signal noted by the Lareb (Netherlands) and through 15 April at the request of PRAC in the Assessment Report for SBSR 2. Through 15 April 2022, a search of the safety database yielded 868 reports with individual ages ranging from 2 to 98 years. Reported vasculitides included vasculitis (not otherwise described), giant cell arteritis and Henoch-Schonlein purpura. The cases were generally confounded or lacked necessary details to confirm the diagnoses and/or a causal relationship. Phase 2/3 Study C4591001 placebo-controlled unblinded adverse events in participants 16 years and older from Dose 1 to 1 month after Dose 2 (data cutoff date 13 March 2021) was also reviewed for the PT Vasculitis. In the Phase 2/3 safety population, vasculitis was not reported in any of 21926 participants in the BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) group or in any of 21921 participants in the placebo group. Observed to expected analyses for the 3 most common subtypes of vasculitis (Henoch-Shonlein purpura, Giant cell arteritis, Skin manifestations of vasculitis) have repeatedly been less than one. Based on the totality of

	the available information, a causal association between BNT162b2 and vasculitis could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: An updated cumulative review of vasculitis (through 15 Apr 2022) was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13). PRAC concluded that based on the data provided no safety concern was identified. Closure is of the signal vasculitis was accepted.	
Cerebral venous sinus thrombosis (CVST)	Previous to the current PSUR reporting period, a cumulative review of CVST through 24 November 2021 was conducted by the MAH (SBSR 2, Appendix 3.4) in response to a request from a competent authority (Swissmedic). In the SBSR 2 PRAC Assessment Report, the MAH was requested to provide more detail on some of the cases and a further cumulative review of the topic. A search of the safety database yielded 527 cases that were reported through 24 November 2021 and 297 from 25 November 2021 to 15 April 2022. Of 37 cases in patients younger than 75 years of age with no medical history or information portending an increased risk for the development reported through 24 November 2021, only 3 were assessed as possible (the remaining were unassessable or unlikely per the WHO-UMC case causality criteria). In the interim update through 15 April 2022, the majority of the 297 cases lacked necessary detail for assessment, had implausible time to onset or described known risk factors (other than vaccination) for the development of CVST. When analyzed by age category, the cases were largely unassessable due to lack of sufficient detail for full assessment. Overall, the assessment of AE reports was that the clinical characteristics of the cases, when provided, were aligned with the known profile of CVST. There was 1 event of CVST in a clinical trial participant who received placebo in pivotal clinical trial C4591001. Retrospective epidemiological studies of CVST after vaccination with BNT162b2 did not conclude an increased risk due to the vaccine and a retrospective analysis of 213 post-vaccine CVST cases did not demonstrate a clinically distinct profile of CVST after mRNA vaccination that differed from historical controls. Another large study showed an increased risk of CVST associated with COVID-19 compared to individuals with influenza or following COVID-19 vaccination with an mRNA vaccine. Observed to expected analyses have been conducted for CVST and when low background rates are used, the ratios are >1 in various age and sex strata. This is not seen when using higher background rates. The variation in reported background rates was notable it is possible that the delivery of healthcare, population demographics and underlying health status of the populations used for the background rate estimates differ from those in the vaccinated population. Based on the totality of the available information, a causal association between BNT162b2 and CVST could not be concluded, and the signal was closed by the MAH.

Rapporteur assessment comment: An updated cumulative review of cerebral venous sinus thrombosis (through 15 Apr 2022) was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13). PRAC concluded that based on the data provided no safety concern was identified. Closure is of the signal cerebral venous sinus thrombosis was accepted.	
Lymphocytic colitis	During the reporting period, this signal was identified from a published (literature) case report of a 69-year-old woman who presented for evaluation of severe abdominal pain, nausea, and diarrhea after her second vaccination with Pfizer/BNT COVID-19 vaccine. Within 24 hours of vaccination, she reported onset of diarrhea (2-3 loose to watery stools per day). Symptoms intensified over the next several days to 3-5 watery stools per day with incontinence, abdominal cramping, and nausea. GI PCR and COVID testing were negative and ondansetron and loperamide were started with minimal benefit. Two-months later, a GI consultation was obtained due to persistent symptoms. Work up demonstrated no anemia with normal CRP, celiac serologies, and GI PCR. Colonoscopy on day 98 post-onset revealed patchy erythema in the descending colon and rectosigmoid. Histologic evaluation of mucosal biopsies revealed lymphocytic colitis characterized by numerous lymphocytes infiltrating the epithelium and abundant plasma cells in the lamina propria. A previous colonoscopy performed in 2012 was unremarkable. At her most recent follow-up on day 113 post-onset, the patient reported gradual improvement of abdominal symptoms and diarrhea. This case report was recorded in the Pfizer safety database. There was no other relevant literature information on lymphocytic colitis and COVID-19 vaccination. A search of the safety database through 20 Jan 2022 yielded 40 cases for review (incl index case); in all the cases, there was either no Pfizer/BNT COVID-19 vaccine used, an unconfirmed diagnosis, lack of clinical detail, or the presence of alternative explanations or risk factors for lymphocytic colitis. Based on the totality of the available information, a causal association between BNT162b2 and lymphocytic colitis could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: This signal of lymphocytic colitis was assessed in the 13th (2nd bi-monthly) SSR (reporting period 16 Dec 2021 – 15 Feb 2022; EMEA/H/C/005735/MEA/002.12). MAH's conclusion was endorsed that there is insufficient evidence to establish causality between lymphocytic colitis and Comirnaty exposure. Closure of the signal lymphocytic colitis was accepted.	
Chronic urticaria	This signal was identified following a request for a cumulative review on the subject from EMA PRAC on 09 May 2022. A search of the Pfizer safety database through 09 May 2022 yielded 244 cases; 31 of which described medical histories of chronic urticaria. Of the cases of new onset

	chronic urticaria, time to onset ranged from 0 to 90 days post vaccination, cases were reported after dose 1, dose 2 and booster doses, 26 cases described the background of underlying autoimmune disorders, 26 reported hypersensitivity conditions and 14 reported histories of COVID-19. In all, 35 cases specifically reported that the urticaria lasted more than 6 weeks (meeting criteria for chronic urticaria). Sixteen of these reported a time to onset that was reasonably temporally associated with vaccination, and among them only 7 (43.7%) of the cases provided a medical history (85.7% of which implied a predisposition to urticaria or an alternate trigger for it). During the placebo-controlled unblinded period of pivotal study C4591001 (data cut-off 15 April 2022), of participants 12 years and older, chronic urticaria was not reported in any of the 23,068 participants in the BNT162b2 group or the 23,063 participants in the placebo group from Dose 1 to data cutoff date. Observed versus expected analyses were < 1 overall, by dose and within strata of age groups. The MAH considers urticaria as an adverse reaction of BNT162b2, however, a causal association between the vaccine and chronic urticaria was not supported based on the available information.
Rapporteur assessment comment: An updated cumulative review of chronic urticaria (through 09 May 2022) was assessed in the 2nd Comirnaty PSUSA (reporting period 19 Jun 2021 – 18 Dec 2021; EMEA/H/C/PSUSA/00010898/202112). MAH's conclusion was accepted that the available information did not support a causal association between chronic urticaria and Comirnaty exposure. The signal chronic urticaria was closed.	
Polymyalgia rheumatica (PMR)	This signal was identified following a request for a cumulative review on the subject by EMA PRAC in the PSUR 1 Assessment Report. A search of the Pfizer safety database through 18 December 2021 yielded 628 cases, the majority of which were excluded from further consideration due to implausible time to onset, medical history or conditions confounding assessment or lack of clinical detail supporting the diagnosis of PMR. Of the reports providing laboratory data (CRP and/or ESR) supportive of the diagnosis of PMR, most were unassessable or unlikely per WHO-UMC causality criteria. The 54 cases reporting an exacerbation of PMR following vaccination were similarly hindered by lack of information. There were no reports of PMR in the pivotal Phase 2/3 Study C4591001 of individuals 16 years of age (21926 vaccine/21921 placebo) and older from Dose 1 to 1 month after Dose 2 that was placebo-controlled (data cutoff date 13 March 2021). Ten subjects reported polymyalgia rheumatica in the medical history and none of these subjects reported a flare up of the underlying disease. The medical literature search yielded several studies that did not support an association between vaccination and autoimmune disorders or flares. Based on the totality of the available information, a causal association between BNT162b2 and PMR could not be concluded, and the signal was closed by the MAH.

Rapporteur assessment comment: The cumulative review of polymyalgia rheumatica (through 18 Dec 2021) was assessed in the 2nd Comirnaty PSUSA (reporting period 19 Jun 2021 – 18 Dec 2021; EMEA/H/C/PSUSA/00010898/202112). PRAC concluded that the data did not suggest a causal association between Comirnaty and polymyalgia rheumatica.	
Subacute thyroiditis	This signal was identified following a request for a cumulative review on the topic by EMA PRAC on 18 January 2022 following the assessment of PSUR 2. The Pfizer safety database search yielded 498 cases through 18 December 2021. There was a similar number of cases reporting each of the PTs: Thyroiditis subacute, Autoimmune thyroiditis and Thyroiditis. The majority of reports described underlying thyroid disorder or concomitant disorders that represented confounding factors and/or did not provide a sufficient amount of information (medical history, laboratory and other diagnostic data) to allow a proper evaluation. The details of 38 cases that included laboratory work ups confirming hyperthyroid activity, did not provide enough relevant information to confirm the causal association with the vaccine. In the placebo-controlled portion of clinical trial C4591001, in the safety population of participants 16 years and older, there was 1 case of autoimmune thyroiditis reported among 21926 participants in the BNT162b2 group compared with 1 case of autoimmune thyroiditis among 21921 participants in the placebo group from dose 1 to 1 month after dose 2 (data cutoff date 13 March 2021). The medical literature consisted of case reports and case series of patients who developed thyroiditis following vaccination with various COVID-19 vaccines, including BNT162b2. Observed to expected analyses were conducted and ratios were below 1 for all age groups, doses and gender strata. Based on the totality of the available information, a causal association between BNT162b2 and subacute thyroiditis could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: The cumulative review of subacute thyroiditis (through 18 Dec 2021) was assessed in the 2nd Comirnaty PSUSA (reporting period 19 Jun 2021 – 18 Dec 2021; EMEA/H/C/PSUSA/00010898/202112). PRAC concluded that no new safety concern was identified. Closure of the signal was accepted.	
Cerebrovascular accident (CVA)/Stroke	This signal was identified following a request from a competent authority (Australia, TGA) for an analysis on 27 January 2022. The Pfizer safety database search using a search strategy covering ischemic and haemorrhagic strokes, yielded 8934 cases through 18 December 2021. There were 4719 reports of females and 4024 of males, when sex was provided and the mean and median ages were 66.9 and 70 years of age, respectively. Cases were reviewed by age group. As would be expected

	based on the known epidemiology of stroke, the number of reported cases was highest in the oldest individuals and proportionally decreased with age; the number of ischemic strokes was greater than haemorrhagic strokes. Most of the reports described known risk factors for stroke and many of the cases in younger individuals were inconsistent with actual strokes upon individual case review. Of the 10 relevant studies in the medical literature, two studies (Shimazawa R et al [case reports] and Hippisley-Cox J et al) reported a correlative association between BNT162b2 vaccine and ischemic or haemorrhagic stroke. The study by Shimazawa R et al was based on 10 post-vaccination fatalities in Japan. Of these 10 cases, 4 females died of ICH. Insufficient details precluded further assessment. The study by Hippisley-Cox et al reported an increased risk of ischaemic stroke after a first dose of BNT162b2 but contextualized that this risk is far greater with COVID-19, emphasizing the importance of vaccination. Seven studies (Jabagi MJ et al, Simpson C.R et al, Cari L et al, Barda N et al, Koh JS et al, Klein NP et al, and Sessa M et al) did not support an association between BNT162b2 vaccine and haemorrhagic or ischemic stroke. In the remaining publication by Patone M et al, an increased risk of haemorrhagic stroke after BNT162b2 vaccination was reported in a study in England but was not replicated in a Scottish study that was somewhat smaller. Overall, the literature data does not support a clear causal association between BNT162b2 and stroke. The medical literature also did not provide a plausible mechanism for how BNT162b2 could increase the risk of haemorrhagic or ischemic strokes. All observed to expected ratios across all age, sex and dose stratifications were below 1 for haemorrhagic and ischemic strokes. Based on the totality of the available information, a causal association between BNT162b2 and hemorrhagic and ischemic stroke could not be concluded, and the signal was closed by the MAH.
Rapporteur assessment comment: MAH's response to the Australian Therapeutic Goods Administration query concerning cerebrovascular accident/stroke data (through 18 Dec 2021) was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13) in which PRAC concluded that no new important safety information could be identified regarding cerebrovascular accident /stroke.	
Amenorrhea	Amenorrhea was identified as a signal by PRAC on 14 February 2022. A search of the Pfizer safety database through 15 February 2022 yielded 9634 reports which were mostly non-serious and non-medically confirmed. Ages ranged from 11 to 66 years (mean 33.4). Of the cases without confounders and occurring in women younger than 45 years of age, causality assessments using the WHO-UMC criteria were all unlikely or unassessable. In the placebo-controlled portion of the C4591001 study, prior to treatment assignment unblinding, there were 8 events of amenorrhoea, with an equal split of 4 events after receipt of placebo vaccination and 4 events after receipt of active vaccination. Participants were followed up for a mean period of 135.8 days following the second

	dose of blinded study vaccine until unblinding (median 145 days; range 85-171 days). The medical literature consisted of studies obtaining mostly self-reported data. One study of almost 4000 women in the US found COVID-19 vaccination (mostly mRNA vaccines) was associated with a < 1 day change in cycle length for dose 1 and dose 2 compared to pre-vaccine cycles. The Lareb (Netherlands) reported amenorrhoea as the most reported category of menstrual abnormalities although changes were small and quickly reversed. A retrospective study in the UK of >1200 women 18 and older did not find an association between COVID-19 vaccination and menstrual changes. Based on the totality of the available information, a causal association between BNT162b2 and amenorrhea could not be concluded, and the signal was closed by the MAH. On 13 June 2022, the PRAC requested that an updated analysis of the topic be submitted in the PSUR 4.
Rapporteur assessment comment: Please refer to the separate signal procedure amenorrhea (EMEA/H/C/005735/SDA/052-EPITT 19784). PRAC concluded that the signal of amenorrhea following Comirnaty vaccination should be closed. Several points should be addressed in the next PSUR (4th PSUR).	
Heavy menstrual bleeding	Heavy menstrual bleeding (HMB) was identified as a signal by PRAC on 14 February 2022. A search of the Pfizer safety database through 15 February 2022 yielded 23,659 cases of heavy menstrual bleeding. The majority are non-serious and non-medically confirmed. Of the much smaller subset of serious, medically confirmed reports that provided information about menstrual patterns, 4 were assessed as possibly related to vaccine using the WHO-UMC causality criteria as requested; one of the 4 was 1 of 2 cases that described a rechallenge. In addition, the O/E ratios do not indicate that reported events are higher than expected based on background incidence rates. In the placebo-controlled portion of the C4591001 study, prior to treatment assignment unblinding, there were 6 events of heavy menstrual bleeding; 4 of these events were after receipt of active vaccination and 2 events after receipt of placebo. The event in the C4591031 study occurred during the placebo-controlled portion of the study and was in a participant who received placebo. In the C4591001 study, participants were followed up for a mean period of 137.5 days following the second dose during the placebo-controlled follow-up period until unblinding (median 132 days; range 89 – 176 days). The participant in the C4591031 study was followed up for 96 days from blinded study vaccine (placebo) until unblinding. The medical literature on the topic reveals that menstrual abnormalities in general are very common and there have been correlations between SARS-CoV-2 pandemic stress, anxiety, and depression with menstrual cycle abnormalities. A clear pathophysiological mechanism for heavy menstrual bleeding itself is not understood. A well-designed US study of self-reported menstrual cycle data by Alison Edelman et al. did not support a significant effect of vaccination on the

	number of days of menstrual bleeding. Studies are limited by their retrospective nature and self-reporting. While most menstruating women do not report menstrual changes associated with COVID-19 vaccination, it seems that variables such as age, BMI, changes in cycle over the previous year and the presents of fibroids and smoking may be playing a role. Based on the totality of the available information, a causal association between BNT162b2 and HMB could not be concluded, and the signal was closed by the MAH. On 13 June 2022, the PRAC responded with a list of questions that the MAH is in the process of preparing for submission by 24 August 2022.
Rapporteur assessment comment: Please refer to the separate signal procedure heavy menstrual bleeding (EMEA/H/C/005735/SDA/053- EPITT 19783). PRAC concluded that heavy menstrual bleeding should be listed as ADR in the Comirnaty PI.	
Loss of/altered taste and smell	This was identified as a signal during the reporting period following a request for a competent authority (Australia, TGA) for an analysis of the topic. A search of the safety database through 01 March 2022, yielded 12,140 potentially relevant cases (1% of all AE reports for BNT162b2). There were 17 fatal cases all unrelated to vaccination but related to intercurrent diseases. To enable a focused review of the most informative cases, the MAH applied an exclusion algorithm focusing on serious and medically confirmed cases, excluding most confounding conditions and concomitant medications which could have contributed to the events. The identified 154 were further reviewed. 76 cases had insufficient information to make a thorough medical evaluation. 67 cases had alternative explanations or confounding factors which could have contributed to the events and there were 11 remaining cases, only five out of the 11 cases where judged "possible related" according to WHO causality assessment. There were no cases with a probable or definite relationship. Review of post-marketing data did not support a causal relationship between vaccination with BNT162b2 and the development of taste and smell disorders. Based on the mid-range background rates from ACCESS, O/E ratios were greater than 1 overall for all ages globally using the 7-day risk window. Using both mid- and high-range ACCESS background rates, the O/E ratios were >1 for certain age groups using both the 7- and 21-day risk windows, suggesting that the number of reported cases may be higher than expected compared to unvaccinated persons The O/E ratios for these events may be overestimated for a few reasons. First, these pre-COVID (2017-2019) background rates from ACCESS reflect the incidence of anosmia and/or ageusia that was treated in either an inpatient or outpatient setting. Given that these symptoms may be mild in some cases, these rates might underestimate the overall incidence (and thus expected cases) of these conditions in a general, unvaccinated populations if not all cases are reported to healthcare providers. Second, they may also underestimate the incidence rate during the COVID-era since anosmia and/or ageusia are symptoms of

	SARS-COV-2 infection. For example, the reported incidence rates for anosmia/ageusia were 1.4-2.3 times higher in 2020 than during 2017-2019 in both of the ACCESS sources used for background estimates. In 2020, the ES_SIDIAP_PC database rate was 35.23/100,000 persons per year, and in the ES-FISABIO database the rate was 67.5/100,000 persons per year. Third, observed cases may include cases of anosmia or ageusia due to recent or current SARS-COV-2 infection that was not documented or diagnosed during the risk window period. Fourth, due to the unprecedented attention to COVID-19 vaccination and outreach to encourage AE reporting, the long-held assumption that reported cases are an underestimation of actual cases may be incorrect. Finally, the ACCESS rates for anosmia and ageusia were defined with ICD codes that captured anosmia, parosmia, and parageusia, while the observed case definition included PTs for additional related conditions. In the pivotal clinical trial C4591001, during the placebo-controlled follow up period from Dose 1 to 1 month after Dose 2 of BNT162b2, 17 events of interest were reported in the vaccine group (N=21926) and 10 in the placebo group (N=21921) in participants ≥ 16 years of age. None of the 5 relevant PTs were reported by 12-15 year old from Dose 1 to 1 month post-Dose 2 in C4591001. None of the 5 PTs were reported by 5 to <12 year old from Dose 1 to 1 month Dose 2 in C4591007. There was a limited amount of medical literature on this topic and it was not supportive of a known relationship between vaccination and loss of taste or smell. Based on the totality of the available information, a causal association between BNT162b2 and anosmia and ageusia could not be concluded, and the signal was closed by the MAH.

Rapporteur assessment comment:

MAH's response to the Australian Therapeutic Goods Administration query concerning loss of/altered taste and smell (data through 18 Dec 2021) was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13). PRAC concluded that the data provided did not support a causal relationship between Comirnaty exposure and the loss of/altered taste and smell.

Important risks	
Myocarditis and Pericarditis	*During the reporting period, myocarditis and pericarditis, which have been considered important identified risks in the US-PVP and EU-PVP, were moved from important potential risks to important identified risks in the company core list of safety concerns. After the DLP of this PSUR, they were also added as adverse reactions to the company CDS v. 14.0 dated 26 July 2022 (Section 4.8, Appendix A and Appendix B). The changes to the core list of safety concerns and CDS were made based on the summation of data that has accumulated in the surveillance of this issue, including the published incidence and reporting rates from multiple sources with consistent findings.*

Rapporteur assessment comment:

Please refer to the assessment of the important identified risk myocarditis and pericarditis in section 2.4.1. of this AR.	
Risks not categorized as important	
Irritability	During the reporting period, placebo-controlled safety data from Clinical Trial C4591007 was unblinded for submission to regulatory authorities to support authorisation of vaccination in individuals 6 months to < 5 years of age. Irritability was the most frequently reported systemic event reported within 7 days after each of the 3 doses of BNT162b2 (3 µg) for the 6 months to < 2 years age group. Irritability was reported by 51.2%, 47.4% and 43.6% of participants in the BNT162b2 group and 47.2%, 40.7% and 37.6% in the placebo group, after dose 1, 2 and 3, respectively. Based on these data, irritability was determined to be an adverse reaction for the age group 6 months to < 2 years.
Rapporteur assessment comment: Please refer regarding irritability to the separate ongoing line extension procedure (EMEA/H/C/005735/X/138) to add a new strength of 3 µg for individuals 6 months to 4 years of age and the RMP (version 5.1) is updated accordingly.	

2.2.3. Signal evaluation plan for ongoing signals

Table 35. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Hearing loss	Following enquiry from a competent authority (EMA PRAC and Health Canada) this signal was reopened during the reporting period and is under evaluation at the cut-off date of this PSUR (18 June 2022). The requested cumulative review is in Appendix 6A.3.

Rapporteur assessment comment:

Regarding hearing loss, please refer to the assessment in section 2.2.1 'Post-approval regulatory' above.

2.3. Evaluation of risks and new information

Follow-up questionnaires

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

> *The MAH is requested to re-assess the need for continuing the follow-up questionnaires anaphylaxis and VAED/VAERD and provide process data (e.g., response rate, extent of additional information collected) separately for cases reporting anaphylaxis and cases reporting VAED/VAERD, if applicable.).*

MAH's response (Appendix 6A of the PSUR):

As described in PSUR 1 and PSUR 2, the pursuit of additional information for specific adverse events via the use of a Data Capture Aid (DCA) remains limited in 2 regards: the number of reports that can have DCAs sent for follow-up information and the dependency on a response. As previously described, the most common reasons that a DCA is not dispatched include lack of contact details or refused contact and receipt of the report from a Health Authority. Of the adverse event reports received by Pfizer potentially meeting criteria for dispatch of a DCA for follow-up to the reporter from 01 December 2021 to 30 June 2022, 23.5% of the reports had DCAs sent in the pursuit of follow-up information. Despite the limitations, it is the opinion of the MAH that the potential for obtaining useful follow-up information justifies the continued use of the DCAs currently and as vaccine use extends to lower age populations.

Rapporteur assessment comment:

Despite that the MAH did not provide process data separately for cases reporting anaphylaxis and cases reporting VAED/VAERD, MAH's response is endorsed that the potential for obtaining useful follow-up information justifies the continued use of the follow-up questionnaires anaphylaxis and VAED/VAERD currently and as vaccine use extends to lower age populations.

Evaluation of important identified risks

Anaphylaxis

Search criteria - PTs: Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock

Clinical trial data

- Number of cases: 3 (0.45% of 668 cases of the total CT dataset), compared to 2 cases (0.28%) retrieved in the PSUR #2.
- The investigator and the Sponsor reported that there was not a reasonable possibility that the events anaphylactic reactions in all cases were related to the blinded study vaccine/BNT162b2, or clinical trial procedure. In 2 cases the anaphylaxis reactions were associated with food allergies and in the remaining case anaphylaxis reaction was attributed to another product (etoricoxib).

Post-authorization data

- Number of cases: 1037 (0.20% of 507,683 cases, the total PM dataset), compared to 3507 cases (0.53%) retrieved in the PSUR #2.
- MC cases (690), NMC cases (347).
- Country of incidence (top 10): Japan (184), Germany (158), Australia (113), UK (105), US (59), Poland (48), France (47), New Zealand (41), Philippines (26), and Sweden (24); the remaining 232 cases were distributed among 34 countries.
- Subjects' gender: female (768), male (219) and unknown (50).
- Subjects' age in years: n = 949, range: 5 - 99, mean: 40.2, median: 40.0.
- Medical history (n = 422): the most frequently (≥ 10 occurrences) reported medical conditions Asthma (90), Food allergy (83), Drug hypersensitivity (66), Hypersensitivity (55), Hypertension (42), Seasonal allergy (38), Anaphylactic reaction (30), COVID-19 (21), Mite

allergy (20), Allergy to arthropod sting (19), Allergy to animal (14), Dermatitis contact (14), Contrast media allergy (12), Mast cell activation syndrome (12), Multiple allergies (12), Diabetes mellitus (11), Urticaria (11), Allergy to chemicals (10), Anaphylactic shock (10), Migraine (10), Obesity (10), and Rubber sensitivity (10).

- COVID-19 Medical history (n = 22): COVID-19 (21), Suspected COVID-19 (3), and Post-acute COVID-19 syndrome (1).
- Co suspects (n = 21 cases): Relevant co-suspect vaccines/medications reported more than once were: adalimumab, herbal pollen NOS, JNJ 78436735 (2 each).
- Number of relevant events: 1073.
- Relevant event seriousness: serious (1073).
- Reported relevant PTs: Anaphylactic reaction (802), Anaphylactic shock (238), Anaphylactoid reaction (33).
- Time to event onset (n = 781), range: <24 hours to 365 days, median: 0 days.
- Duration of relevant events (n = 249 out of 1037 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 246 days, median 0 days.
- Relevant event outcome : fatal (8), resolved/resolving (647), resolved with sequelae (23), not resolved (134), unknown (263).
- Of the 433 cases reporting medical history/co-suspects, 324 cases reported relevant medical history/risk factors (e.g., asthma, drug hypersensitivity, food allergies, autoimmune disorders, hypersensitivity, prior anaphylactic reactions) and/or co-suspect (e.g., adalimumab, infliximab, influenza vaccine inact SAG 4V, herbal pollen NOS, JNJ 78436735, immunoglobulin human normal), which may have contributed to the anaphylaxis related events.

Analysis by age group

- Post-marketing:
    - Paediatric (120), Adults (751), Elderly (80) and Unknown (86). No significant difference was observed in the reporting proportion of anaphylaxis relevant PTs between paediatric, adult and elderly populations (0.38% in paediatric vs 0.21% in adults vs 0.14% in elderly).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 181 (17.5% of the cases reporting anaphylaxis). The reporting proportion of anaphylaxis related events with fatal outcome with comorbid conditions is 1.7 % compared to the reporting proportion of 3.3 % observed in the individuals without comorbidities. A meaningful comparison is not possible due to the low number of fatal anaphylactic related cases.

Literature

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

O/E analysis

- O/E analysis was performed for Anaphylaxis. An O/E ratio of 2.404 (95% CI 2.353, 2.455) 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 SMSR 2 (through 31 January 2021) and has remained consistent with that reported in the most recent SBSR. 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

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

This risk is communicated in the BNT162b2 CDS, Section 4.4, Special warnings and precautions for use, which includes information on appropriate action to be taken, as follows: "As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine." This risk is also listed in the CDS Section 4.8, Undesirable effects, Appendix A, Appendix B.

In line with the removal of anaphylaxis from the list of safety concerns in the EU-RMP v. 5.1 submitted on 08 July 2022, the MAH proposes to remove the important identified risk of anaphylaxis from the list of safety concerns for the next PSUR reporting period, because anaphylaxis is a known risk of vaccines that is understood by HCPs who administer vaccines and patients and does not considerably impact the benefit/risk profile of the vaccine. Product labelling and standards of medical care during the vaccination procedure provide adequate risk mitigation.

This risk will continue to be monitored through routine pharmacovigilance.

Rapporteur assessment comment:

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

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

Myocarditis and Pericarditis

There were 8533 potentially relevant cases of Myocarditis and Pericarditis: 5423 cases reported myocarditis and 4156 cases reported pericarditis (in 1046 of these 8533 cases, the subjects developed both myocarditis and pericarditis):

Myocarditis

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

Overall - All ages

- Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.15 % of 668 cases of the total CT dataset), compared to 2 cases (0.3% of 721 cases of the total CT dataset) retrieved in the PSUR #2.
- Country of incidence: US.
- Subject's gender: Male (1).
- Subject's age in years: 43 years.
- Medical history: PT Abstains from alcohol, Abstains from recreational drugs, Anxiety, Attention deficit hyperactivity disorder, Clinical trial participant, Dyspepsia, Gastroesophageal reflux disease, Neuralgia, Non-tobacco user, Postural orthostatic tachycardia syndrome, Prophylaxis, Seasonal allergy, Stress, Tachycardia, Thyroiditis, Vasectomy (1 each).
- COVID-19 Medical history: COVID-19 (1).
- Co suspects: None.
- Number of relevant serious events: 1.
- Reported relevant PTs: Myocarditis (not related to BNT162b2).
- Relevant event outcome: Resolved (1).
- Time to onset of relevant events: 98 days after dose 3.
- Duration of myocarditis was reported as 2 days.

- Post-Authorisation Data
  - Number of cases: 5422 (1.1% of 507,683 cases of the total PM dataset), compared to 6347 cases (1.0%) retrieved in the PSUR #2.
  - Country/region of incidence (≥10): Germany (1342), UK (1230), Australia (509), France (344), Taiwan, Province Of China (280), Canada (216), Austria (193), Japan (163), Italy (151), Sweden (119), US (118), New Zealand (107), Greece (77), Israel (64), Finland (51), Spain (45), Netherlands (44), Hong Kong (41), Poland (35), Belgium, Denmark (29 each), Switzerland (25), Norway, Portugal (24 each), Malaysia (22), Ireland (21), Czech Republic (16), Brazil (15), Romania (10). The remaining 78 cases were distributed among 25 countries.
  - MC (2710), NMC (2712).
  - Subjects' gender: female (1997), male (3307) and unknown (118).
  - Subjects' age in years: n = 4981, range: 6 -98, mean: 35.3, median: 32.
  - Medical history (n = 1699): the most frequently (≥50 occurrences) reported medical conditions included Hypertension (214), Asthma (140), Seasonal allergy (130), Tobacco user (96), Drug hypersensitivity (67), Immunodeficiency (64), Obesity (62), Hypothyroidism, Non-tobacco user (59 each), and Food allergy (58).
  - COVID-19 Medical history (n = 371): COVID-19 (191), Suspected COVID-19 (179), Post-acute COVID-19 syndrome (9), SARS-CoV-2 test positive (6), Asymptomatic COVID-19 (2), Coronavirus infection, COVID-19 pneumonia, COVID-19 treatment (1 each).

- Co suspect vaccines/medications (>1 occurrence): COVID-19 vaccine mRNA (MRNA 1273) (10), influenza vaccine (5), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (4), adalimumab, COVID-19 vaccine, and pembrolizumab (2 each).
- Number of relevant events: 5458.
- Relevant event seriousness: serious (5458).
- Reported relevant PTs: Myocarditis (4639), Myopericarditis (697), Carditis (113), Eosinophilic myocarditis (4), Giant cell myocarditis, Hypersensitivity myocarditis (2 each), and Immune-mediated myocarditis (1).
- Relevant event outcome: fatal (87), resolved/resolving (1925), resolved with sequelae (160), not resolved (1608), unknown (1682).
- Of the 5422 cases, in 1108 cases (20.4% of the cases reporting myocarditis related events) the events were confounded by subject' s relevant medical history (1016 cases; e.g., COVID-19, seasonal allergy, tobacco user, drug hypersensitivity, food allergy, myocarditis, mite allergy, autoimmune thyroiditis, cardiac failure, allergy to animal, overweight, alcohol use, cardiac disorder, pericarditis, allergy to metals, breast cancer, chemotherapy, allergy to plants, dust allergy, rheumatoid arthritis, influenza, myopericarditis, systemic lupus erythematosus, mycotic allergy, radiotherapy, allergy to arthropod sting, allergy to chemicals, Epstein Barr virus infection, autoimmune disorder, Lyme disease, rheumatic disorder) and/or relevant co-suspect/concomitant medications (92 cases; e.g., influenza vaccine, isotretinoin, mesalazine, olanzapine, quetiapine, rituximab, cyclophosphamide, epirubicin, hepatitis B vaccine RHBSAG (yeast), minocycline, norepinephrine, sulfasalazine, zuclopenthixol, COVID-19 vaccine mRNA (mRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), COVID-19 vaccine, pembrolizumab, clozapine, hepatitis A vaccine, influenza vaccine INACT SAG 3V, ipilimumab, JNJ 78436735, nivolumab).
- Of the 5422 cases, 236 cases involved elderly (age >70 years) subjects and 61% cases involved male subjects.

<u>Subjects aged less than 5 years</u>

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.

Rapporteur assessment comment:
Comirnaty exposure in persons aged less than 5 years is considered off-label use during the interval period of the current 3rd PSUR.

<u>Subjects aged 5 - 11 years</u>

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data

- Number of cases: 48 cases (0.01 % of 507,683 cases of the total PM dataset; 0.6 % of the 8375 subjects aged 5-11 years); 10 cases (0.002%) were retrieved in the PSUR #2.
- Country/region of incidence: Australia (15), Canada, Japan (6 each), Italy, Portugal, Spain (3 each), Greece, Taiwan, Province of China (2 each), Austria, Denmark, Finland, France, New Zealand, Philippines, UK, US (1 each).
- Subjects' age in years: n = 48, range: 6 – 11, mean: 9.2, median: 9.5.
- Medical history (n = 8): Asthma, Atrioventricular block, Attention deficit hyperactivity disorder, Autoimmune thyroiditis, Cardiac failure, Cerebral palsy, Condition aggravated, Dependence on respirator, Ejection fraction decreased, Hypoxic-ischaemic encephalopathy, Intellectual disability, Motor dysfunction, Myocarditis, Neonatal asphyxia, Non-tobacco user, Obesity, Respiratory tract infection, Rhinitis allergic, Type 1 diabetes mellitus (1 each).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co suspect vaccine/medications: None.
- Most frequently co-reported PTs (>5 occurrences): Chest pain (28), Dyspnoea, Pyrexia (10 each), Troponin increased (7), Chest discomfort, Electrocardiogram abnormal, Tachycardia (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 36.

Table 36. Myocarditis in Subjects aged 5 – 11 Years (N=48)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	16	26	0
	No	3	3	0
Relevant PT[a]	Myocarditis	13	22	0
	Myopericarditis	3	7	0
	Carditis	3	0	0
Hospitalisation required/prolonged	Yes	5	11	0
	No	14	18	0
Relevant suspect dose	Dose 1	15	15	0
	Dose 2	4	13	0
	Dose 3	0	1	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=39	≤ 24 hours	0	3	0
	1-5 days	7	13	0
	6-13 days	6	8	0
	14-20 days	1	1	0
	Unknown	5	4	0
Event Outcome	Fatal	1	1	0
	Not resolved	4	4	0
	Resolved	4	12	0
	Resolving	5	8	0
	Unknown	5	4	0
Duration of event[b] n=4, median = 1 day	Up to 3 days	0	2	0
	4-6 days	0	0	0
	7-25 days	0	2	0

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

Fatal myocarditis cases in subjects aged 5-11 years (2 cases, medically confirmed):

- A 6-year-old male subject from [redacted]

- Medical history: Autoimmune thyroiditis, Rhinitis allergic, Type 1 diabetes mellitus.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis, Cardio-respiratory arrest, COVID-19.
- Time to onset (myocarditis): 7 days after dose 1.
- Causes of death: Cardio-respiratory arrest; Myocarditis.
- Autopsy: Results awaited at the time of reporting.

- An 11-year-old female subject from [redacted]:
  - Medical history: Cerebral palsy, Dependence on respirator, Hypoxic-ischaemic encephalopathy, Intellectual disability, Motor dysfunction, Neonatal asphyxia.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Blood pressure decreased, Blood pressure immeasurable, Bradycardia, Cardio-respiratory arrest, Cyanosis, Heart rate decreased, Myocarditis, Respiratory failure.
  - Time to onset (myocarditis): 1 day after dose 2.
  - Causes of death: Blood pressure decreased; Blood pressure immeasurable; Bradycardia; Cardiac failure acute; Cardio-respiratory arrest; Cyanosis; Heart rate decreased; Myocarditis; Respiratory failure.
  - Autopsy: Pleural X-ray was performed as autopsy imaging and did not show abnormal findings.

Rapporteur assessment comment:

During the current reporting period, there were 48 cases reporting myocarditis in children aged 5-11 years compared to 10 myocarditis cases reported in the previous 2nd PSUR. Although the Comirnaty exposure in persons aged 5-11 years is considered increased based on the EU/EEA exposure (current reporting period an estimated 3,569,821 administered doses in 5-9 years versus 391,327 administered doses in 5-9 years in the previous reporting period), worldwide interval exposure in persons aged 5-11 years (or any other age category) is not presented in the PSUR and therefore the relative post-marketing reporting rate of myocarditis cases in persons aged 5-11 years is not known.

There were 2 medically confirmed fatal cases compared to no fatal cases in the previous reporting period. The MAH only briefly described the 2 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 5-11 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 12 - 15 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.

- Post-Authorisation Data
    - Number of cases: 366 (0.07 % of 507,683 cases of the total PM dataset; 2.7 % of the 13,366 subjects aged 12-15 years), compared to 488 cases (0.07% of all cases in the total PM dataset) retrieved in the PSUR #2.
    - Country/region of incidence (≥10): Taiwan, Province of China (87), Germany (64), UK (30), Australia, Japan (23 each), Canada (18), France (15), Italy (14), Israel, Malaysia (11 each), Hong Kong (10). The remaining 60 cases were distributed among 20 countries.
    - Subjects' age in years: n = 366, range: 12-15.3, mean: 13.9, median: 14.
    - Medical history (n = 72): the most frequently (≥2 occurrence) reported medical conditions included Asthma (7), Attention deficit hyperactivity disorder, Food allergy, Obesity, Seasonal allergy (4 each), Glucose-6-phosphate dehydrogenase deficiency, Hypersensitivity, Migraine, Non-tobacco user, Pericarditis, Rhinitis allergic (3 each), Anxiety, Autism spectrum disorder, Childhood asthma, Cough, Dermatitis atopic, Mite allergy, Pneumonia, Prophylaxis, Tonsillectomy (2 each).
    - COVID-19 Medical history (n = 11): COVID-19 (9), Suspected COVID-19 (2), Post-acute COVID-19 syndrome (1).
    - Co suspect vaccine/medications: None.
    - Most frequently co-reported PTs (>5 occurrences): Chest pain (174), Pyrexia (80), Chest discomfort (64), Dyspnoea (60), Headache (39), Palpitations (36), Pericarditis (34), Fatigue (31), Tachycardia (25), Inappropriate schedule of product administration, Troponin increased (23 each), Vomiting (20), Electrocardiogram ST segment elevation (18), Dizziness, Nausea (17 each), Malaise (16), C-reactive protein increased (15), Myalgia, Troponin I increased (14 each), Cough (13), Asthenia, Off label use, Pain in extremity (11 each), Blood creatine phosphokinase MB increased, Vaccination site pain (10 each), Chills (9), Blood creatine phosphokinase increased, Diarrhoea, Pain (8 each), Decreased appetite, Immunisation, Pericardial effusion, Syncope (7 each), Arthralgia, Electrocardiogram abnormal, Heart rate increased, Multisystem inflammatory syndrome in children, Nasopharyngitis (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 37.

Table 37. Myocarditis in Subjects aged 12 – 15 Years (N=366)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	42	232	1
	No	19	71	1
Relevant PT[a]	Myocarditis	56	269	2
	Myopericarditis	5	31	0
	Hypersensitivity myocarditis	0	1	0
	Carditis	0	2	0
Hospitalisation required/prolonged	Yes	32	226	1
	No	29	77	1
Relevant suspect dose	Dose 1	16	49	0
	Dose 2	33	186	0
	Dose 3	4	43	0
	Unknown	8	25	2
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=274	≤ 24 hours	2	17	0
	1-5 days	29	158	0
	6-13 days	7	21	0
	14-21 days	2	11	0
	22-31 days	1	0	0
	>31 days	6	20	0
	Unknown	14	78	2
Event Outcome	Fatal	1	2	0
	Not resolved	11	45	0
	Resolved	21	88	1
	Resolved with sequelae	0	1	0
	Resolving	21	104	0
	Unknown	7	63	1
Duration of event[b] n=39, median=7 days	Up to 3 days	3	8	0
	4-6 days	0	6	0
	7-25 days	4	11	0
	26-134 days	2	5	0

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

Fatal myocarditis cases in subjects aged 12-15 years (2 cases, medically confirmed; 1 case non-medically confirmed):

- A 13-year-old male subject from [redacted], [redacted]:
    - Medical history: None.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Cardiac failure, Myocarditis.
    - Time to onset (myocarditis): 69 days after dose 2.
    - Causes of death: Cardiac failure; Myocarditis.
    - Autopsy: Not reported if autopsy was performed.
- A 13-year-old male subject from [redacted]:
    - Medical history: Abdominal pain, Chest pain.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Anuria, Asthenia, Cardiac arrest, Compartment syndrome, Enterovirus infection, Malaise, Multi-organ disorder, Multiple organ dysfunction syndrome, Myocarditis, Pulseless electrical activity, Renal failure, Rhinovirus infection, Ventricular tachycardia.

- Time to onset (myocarditis): 5 days after dose 2.
- Causes of death: Asthenia; Cardiac arrest; Compartment syndrome; Enterovirus infection; Malaise; Multi-organ disorder; Myocarditis; Pulseless electrical activity; Renal failure; Rhinovirus infection; Ventricular tachycardia.
- Autopsy: Not reported if autopsy was performed.

- A 13-year-old female subject from [redacted]:
  - Medical history: None.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Myocarditis.
  - Time to onset (myocarditis): 6 days after dose 1.
  - Causes of death: Myocarditis.
  - Autopsy: Adverse event following immunisation.

Rapporteur assessment comment:

During the current reporting period, there were 366 cases reporting myocarditis in persons aged 12-15 years compared to 488 myocarditis cases reported in the previous 2nd PSUR. There were 3 fatal cases compared to 3 fatal cases in the previous reporting period.

The MAH only briefly presented the 3 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 12-15 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 16 - 17 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 345 (0.07 % of 507,683 cases of the total PM dataset; 4.2 % of the 8313 subjects aged 16-17 years), compared to 470 cases (0.07%) retrieved in the PSUR #2.
  - Country of incidence (≥10): Germany (88), Taiwan, Province of China (55), UK (29), Australia (18), Austria (17), France, Poland (14 each), Italy, Japan (12 each), Greece (11). The remaining 75 cases were distributed among 26 countries.Subjects' age in years: n = 345, range: 16 -17, mean: 16.6, median: 17.0.
  - Medical history (n = 71): the most frequently (>2 occurrence) reported medical conditions includd Seasonal allergy (9), Asthma, Obesity (4 each), Food allergy, Mite allergy, Nasopharyngitis, Overweight (3 each).
  - COVID-19 Medical history (n = 10): COVID-19 (8), Suspected COVID-19 (2).

- Co suspect vaccine/medications: Clonazepam, infliximab, and levomethadone (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (147), Pyrexia (72), Dyspnoea (53), Chest discomfort (43), Palpitations (34), Tachycardia (33), Fatigue (29), Headache (27), Inappropriate schedule of product administration (26), Pericarditis (24), Troponin increased (23), Dizziness, Vomiting (18 each), Malaise, Nausea (17 each), Asthenia (12), Chills, Immunisation, Off label use (10 each), Arrhythmia, Blood creatine phosphokinase increased, C-reactive protein increased, Electrocardiogram ST segment elevation, Pain in extremity, Pericardial effusion, Syncope, Troponin I increased (9 each), Cough (8), Myocardial necrosis marker increased, Pain, Troponin T increased (7 each), Angina pectoris, Back pain, Blood creatine phosphokinase MB increased, Diarrhoea, Electrocardiogram abnormal, Lethargy (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 38.

Table 38. Myocarditis in Subjects aged 16 – 17 Years (N=345)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	28	202	2
	No	23	90	0
Relevant PT[a]	Myocarditis	48	243	2
	Myopericarditis	4	47	0
	Carditis	0	5	0
Hospitalisation required/prolonged	Yes	27	223	0
	No	24	69	2
Relevant suspect dose	Dose 1	13	39	1
	Dose 2	23	154	0
	Dose 3	9	65	1
	Unknown	6	34	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=249	≤24 hours	7	18	1
	1-5 days	13	149	1
	6-13 days	6	19	0
	14-21 days	1	7	0
	22-31 days	2	3	0
	32-90 days	4	14	0
	91-150 days	1	5	0
	Unknown	18	81	0
Event Outcome	Fatal	0	0	0
	Not resolved	11	60	0
	Resolved	9	78	1
	Resolved with sequelae	1	2	0
	Resolving	11	80	0
	Unknown	20	75	1
Duration of event[b] n=30, median= 8 days	Up to 3 days	1	7	0
	4-6 days	0	3	0
	7-25 days	2	13	0
	26-68 days	0	4	0

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

Rapporteur assessment comment:

During the current reporting period, there were 345 cases reporting myocarditis in persons aged 16-17 years compared to 470 myocarditis cases reported in the previous 2nd PSUR.

There were no fatal cases compared to 2 fatal cases in the previous reporting period.

Subjects aged 18 - 24 years

- Clinical Trial Data
    - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
    - Number of cases: 968 (0.2 % of 507,683 cases of the total PM dataset, 0.18 % of the 38293 subjects aged 18-24 years), compared to 1187 cases (2.3%) retrieved in the PSUR #2.
    - Country of incidence (≥10): Germany (289), UK (114), France (105), Australia (99), Taiwan, Province of China (46), Italy (43), Austria (38), Sweden (32), Japan (25), US (18), Greece, New Zealand (16 each), Israel (14), Canada, Spain (13 each), Finland (11), Denmark (10). The remaining 66 cases were distributed among 18 countries.
    - Subjects' age in years: n = 968, range: 18-24, mean: 21, median: 21.
    - Medical history (n = 237): the most frequently (>2 occurrence) reported medical conditions included PT Tobacco user (28), Asthma (23), Seasonal allergy (16), Myocarditis (12), Hypertension, Non-tobacco user (11 each), Immunodeficiency, Obesity (9 each), Attention deficit hyperactivity disorder (8), Hypersensitivity, Nicotine dependence (7 each), Alcohol use, Contraception, Mite allergy (6 each), Acne, Crohn's disease, Drug hypersensitivity, Migraine, Overweight, Substance use (5 each), Anaemia, Autism spectrum disorder, Epstein-Barr virus infection (4 each), Appendicectomy, Chest pain, Food allergy, Hypothyroidism, Oral contraception, Pericarditis, Pharyngitis, Psoriasis, Syncope, Wisdom teeth removal (3 each).
    - COVID-19 Medical history (n = 52): COVID-19 (26), Suspected COVID-19 (22), SARS-CoV-2 test positive (3), and Asymptomatic COVID-19 (1).
    - Co suspect vaccine/medications: Drug COVID-19 vaccine, COVID-19 vaccine MRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), insulin, levothyroxine, and zuclopenthixol (1 each).
    - Most frequently co-reported PTs (>5 occurrences): Chest pain (354), Dyspnoea (168), Pyrexia (134), Pericarditis (116), Fatigue (115), Palpitations (112), Chest discomfort (104), Troponin increased (75), Tachycardia (74), Headache (61), Inappropriate schedule of product administration (59), Off label use (48), Dizziness, Immunisation (46 each), Interchange of vaccine products (38), Asthenia (33), Chills (32), Malaise, Myalgia (29 each), Angina pectoris (28), Pain, Syncope (25 each), Nausea (23), Arrhythmia, Dyspnoea exertional (21 each), Pericardial effusion (20), Influenza like illness (19), Cough, Vomiting (18 each), Pain in extremity (17), C-reactive protein increased, Heart rate increased (15 each), Electrocardiogram ST segment elevation, Hyperhidrosis, Lethargy (14 each), Electrocardiogram abnormal (13), Diarrhoea (12), Oropharyngeal pain (11), Arthralgia, Blood creatine phosphokinase increased, COVID-19, Myocardial infarction, Myocardial necrosis marker increased, Troponin I increased, Troponin T increased (10 each), Acute myocardial infarction, Paraesthesia (9 each), Abdominal pain, Abdominal pain upper, Back pain, Cardiac failure, Drug ineffective, Feeling abnormal, Inflammation, Sinus tachycardia (8 each), Hypertension, Hypoaesthesia, Limb discomfort, Lymphadenopathy, Night sweats, Pulmonary embolism, Vaccination site pain, Ventricular hypokinesia (7 each), Costochondritis,

Feeling hot, Incorrect route of product administration, Insomnia, Left ventricular dysfunction, Loss of consciousness, Somnolence (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 39.

Table 39. Myocarditis in Subjects aged 18 – 24 Years (N=968)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	110	471	3
	No	97	283	4
Relevant PT[a]	Myocarditis	179	600	7
	Myopericarditis	23	147	0
	Carditis	5	14	0
Hospitalisation required/prolonged	Yes	108	484	5
	No	99	271	2
Relevant suspect dose	Dose 1	48	145	3
	Dose 2	84	316	1
	Dose 3	55	235	0
	Unknown	22	60	3
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n= 724	≤24 hours	18	39	1
	1-5 days	73	362	2
	6-13 days	15	57	1
	14-21 days	9	43	0
	22-31 days	4	12	0
	32-60 days	6	35	0
	61-220 days	13	34	0
	Unknown	69	179	3
Event Outcome	Fatal	0	4	0
	Not resolved	66	234	1
	Resolved	25	139	1
	Resolved with sequelae	10	27	1
	Resolving	52	195	1
	Unknown	54	162	3
Duration of event[b] n= 71, median= 7 days	Up to 3 days	4	14	0
	4-6 days	4	9	0
	7-25 days	1	18	0
	26-195 days	2	18	1

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

Fatal myocarditis cases in subjects aged 18-24 years (4 cases, medically confirmed)

- A 23-year-old male subject from [redacted]:
  - Medical history: Non-tobacco user.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Circulatory collapse, Endocarditis, Myocarditis, Sudden cardiac death.
  - Time to onset (myocarditis): unknown days after dose 2.
  - Causes of death: Circulatory collapse; Endocarditis; Myocarditis; Sudden cardiac death.
  - Autopsy: Autopsy was performed, results were not provided at the time of reporting.
- A 20-year-old male subject from [redacted], [redacted]:
  - Medical history: None.

- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): 20 days after dose 1.
- Cause of death: Myocarditis.
- Autopsy: Autopsy results showed cause of death as myocarditis.

- A 19-year-old male subject from [redacted]:
  - Medical history: Asthma, COVID-19, Interchange of vaccine products, Rhinitis allergic.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Arrhythmia, Hernia, Hypoxia, Loss of consciousness, Myocardial necrosis, Myocardial necrosis marker increased, Myocarditis, Sudden death, Ventricular hypokinesia.
  - Time to onset (myocarditis): 3 days after dose 3.
  - Causes of death: Arrhythmia; Hernia; Hypoxia; Loss of consciousness; Myocardial necrosis; Myocardial necrosis marker increased; Myocarditis; Sudden death; Ventricular hypokinesia.
  - Autopsy: The autopsy revealed extensive necrosis of the left ventricular myocardium (myocardial necrosis); myocarditis/fulminant myocarditis.
- A 23-year-old male subject from [redacted]:
  - Medical history: Hypertension, Obesity.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Death, Myocarditis.
  - Time to onset (myocarditis): 16 days after dose 3.
  - Cause of death: Myocarditis.
  - Autopsy: Information not available.

Rapporteur assessment comment:

During the current reporting period, there were 968 cases reporting myocarditis in persons aged 18-24 years compared to 1,187 myocarditis cases reported in the previous 2nd PSUR. There were 4 fatal cases compared to 2 fatal cases in the previous reporting period.

The MAH only briefly presented the 4 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 18-24 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 25 - 29 years

- Clinical Trial Data
    - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
    - Number of cases: 519 (0.1% of 507,683 cases of the total PM dataset, 1.2 % of the 43518 subjects aged 25-29 years), compared to 589 cases (0.09%) retrieved in the PSUR #2.
    - Country of incidence (≥10): Germany (150), UK (113), Australia (54), France (39), Austria (27), Sweden, Taiwan, Province of China (17 each), Japan (14), Italy (13), New Zealand (11). The remaining 64 cases were distributed among 25 countries.
    - Subjects' age in years: n = 519, range: 25-29, mean: 27.1, median: 27.
    - Medical history (n = 141): the most frequently (>2 occurrence) reported medical conditions included Seasonal allergy (20), Asthma (14), Tobacco user (13), Food allergy (10), Hypertension, Mite allergy (8 each), Allergy to animal, Chest pain (7 each), Non-tobacco user (6), Hypersensitivity, Hypothyroidism (5 each), Anxiety, Depression, Drug hypersensitivity, Migraine, Myocarditis, Steroid therapy (4 each), Autoimmune thyroiditis, Contraception, Gastrooesophageal reflux disease, Polycystic ovaries (3 each).
    - COVID-19 Medical history (n = 43): COVID-19 (22), Suspected COVID-19 (21), Post-acute COVID-19 syndrome (2), and SARS-CoV-2 test positive (1).
    - Co suspect vaccine/medications (n = 8): COVID-19 vaccine mRNA (MRNA 1273) (3), adalimumab, fluticasone, influenza vaccine, levothyroxine, and methylphenidate (1 each).
    - Most frequently co-reported PTs (>5 occurrences): Chest pain (217), Dyspnoea (153), Palpitations (122), Fatigue (110), Tachycardia (98), Pericarditis (88), Chest discomfort, Pyrexia (71 each), Headache (47), Immunisation (42), Dizziness (39), Arrhythmia (31), Myalgia (25), Off label use, Pain in extremity (24 each), Interchange of vaccine products, Troponin increased (23 each), Heart rate increased, Inappropriate schedule of product administration, Malaise, Pain (22 each), Angina pectoris (21), Lymphadenopathy (18), Asthenia, Nausea (16 each), Chills, Pericardial effusion (15 each), Influenza like illness, Paraesthesia, Syncope, Vaccination site pain (14 each), Arthralgia (13), Lethargy (10), COVID-19, Dyspnoea exertional, Influenza, Migraine, Vomiting (9 each), Back pain, Cardiac flutter, Heart rate irregular, Tremor (8 each), Abdominal pain upper, Blood pressure increased, Cardiac disorder, Diarrhoea, Extrasystoles, Hyperhidrosis, Peripheral swelling (7 each), Abdominal pain, Cough, Electrocardiogram ST segment elevation, Feeling abnormal, Hypertension, Inflammation, Myocardial infarction, Rash, Sleep disorder (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 40.

Table 40. Myocarditis in Subjects aged 25 – 29 Years (N=519)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	69	169	0
	No	110	168	3
Relevant PTs[a]	Myocarditis	150	285	3
	Myopericarditis	27	48	0
	Carditis	4	5	0
Hospitalisation required/prolonged	Yes	58	171	1
	No	121	166	2
Relevant suspect dose	Dose 1	62	93	1
	Dose 2	43	108	1
	Dose 3	52	103	1
	Dose 4	0	1	0
	Unknown	22	32	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n= 335	≤ 24 hours	16	23	0
	1-5 days	49	131	0
	6-13 days	12	27	0
	14-21 days	15	20	0
	22-31 days	3	10	0
	32-60 days	5	13	0
	61-366 days	3	8	0
	Unknown	78	106	3
Event Outcome	Fatal	2	3	0
	Not resolved	70	108	0
	Resolved	21	41	0
	Resolved with sequelae	9	12	0
	Resolving	27	82	1
	Unknown	52	92	2
Duration of event[b] n=34, median= 27 days	Up to 3 days	2	3	0
	4-6 days	1	3	0
	7-25 days	4	2	0
	26-259 days	10	9	0

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

Fatal myocarditis cases in subjects aged 25-29 years (2 cases, medically confirmed; 3 case non-medically confirmed)

- A 29-year-old male subject from [redacted]:
  - Medical history: Hepatic steatosis.
  - Co-suspect medications: COVID-19 vaccine mRNA (MRNA 1273).
  - PTs with fatal outcome: Arrhythmia, Myocarditis.
  - Time to onset (myocarditis): unknown days after dose 2.
  - Causes of death: Arrhythmia; Myocarditis.
  - Autopsy: Autopsy revealed arrhythmia
- A 27-year-old male subject from [redacted]
  - Medical history: None.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use, Chest pain.
  - Time to onset (myocarditis): 10 days after dose 3.

- Causes of death: Myocarditis.
- Autopsy: Not reported if autopsy was performed

- A 26-year-old male subject from [redacted]:
  - Medical history: Aneurysm, Surgery, Vein of Galen aneurysmal malformation.
  - Co-suspect medications: Influenza vaccine.
  - PTs with fatal outcome: Myocarditis, Arrhythmia, Inflammation, Left ventricular dysfunction.
  - Time to onset (myocarditis): 4 days after dose 3.
  - Causes of death: Arrhythmia; Inflammation; Left ventricular dysfunction; Myocarditis.
  - Autopsy: Autopsy results showed myocarditis.
- A 26-year-old female subject from [redacted]:
  - Medical history: None.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use.
  - Time to onset (myocarditis): unknown days after dose 2.
  - Causes of death: Myocarditis.
  - Autopsy: Autopsy results showed myocarditis.
- A 27-year-old female subject from [redacted]:
  - Medical history: None.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use.
  - Time to onset (myocarditis): unknown days after dose 2.
  - Causes of death: Myocarditis.
  - Autopsy: Autopsy results showed myocarditis.

Rapporteur assessment comment:

During the current reporting period, there were 519 cases reporting myocarditis in persons aged 25-29 years compared to 589 myocarditis cases reported in the previous 2nd PSUR. There were 5 fatal cases compared to 7 fatal cases in the previous reporting period.

The MAH only briefly presented the 5 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 25-29 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 30 - 39 years

- Clinical Trial Data
    - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
    - Number of cases: 983 (0.2 % of 507,683 cases of the total PM dataset, 1.0 % of the 97870 subjects aged 30-39), compared to 995 cases (0.15%) retrieved in the PSUR #2.
    - Country of incidence (≥10): UK (310), Germany (247), Australia (114), France (51), Austria (35), Taiwan, Province of China (33), New Zealand, Sweden (18 each), Italy, US (17 each), Finland (13), Canada, Greece (12 each), Japan (11), and Belgium (10). The remaining 65 cases were distributed among 23 countries.
    - Subjects' age in years: n = 983, range: 30-39, mean: 34.3, median: 34.
    - Medical history (n = 290): the most frequently (>2 occurrence) reported medical conditions included Asthma (27), Seasonal allergy (26), Hypothyroidism (18), Tobacco user (17), Immunodeficiency (14), Drug hypersensitivity (13), Hypertension, Migraine, Myocarditis, Non-tobacco user (12 each), Food allergy (11), Breast feeding, Clinical trial participant (10 each), Diabetes mellitus, Dyspnoea, Obesity, Pregnancy (9 each), Autoimmune thyroiditis, Steroid therapy (6 each), Alcohol use, Colitis ulcerative, Dust allergy, Fibromyalgia, Histamine intolerance, Hyperhidrosis, Malaise, Pain, Pericarditis (5 each), Chest pain, Coeliac disease, Depression, Headache, Lymphadenopathy, Mast cell activation syndrome, Mite allergy, Pneumonia, Polycystic ovaries, Post viral fatigue syndrome (4 each), Allergy to animal, Allergy to metals, Cardiac disorder, Crohn's disease, Drug intolerance, Fatigue, Gastrooesophageal reflux disease, Hypersensitivity, Hypophosphataemia, Lactose intolerance, Multiple sclerosis, Muscular weakness, Mycotic allergy, Myocardial infarction, Nicotine dependence, Osteoporosis, Pancreatic failure, Postural orthostatic tachycardia syndrome, Pulmonary embolism, Small fibre neuropathy (3 each).
    - COVID-19 Medical history (n = 82): COVID-19 (41), Suspected COVID-19 (39), Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (1 each).
    - Co suspect vaccine/medications: Drug COVID-19 vaccine mRNA (MRNA 1273) (3), Amoxicillin, clozapine, colchicine, COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19), ipilimumab, losartan, nivolumab, propranolol (1 each).
    - Most frequently co-reported PTs (>5 occurrences): Chest pain (383), Dyspnoea (294), Palpitations (284), Fatigue (276), Pericarditis (240), Tachycardia (215), Pyrexia (128), Chest discomfort (110), Headache (104), Immunisation (100), Dizziness (92), Off label use (78), Inappropriate schedule of product administration (60), Interchange of vaccine products (58), Arrhythmia (54), Pain in extremity (51), Heart rate increased (48), Malaise, Myalgia (46 each), Pain (44), Asthenia (40), Syncope (39), Paraesthesia (38), COVID-19 (36), Drug ineffective (35), Angina pectoris, Troponin increased (34 each), Arthralgia, Hypoaesthesia (33 each), Chills, Nausea (32 each), Hyperhidrosis, Lymphadenopathy, Vomiting (25 each), Dyspnoea exertional (24), Cardiac flutter (23), Vaccination site pain (22), Cough, Feeling abnormal, Pericardial effusion (21 each), Exercise tolerance decreased (20), Discomfort, Influenza like illness (19 each), Anxiety, Back pain, Hypertension (18 each), Diarrhoea (16), Heavy menstrual

bleeding, Insomnia, Neck pain (15 each), Burning sensation (14), Hypotension, Loss of personal independence in daily activities, Oropharyngeal pain (13 each), Heart rate irregular, Menstruation irregular, Presyncope, Product use issue (12 each), Cardiac discomfort, Condition aggravated, Extrasystoles, Inflammation, Lethargy, Muscle twitching, Myocardial infarction, Pulmonary oedema, Rash (11 each), Cardiac disorder, Cardiomegaly, Disturbance in attention, Tinnitus (10 each), Atrial fibrillation, Cardiac failure, Electrocardiogram abnormal, Maternal exposure during pregnancy, Migraine, Muscular weakness, Panic attack, Pruritus, Somnolence, Supraventricular tachycardia, Thrombosis, Tremor (9 each), Abdominal pain upper, Fibrin D dimer increased, Influenza, Limb discomfort, Musculoskeletal stiffness, Night sweats, Pleural effusion, Vision blurred (8 each), Abdominal pain, Amenorrhoea, Body temperature increased, Ejection fraction decreased, Heart rate decreased, Loss of consciousness, Muscle spasms, Sleep disorder, Suspected COVID-19, Ventricular extrasystoles (7 each), Asthma, Blood pressure increased, Cardiac arrest, Cardiovascular disorder, Congestive cardiomyopathy, Eczema, Feeling cold, Gait disturbance, Haemorrhage, Heart rate, Illness, Menstrual disorder, Nasopharyngitis, Pulmonary embolism (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 41.

Table 41. Myocarditis in Subjects aged 30 – 39 Years (N=983)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	125	263	6
	No	276	305	8
Relevant PT[a]	Myocarditis	363	505	12
	Myopericarditis	27	51	0
	Carditis	13	13	2
	Immune-mediated myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	104	233	2
	No	297	335	12
Relevant suspect dose	Dose 1	132	178	7
	Dose 2	116	204	2
	Dose 3	111	143	3
	Dose 4	0	2	0
	Unknown	42	42	2
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=549	≤24 hours	23	31	0
	1-5 days	78	156	2
	6-13 days	28	70	0
	14-21 days	16	31	0
	22-31 days	17	26	0
	32-60 days	12	22	0
	61-449 days	12	25	0
	Unknown	218	210	12
Event Outcome	Fatal	4	2	0
	Not resolved	123	209	4
	Resolved	43	75	3
	Resolved with sequelae	11	16	0
	Resolving	70	98	0
	Unknown	153	171	7
Duration of event[b] n=51, median=20 days	Up to 3 days	2	7	0
	4-6 days	2	6	0
	7-25 days	6	7	0
	26-128 days	10	11	0

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

Fatal myocarditis cases in subjects aged 30-39 years (4 cases, medically confirmed; 1 case non-medically confirmed):

- A 36-year-old male subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardio-respiratory arrest, Myocarditis.
- Time to onset (myocarditis): 68 days after unknown dose.
- Causes of death: Cardio-respiratory arrest; Myocarditis.
- Autopsy: Autopsy revealed myocarditis and cardio-respiratory arrest.

- A 33-year-old female subject from [redacted]:
  - Medical history: None.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Abdominal pain, Arrhythmia, Cardiac arrest, Chest pain, Circulatory collapse, Myocarditis, Resuscitation.
  - Time to onset (myocarditis): 20 days after dose 1.
  - Causes of death: Abdominal pain; Arrhythmia; Cardiac arrest; Chest pain; Circulatory collapse; Myocarditis.
  - Autopsy: Autopsy information was not reported.
- A 34-year-old male subject from [redacted]:
  - Medical history: Dyspnoea, Malaise.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Arrhythmia, Cardiac arrest, Cardiogenic shock, Circulatory collapse, Dyspnoea, Hypertension, Hypoxia, Left ventricular dysfunction, Myocarditis, Pulmonary oedema, Syncope.
  - Time to onset (myocarditis): Unknown days after unknown dose.
  - Causes of death: Arrhythmia; Cardiac arrest; Cardiogenic shock; Circulatory collapse; Dyspnoea; Hypertension; Hypoxia; Left ventricular dysfunction; Pulmonary oedema; Syncope.
  - Autopsy: Autopsy revealed cause of death as myocarditis.
- A 36-year-old female subject from [redacted]:
  - Medical history: Depressed mood, Familial risk factor, Perinatal depression, Pregnancy, Tobacco user.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Hypoaesthesia, Menstruation irregular, Myocardial injury, Myocarditis, Myopericarditis, Neck pain, Pain in extremity, Pain in jaw, Paraesthesia, Pleural effusion, Thrombosis, Vaccination site pain.
  - Time to onset (myocarditis and myopericarditis): Unknown duration after first dose.
  - Causes of death: COVID-19 immunisation; Myocarditis.

- Autopsy: Autopsy revealed extensive and severe bilateral lung congestion but no evidence of ischemic, hypertensive or valvular heart disease. No evidence of subarachnoid haemorrhage was present. COVID-19 swabs were negative. Histology showed a single focus of myocarditis, with extensive lung congestion suggestive of sudden cardiac death and smoking related changes.

- A 38-year-old female subject from [redacted]:
  - Medical history: Cerebral palsy.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Back pain, Diarrhoea, Dyspepsia, Myocarditis, Pain, Pain in extremity.
  - Time to onset (myocarditis): 41 days after dose 3.
  - Causes of death: Myocarditis.
  - Autopsy: Autopsy revealed cause of death as myocarditis.

Rapporteur assessment comment:

During the current reporting period, there were 983 cases reporting myocarditis in persons aged 30-39 years compared to 995 myocarditis cases reported in the previous 2nd PSUR. There were 4 fatal cases compared to 7 fatal cases in the previous reporting period.

The MAH only briefly presented the 4 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 30-39 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged ≥40 years

- Clinical Trial Data
  - Number of cases: 1 case of BNT162b2 (0.15 % of 668 cases of the total CT dataset); 1 case (0.14%) was retrieved in the PSUR #2. Please see above the "Overall- All Ages" subsection for complete details.

- Post-Authorisation Data
  - Number of cases: 1752 (0.3 % of 507,683 cases of the total PM dataset, 0.7 % of the 236404 subjects ≥ 40 years), compared to 1876 cases (0.3%) retrieved in the PSUR #2.
  - Country of incidence (≥10): Germany (472), UK (464), Australia (168), France (116), Austria (66), Japan (58), New Zealand (53), Italy (41), Taiwan, Province of China (39), Canada (38), Sweden (37), Greece, US (25 each), Norway (16), Netherlands (15), Finland (14), Israel (12), Spain (11), Belgium, Denmark (10 each). The remaining 62 cases were distributed among 21 countries.
  - Subjects' age in years: n = 1752, range: 40-98, mean: 55, median: 53.

- Medical history (n = 754): the most frequently (>5 occurrences) reported medical conditions included Hypertension (164), Seasonal allergy (53), Asthma (50), Drug hypersensitivity (35), Immunodeficiency (34), Obesity (32), Hypothyroidism, Tobacco user (30 each), Atrial fibrillation (29), Diabetes mellitus (28), Cardiac failure (26), Dyslipidaemia (25), Food allergy, Non-tobacco user, Type 2 diabetes mellitus (23 each), Hypersensitivity (21), Gastrooesophageal reflux disease (18), Anxiety, Depression (17 each), Clinical trial participant (16), Autoimmune thyroiditis, Breast cancer, Chronic obstructive pulmonary disease, Hyperlipidaemia (15 each), Migraine, Myocarditis (14 each), Coronary artery disease (13), Cardiac disorder, Chemotherapy, Ex-tobacco user, Hypercholesterolaemia, Overweight (12 each), Myocardial infarction, Sleep apnoea syndrome, Thyroidectomy, Tobacco abuse (11 each), Allergy to animal, Allergy to metals, Fibromyalgia, Rubber sensitivity (10 each), Appendicectomy, Arteriosclerosis, Fatigue, Interchange of vaccine products, Rheumatoid arthritis (9 each), Alcohol use, Menopause, Mite allergy, Osteoporosis, Radiotherapy, Systemic lupus erythematosus (8 each), Blood cholesterol increased, Cardiac ablation, Dyspnoea, Gout, Hysterectomy, Mitral valve incompetence, Nasopharyngitis, Pulmonary embolism, Steroid therapy, Surgery (7 each), Abstains from alcohol, Allergy to arthropod sting, Allergy to plants, Arrhythmia, Arthritis, Blood cholesterol abnormal, Cerebrovascular accident, Cholecystectomy, Chronic kidney disease, Colitis ulcerative, Hormone replacement therapy, Inflammatory bowel disease, Influenza, Insomnia, Neoplasm, Nicotine dependence, Osteoarthritis, Supraventricular tachycardia, Tachycardia (6 each).
- COVID-19 Medical history (n = 132): Suspected COVID-19 (70), COVID-19 (65), Post-acute COVID-19 syndrome (5), Asymptomatic COVID-19, Coronavirus infection, COVID-19 pneumonia, COVID-19 treatment, SARS-CoV-2 test positive (1 each).
- Co suspect vaccine/medications: Influenza vaccine (3), pembrolizumab (2), adalimumab, cisplatin, COVID-19 vaccine, COVID-19 vaccine mRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), gabapentin, glyceryl trinitrate, hepatitis A vaccine, ibuprofen, influenza vaccine INACT SAG 3V, paracetamol, risankizumab, rivaroxaban, vinorelbine, vitamins NOS (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (572), Dyspnoea (509), Fatigue (493), Palpitations (463), Pericarditis (407), Tachycardia (339), Off label use (285), Interchange of vaccine products (266), Immunisation (264), Pyrexia (235), Headache (189), Chest discomfort (180), Dizziness (174), Arrhythmia (139), Asthenia (101), Malaise, Syncope (89 each), Inappropriate schedule of product administration, Pain in extremity (88 each), Nausea (86), Pain (83), Angina pectoris (73), Cardiac failure (71), Chills (67), Myalgia (66), Arthralgia (64), Pericardial effusion (61), Heart rate increased (58), Dyspnoea exertional, Troponin increased (57 each), Atrial fibrillation (53), Hyperhidrosis (52), Myocardial infarction (50), Cough (49), Back pain (45), Hypertension (43), Paraesthesia (42), Vomiting (40), Diarrhoea, Lethargy (39 each), COVID-19, Lymphadenopathy (35 each), Cardiac flutter, Vaccination site pain (33 each), Extrasystoles, Influenza like illness (32 each), Cardiac disorder, Hypoaesthesia (30 each), Decreased appetite (28), Drug ineffective, Insomnia (27 each), Thrombosis (26), Abdominal pain upper, Blood pressure increased (25 each), Cardiomyopathy, Condition aggravated, C-reactive protein increased, Exercise tolerance decreased (24 each), Anxiety, Feeling abnormal, Neck pain (23 each), Electrocardiogram abnormal, Somnolence, Vertigo (21 each), Abdominal pain, Acute myocardial infarction, Cardiac discomfort, Inflammation, Pulmonary embolism, Tremor

(20 each), Cardiac arrest, Gait disturbance, Muscular weakness, Ventricular extrasystoles (19 each), Hypotension (18), Cerebrovascular accident, Limb discomfort, Rash (17 each), Cardiomegaly, N-terminal prohormone brain natriuretic peptide increased, Peripheral swelling, Swelling, Ventricular tachycardia, Vision blurred (16 each), Breast pain, Bundle branch block left, Dyspepsia, Heart rate irregular, Impaired work ability, Musculoskeletal chest pain, Pneumonia, Presyncope (15 each), Axillary pain, Congestive cardiomyopathy, Coronary artery disease, Discomfort, Feeling hot, Influenza, Oedema peripheral, Pulmonary oedema, Tinnitus, Troponin T increased (14 each), Disturbance in attention, Ejection fraction decreased, Loss of personal independence in daily activities, Oedema, Pain in jaw, Sinus tachycardia (13 each), Acute coronary syndrome, Blood creatine phosphokinase increased, Feeling cold, Illness, Left ventricular dysfunction, Oropharyngeal pain, Performance status decreased, Suspected COVID-19, Weight decreased (12 each), Atrial flutter, Atrioventricular block, Migraine, Musculoskeletal pain, Pleural effusion (11 each), Cardiogenic shock, Fibrin D dimer increased, Heart rate abnormal, Joint swelling, Memory impairment, Supraventricular tachycardia, Ventricular hypokinesia (10 each), Bradycardia, Confusional state, Electrocardiogram ST segment elevation, Feeling of body temperature change, Head discomfort, Lymph node pain, Mitral valve incompetence, Muscle spasms, Muscle twitching, Myositis, Orthopnoea, Sleep disorder, Stress, Throat tightness (9 each), Acute kidney injury, Blood pressure decreased, Burning sensation, Cold sweat, Cyanosis, Death, Depression, General physical health deterioration, Heavy menstrual bleeding, Hypokinesia, Left ventricular failure, Nasopharyngitis, Respiratory failure, Transient ischaemic attack, Urticaria, Wheezing (8 each), Abdominal discomfort, Amnesia, Arthritis, Brain natriuretic peptide increased, Bronchospasm, Cardio-respiratory arrest, Disease recurrence, Ear pain, Echocardiogram abnormal, Electrocardiogram ST segment depression, Herpes zoster, Hypersensitivity, Loss of consciousness, Menstrual disorder, Myocardial necrosis marker increased, Pallor, Thrombocytopenia, Visual impairment (7 each), Blood pressure abnormal, Body temperature increased, Bronchitis, Cardiac dysfunction, Cardiac failure acute, Depressed level of consciousness, Dysgeusia, Fall, Heart rate decreased, Mobility decreased, Night sweats, Pleuritic pain, Pruritus, Sepsis, Vaccination failure, Vaccination site swelling, Ventricular arrhythmia (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 42.

Table 42. Myocarditis in Subjects aged ≥40 Years (N=1752)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	357	374	3
	No	565	437	16
Relevant PTs[a]	Myocarditis	791	716	19
	Myopericarditis	110	81	0
	Carditis	24	14	0
	Eosinophilic myocarditis	1	3	0
	Giant cell myocarditis	0	2	0
	Hypersensitivity myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	331	350	4
	No	592	462	15
Relevant suspect dose	Dose 1	213	172	3
	Dose 2	273	250	9
	Dose 3	346	308	6
	Dose 4	8	4	0
	Unknown	83	77	1
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=958	≤24 hours	60	36	0
	1-5 days	167	166	1
	6-13 days	88	90	4
	14-21 days	58	56	1
	22-31 days	34	26	0
	32-60 days	40	42	0
	61-367 days	45	43	1
	Unknown	435	359	12
Event Outcome	Fatal	23	36	0
	Not resolved	294	250	4
	Resolved	97	107	1
	Resolved with sequelae	33	32	2
	Resolving	143	147	0
	Unknown	337	245	12
Duration of event[b] n=89, median=34 days	Up to 3 days	2	9	0
	4-6 days	1	8	0
	7-25 days	7	9	0
	26-170 days	18	19	1
	171-822 days	10	5	0

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

Fatal myocarditis cases in subjects aged ≥40 Years

There were 59 cases that reported 59 relevant events with fatal outcome in this age group. Of the 59 cases, 40 cases were medically confirmed and 19 were non-medically confirmed cases. There were 23 female and 36 male subjects. Subjects' ages ranged from 40 years to 96 years. The cases were reported from Japan (17), Germany (12), UK (7), Australia (5), Austria, France, Sweden (3 Each), New Zealand, Taiwan, Province of China (2 each), Hong Kong, Italy, Netherlands, Norway, and Switzerland (1 each).

The fatal events in these cases were coded to the PTs Abdominal pain upper, Acute coronary syndrome, Acute myocardial infarction, Amnesia, Aortic dissection, Aortic rupture, Aortitis, Arrhythmia, Arteriosclerosis coronary artery, Arteritis coronary, Arthralgia, Asthenia, Atrial fibrillation, Atrioventricular block complete, Back pain, Bacteraemia, Basal ganglia haemorrhage, Blood creatine phosphokinase increased, Blood creatinine increased, Blood lactic acid, Bradycardia, Brain injury, Cardiac arrest, Cardiac disorder, Cardiac dysfunction, Cardiac failure, Cardiac failure high output, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, Cardio-respiratory arrest, Cerebral haemorrhage, Chest pain, Chronic kidney disease, Circulatory collapse, Colitis, Coma, Coronary artery stenosis, C-reactive protein increased, Cytology abnormal, Death, Dizziness, Dyspnoea, Dyspnoea exertional, Electrocardiogram ST segment depression, Embolism, Encephalitis, Encephalomalacia, Endocarditis, Eosinophilic myocarditis, Fatigue, Haemorrhage, Haemosiderosis, Hepatotoxicity, Hyperhidrosis, Hypersensitivity myocarditis, Immunisation, Infection, Inflammation, Influenza like illness, Interchange of vaccine products, Internal haemorrhage, Intracranial pressure increased, Ischaemic

cardiomyopathy, Malaise, Memory impairment, Multiple organ dysfunction syndrome, Myalgia, Myocardial fibrosis, Myocardial infarction, Myocardial necrosis, Myocarditis, Myopericarditis, Myositis, Obstruction, Off label use, Pain in extremity, Palpitations, Pericarditis, Peripheral coldness, pH body fluid, Pneumonia, Pneumonia aspiration, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary hypertension, Pulmonary oedema, Pulseless electrical activity, Pyrexia, Respiration abnormal, Respiratory failure, Right ventricular failure, Sepsis, Spinal cord haemorrhage, Sudden death, Syncope, Tachycardia, Tachypnoea, Thrombocytopenia, Thrombosis, Troponin I, Troponin increased, Vasculitis, Vasculitis necrotising, Ventricular fibrillation, Ventricular hypokinesia, Viral myocarditis, Vomiting (1 each).

Only 1 case reported a co-suspect medication (pembrolizumab). The most frequently reported (>1 occurrence) medical histories were coded to the PTs Hypertension (8), Cardiac failure, Diabetes mellitus, Obesity (4 each), Cardiac disorder (3), Cardiac failure chronic, Dyslipidaemia, and Type 2 diabetes mellitus (2 each). The most frequently reported (>2 occurrence) cause of death in these cases were coded to the PTs Myocarditis (47), Cardiac arrest (9), Death (7), Cardiac failure, Pericarditis (5 each), Cardio-respiratory arrest, Chest pain, Dyspnoea, Sudden death (4 each), Pneumonia, Syncope (3 each).

Rapporteur assessment comment:

During the current reporting period, there were 1752 cases reporting myocarditis in persons aged ≥40 years compared to 1876 myocarditis cases reported in the previous 2nd PSUR. There were 59 fatal cases compared to 42 fatal cases in the previous reporting period.

The MAH only briefly presented the 59 fatal cases and did not provide an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged ≥ 40 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects with booster dose

- Clinical Trial Data
    - The case involved a 43-year-old male participant, who received homologous booster dose. Please see above the "Overall- All Ages" subsection for complete details.
- Post-Authorisation Data
    - Number of cases: 1682 (0.3 % of 507,683 cases of the total PM dataset, 1.4 % of the 117750 subjects who received a booster dose), compared to 381 cases (0.06%) in the PSUR #2.
    - Country/region of incidence (≥10): UK (617), Germany (422), France (113), Austria (72), Italy (53), Japan (48), Israel (44), New Zealand (41), US (32), Greece, Sweden (21 each), Finland (19), Netherlands, Taiwan, Province of China (17 Each), Denmark (16), Australia, Hong Kong (15 each), Switzerland (13), Spain (12), Ireland (10); the remaining 64 cases were distributed among 19 countries.
    - MC (702), NMC (980).
    - Subjects' gender: female (656), male (988), and unknown (38).

- Subjects' age in years: n = 1552, range: 11 -94, mean: 39.3, median: 36.
- Medical history (n = 633): the medical conditions reported (>4 occurrence) included Hypertension (87), Asthma (46), Immunodeficiency (34), Tobacco user (31), Seasonal allergy (30), Hypothyroidism (28), Clinical trial participant (22), Myocarditis (21), Diabetes mellitus (20), Atrial fibrillation, Non-tobacco user (19), Obesity (18), Depression, Migraine (17 each), Steroid therapy (14), Food allergy (13), Anxiety, Dyslipidaemia (12 each), Drug hypersensitivity, Gastrooesophageal reflux disease, Interchange of vaccine products (11 each), Chest pain, Mite allergy, Overweight (10 each), Rheumatoid arthritis, Type 2 diabetes mellitus (9 each), Alcohol use, Chronic obstructive pulmonary disease, Dyspnoea, Fibromyalgia, Hyperlipidaemia, Myocardial infarction (8 each), Autoimmune thyroiditis, Cardiac disorder, Coronary artery disease, Ex-tobacco user, Nasopharyngitis (7 each), Cerebrovascular accident, Colitis ulcerative, Crohn's disease, Hypersensitivity, Inflammatory bowel disease, Insomnia, Mitral valve incompetence, Neoplasm, Nephrolithiasis, Nicotine dependence, Osteoarthritis, Pain, Pericarditis, Pneumonia, Pulmonary embolism, Sleep apnoea syndrome (6 each), Abstains from alcohol, Allergy to animal, Appendicectomy, Arteriosclerosis, Attention deficit hyperactivity disorder, Coeliac disease, Congestive cardiomyopathy, Contraception, Endometriosis, Epstein-Barr virus infection, Fatigue, Gastritis, Gout, Hodgkin's disease, Hormone replacement therapy, Menopause, Myopericarditis, Osteoporosis, Palpitations, Pregnancy, Radiotherapy, Supraventricular tachycardia, Surgery, Urinary tract infection (5 each).
- COVID-19 Medical history (n = 128): Suspected COVID-19 (80), COVID-19 (49), Post acute COVID-19 syndrome (4), SARS-CoV-2 test positive (2), and Asymptomatic COVID-19 (1).
- Co suspect vaccines (n= 20) reported more than once: Influenza vaccine (5), pembrolizumab (2), amoxicillin, cisplatin, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), fluticasone, gabapentin, hepatitis A vaccine, infliximab, influenza vaccine INACT SAG 3V, JNJ 78436735, paracetamol, propranolol, vinorelbine, zuclopenthixol (1 each).
- Number of relevant events: 1696.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Myocarditis (1458), Myopericarditis (211), Carditis (25), and Eosinophilic myocarditis (2).
- Relevant event outcome: fatal (39), resolved/resolving (528); resolved with sequelae (29), not resolved (453), unknown (649).
- Most frequently co-reported PTs (>20 occurrence): Chest pain (691), Immunisation (537), Fatigue (494), Pericarditis (467), Dyspnoea (466), Palpitations (443), Off label use (442), Interchange of vaccine products (379), Tachycardia (358), Pyrexia (311), Headache (174), Chest discomfort (163), Dizziness (111), Malaise , Pain (86 each), Pain in extremity (84), Nausea (77), Syncope (73), Arrhythmia (71), Chills , Heart rate increased (70 each), Angina pectoris (66), Myalgia (65), Asthenia (59), Arthralgia (58), Troponin increased (52), Lymphadenopathy (51), Vomiting (45), Dyspnoea exertional (43), Back pain, Pericardial effusion (41 each), Hypertension (38), Diarrhoea, Influenza like illness (37), Atrial fibrillation (36), Cough (35), Cardiac flutter, Hyperhidrosis (34 each), Cardiac failure, Vaccination site pain (30), COVID-19 (27), Oropharyngeal pain

(26), C-reactive protein increased, Neck pain (24 each), Insomnia (23), Axillary pain, Hypoaesthesia, Paraesthesia (22 each), Cardiac disorder, Myocardial infarction (21 each), Blood pressure increased, Extrasystoles (20 each).

The number of myocarditis cases occurred after a booster dose in each age group is reported in Table 44 below by gender.

Table 44. Myocarditis in Subjects who Received a Booster dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases			Unknown dose No. of Cases		
		F	M	U	F	M	U	F	M	U
Age group	0 to 17 years	1	3	0	6	42	0	7	69	1
	18 to 24 years	4	30	0	31	109	0	22	108	0
	25 to 29 years	7	10	0	29	55	0	17	42	1
	30 to 39 years	25	24	0	60	65	3	28	61	0
	40 years and older	142	109	5	134	113	2	86	101	0
	Unknown	30	12	7	21	25	8	6	10	11
	TOTAL	209	188	12	281	409	13	166	391	13

F=female; M=male; U=unknown

Rapporteur assessment comment:

During the current reporting period, there were 1,652 cases reporting myocarditis in persons who received a booster dose compared to 381 myocarditis cases reported in the previous 2nd PSUR. There were 39 fatal cases compared to 4 fatal cases in the previous reporting period.

The 39 fatal cases are assumed to be imbedded in the fatal cases stated in the age categories above, which are subject for a request for supplementary information.

During the reporting period there were 1639 cases of medically confirmed myocarditis with a latency 21 days or less in subjects receiving booster dose. All cases were assessed as serious due to hospitalisation and/or medically significant (1002) or due to medically significant (637). In 1314 cases myocarditis occurred within 1 week post vaccine administration. In most of these cases, the insufficient description of During the current reporting period, there were 968 cases reporting myocarditis in persons aged 18-24 years compared to 1187 myocarditis cases reported in the previous 2nd PSUR. There were 4 fatal cases compared to 2 fatal cases in the previous reporting period cardiovascular and/or non-cardiovascular medical history and the lack of diagnostic tests confirming the aetiologies of myocarditis preclude a clear causality assessment on an individual case basis.

Rapporteur assessment comment:

During the current reporting period, there were 1,639 cases reporting medically confirmed myocarditis with a TTO 21 days or less compared to 2,007 medically confirmed myocarditis cases reported in the previous 2nd PSUR. The MAH stated that most of the cases had insufficient information that precluded a clear causality assessment on an individual case basis.

Rapporteur assessment comment:

In general, the MAH should focus the analysis of myocarditis cases on aspects of these ADRs not fully known or addressed in the Comirnaty PI (myocarditis is already an ADR stated in section 4.8), and if the warning in section 4.4 regarding myocarditis is still in line with current knowledge. Therefore, the

analysis should focus more on information concerning the course, outcome, and possible risk factors of the myocarditis cases following Comirnaty exposure. **Request for next PSUR**

Myocarditis

Clinical trial data

During the reporting period, one myocarditis case (after homologous booster dose) was retrieved and considered not related to Comirnaty exposure.

Post-marketing

- Aged 5-11 years: There were 48 cases reporting myocarditis (2 fatal cases) compared to 10 myocarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 12-15 years: There were 366 cases reporting myocarditis (3 fatal cases) compared to 488 myocarditis cases (3 fatal cases) reported in the previous 2nd PSUR.
- Aged 16-17 years: There were 345 cases reporting myocarditis (no fatal cases) compared to 470 myocarditis cases (2 fatal cases) reported in the previous 2nd PSUR.
- Aged 18-24 years: There were 968 cases reporting myocarditis (4 fatal cases) compared to 1187 myocarditis cases (2 fatal cases) reported in the previous 2nd PSUR.
- Aged 25-29 years: There were 519 cases reporting myocarditis (5 fatal cases) compared to 589 myocarditis cases (7 fatal cases) reported in the previous 2nd PSUR.
- Aged 30-39 years: There were 983 cases reporting myocarditis (4 fatal cases) compared to 995 myocarditis cases (7 fatal cases) reported in the previous 2nd PSUR.
- Aged ≥40 years : There were 1752 cases reporting myocarditis (59 fatal cases) compared to 1876 myocarditis cases (42 fatal cases) reported in the previous 2nd PSUR.

The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 5-11 years, aged 12-15, aged 18-24, aged 25-29, aged 30-39, and aged ≥40 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, a WHO causality assessment,and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable. **Request for supplementary information**

Pericarditis

Search criteria: Autoimmune pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Overall - All ages

- Clinical Trial Data
    - Number of cases: No cases were retrieved during the current reporting period, compared to 1 case (0.14 %) retrieved in the PSUR #2.
- Post-Authorisation Data
    - Number of cases: 4156 (0.8% of 507,683 cases of the total PM dataset), compared to 5311 cases (0.8%) retrieved in the PSUR #2.
    - Country of incidence: Australia (1085), UK (903), France (580), Italy (281), Germany (271), Canada (174), New Zealand (111), Netherlands (97), Sweden (71), Japan (68). The remaining 515 cases were distributed among 44 countries.

- MC (2370), NMC (1786).
- Subjects' gender: female (2049), male (2017) and unknown (90).
- Subjects' age in years: n = 3847, range: 4 -98 years, mean: 39.8, median: 37.0.
- Medical history: (n = 1292) the most frequently (≥1%) reported relevant medical history included: Hypertension (154), Asthma (109), Pericarditis (95), Seasonal allergy (60), Drug hypersensitivity, Tobacco user (58 each), Immunodeficiency (54), Hypothyroidism (51), Obesity (46), Hypersensitivity, Non-tobacco user (40 each).
- COVID-19 Medical history (n = 321): COVID-19 (189), Suspected COVID-19 (130), Post-acute COVID-19 syndrome (7), SARS CoV 2 test positive (5), COVID-19 pneumonia, Exposure to SARS CoV 2 (2 each).
- Co-suspects (n=48 cases): frequently (>3 occurrences) reported relevant co-suspect vaccines/medications were COVID-19 vaccine mRNA (mRNA 1273), Influenza vaccine (8 each), COVID-19 vaccine, Influenza vaccine INACT SAG 3V, Influenza vaccine INACT SPLIT 4V (3 each).
- Number of relevant events: 4164.
- Relevant event seriousness: serious (4164).
- Reported relevant PTs: Pericarditis (4133), Pleuropericarditis (26), Pericarditis constrictive (5).
- Relevant event outcome: fatal (19), resolved/resolving (1311), resolved with sequelae (82), not resolved (1428), unknown (1325).

Subjects aged less than 5 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 1; 1 case was retrieved in the PSUR #2.
  - Country of incidence: Australia.
  - Subject's age in year: 4.
  - Gender: female.
  - Medical history: unknown.
  - Co suspects: none.
  - Relevant PT: Pericarditis
  - Medically Confirmed: yes.
  - Hospitalisation required: no
  - Time to onset (pericarditis): ≤24 hours after the 1st dose.
  - Co-reported PTs: Chest discomfort, Chest pain, Dyspnoea, Fatigue, Headache, Myalgia, Pyrexia, and Product administered to patient of inappropriate age.

Rapporteur assessment comment:

Comirnaty exposure in persons aged less than 5 years is considered off-label use during the interval period of the current 3rd PSUR.

Subjects aged 5 - 11 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 30 (0.006 % of 507,683 cases of the total PM dataset, 0.4 % of the 8375 subjects aged 5-11 years); 4 cases (0.0006%) were retrieved in the PSUR #2.
  - Country of incidence: Australia (19), Canada (3), Italy, Japan (2 each), Germany, Israel, New Zealand, UK (1 each).
  - Subjects' age in year: n = 30, range: 5 -11, mean: 9.4, median: 10.0.
  - Medical history: Coeliac disease, Kawasaki's disease, Urinary tract infection viral (1 each).
  - COVID-19 Medical history: COVID-19 (1)
  - Co suspects: none.
  - Most frequently co-reported PTs (>2 occurrences): Chest pain (24), Dyspnoea (12), Electrocardiogram abnormal (7), Chest discomfort (6), Palpitations (5), Myocarditis (4), Pyrexia (3).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 45.

Table 45. Pericarditis in Subjects aged 5-11 years (N=30)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	7	18	0
	No	2	3	0
Relevant PT[a]	Pericarditis	9	21	0
Hospitalisation required/prolonged	Yes	1	2	0
	No	8	19	0
Relevant suspect dose	Dose 1	7	19	0
	Dose 2	2	2	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=30	≤ 24 hours	0	2	0
	1-5 days	4	10	0
	6-13 days	1	2	0
	14-21 days	1	1	0
	22-31 days	0	3	0
	Unknown	3	3	0
Event Outcome	Fatal	0	0	0
	Not resolved	3	3	0
	Resolved	0	8	0
	Resolving	2	8	0
	Unknown	4	2	0
Duration of event[b] n=2, median: 18	4-6 days	0	1	0
	11-26 days	0	1	0

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

Rapporteur assessment comment:

During the current reporting period, there were 30 cases reporting pericarditis in children aged 5-11 years compared to 4 pericarditis cases reported in the previous 2nd PSUR. Although the Comirnaty exposure in persons aged 5-11 years is considered increased based on the EU/EEA exposure (current reporting period an estimated 3,569,821 administered doses in 5-9 years versus 391,327 administered doses in 5-9 years in the previous reporting period), worldwide interval exposure in persons aged 5-11 years (or any other age category) is not presented in the PSUR and therefore the relative post-marketing reporting rate of myocarditis cases in persons aged 5-11 years is not known.

There were no fatal cases compared to no fatal cases in the previous reporting period.

Subjects aged 12 - 15 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 118 (0.02 % of 507,683 cases of the total PM dataset, 0.9 % of the 13,366 subjects aged 12-15 years), compared to 215 cases (0.03%) retrieved in the PSUR #2.
  - Country of incidence: Australia (31), UK (13), Taiwan, Province of China (11), France, Japan (8 each), Canada, Italy (7 each), Malaysia (6). The remaining 27 cases were distributed among 12 countries.
  - Subjects' age in years: n = 118, range: 12.0 -15.3, mean: 13.7, median: 14.0.
  - Medical history (n = 20): the medical conditions reported more than once included Adenotonsillectomy, Asthma, Glucose-6-phosphate dehydrogenase deficiency, and Hypersensitivity (2 each).
  - COVID-19 Medical history (n = 5): COVID-19 (4), Suspected COVID-19 (1).
  - Co suspects: none.
  - Most frequently co-reported PTs (≥2%): Chest pain (60), Myocarditis (34), Dyspnoea (25), Palpitations (23), Pyrexia (22), Chest discomfort, Fatigue (15 each), Headache, Tachycardia (9 each), Dizziness, Malaise (7 each), Asthenia, Inappropriate schedule of product administration (6 each), Cough, Heart rate increased, Nausea, Pain, Pericardial effusion (5 each), Dyspnoea exertional, Syncope, Vomiting (4 each), Arthralgia, Chills, COVID-19, Electrocardiogram abnormal, Electrocardiogram ST segment elevation, Troponin increased (3 each), Angina pectoris, Back pain, Drug ineffective, Electrocardiogram ambulatory abnormal, Exercise tolerance decreased, Immune system disorder, Lethargy, Musculoskeletal chest pain, Myalgia, Nasopharyngitis, Oropharyngeal pain, Pleural effusion, Pleuritic pain, and Sinus tachycardia (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=118)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	15	72	2
	No	9	20	0
Relevant PT[a]	Pericarditis	24	91	2
	Pleuropericarditis	0	1	0
Hospitalisation required/prolonged	Yes	4	42	2
	No	20	50	0
Relevant suspect dose	Dose 1	11	38	0
	Dose 2	8	42	0
	Dose 3	2	4	0
	Unknown	3	8	2
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=118	≤ 24 hours	3	5	0
	1-5 days	10	35	0
	6-13 days	4	9	0
	14-21 days	1	2	0
	22-31 days	0	3	0
	32-60 days	0	2	0
	61-180 days	0	3	0
	Unknown	6	33	2
Event Outcome	Fatal	0	0	0
	Not resolved	11	25	0
	Resolved	4	12	1
	Resolved with sequelae	0	1	0
	Resolving	4	29	0
	Unknown	5	25	1
Duration of event[b] n=6, median: 9	4-6 days	0	2	0
	7-10 days	0	2	0
	11-26 days	1	0	0
	27-57 days	1	0	0

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

Rapporteur assessment comment:

During the current reporting period, there were 118 cases reporting pericarditis in persons aged 12-15 years compared to 215 pericarditis cases reported in the previous 2nd PSUR. There were no fatal cases compared to no fatal cases in the previous reporting period.

Subjects aged 16 - 17 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 106 (0.02 % of 507,683 cases of the total PM dataset, 1.3 % of the 8313 subjects aged 16-17 years), compared to 174 cases (0.03%) retrieved in the PSUR #2.
  - Country of incidence: Australia (25), UK (20), France (15), Italy (11), Germany (6), Taiwan, province of China (5). The remaining 24 cases were distributed among 14 countries.
  - Subjects' age in years: n = 106, range: 16 -17, mean: 16.5, median: 16.0.
  - Medical history (n = 17): the medical conditions reported more than once included the PTs Asthma, Food allergy, Pericarditis, Seasonal allergy (2 each).
  - COVID-19 Medical history (n = 6): COVID-19 (5), Suspected COVID-19 (1).

- Co suspects (n= 2 cases): COVID-19 vaccine MRNA (MRNA 1273), HPV vaccine VLP RL1 9V (yeast), Influenza vaccine INACT SPLIT 4V, Pneumococcal vaccine polysacch 23V (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (56), Dyspnoea (25), Myocarditis, Pyrexia (22 each), Fatigue, Palpitations (19 each), Tachycardia (15), Chest discomfort (14), Inappropriate schedule of product administration, Nausea, Pain (7 each), Headache, Pericardial effusion, Vomiting (6 each), Electrocardiogram abnormal, Malaise, Myopericarditis (5 each), Chills, Cough, Dizziness, Troponin increased, Abdominal pain upper, Influenza like illness, Lethargy, Pain in extremity (3 each), Asthenia, Back pain, Cellulitis, Cold sweat, C-reactive protein increased, Decreased appetite, Feeling hot, Heart rate irregular, Hyperhidrosis, Interchange of vaccine products, Myalgia, Off label use, Product use issue, Syncope, Vaccination site pain (2 each).

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=106)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	20	50	1
	No	15	20	0
Relevant PT[a]	Pericarditis	35	70	1
Hospitalisation required/prolonged	Yes	7	21	0
	No	28	49	1
Relevant suspect dose	Dose 1	12	23	1
	Dose 2	20	26	0
	Dose 3	2	13	0
	Unknown	1	8	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=106	≤ 24 hours	1	6	0
	1-5 days	9	20	1
	6-13 days	3	5	0
	14-21 days	1	3	0
	22-31 days	2	3	0
	32-60 days	5	2	0
	61-180 days	2	3	0
	181-375 days	0	1	0
	Unknown	12	27	0
Event Outcome	Fatal	0	0	0
	Not resolved	11	17	1
	Resolved	4	19	0
	Resolved with sequelae	0	1	0
	Resolving	11	13	0
	Unknown	9	20	0
Duration of event[b] n=7, median: 10	Up to 3 days	1	2	0
	7-10 days	0	1	0
	11-26 days	0	1	0
	27-57 days	0	1	0
	58-180 days	0	1	0

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

Rapporteur assessment comment:

During the current reporting period, there were 106 cases reporting pericarditis in persons aged 16-17 years compared to 174 pericarditis cases reported in the previous 2nd PSUR.

There were no fatal cases compared to no fatal cases in the previous reporting period.

Subjects aged 18 - 24 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 479 (0.09 % of 507,683 cases of the total PM dataset, 1.3% of the 38,293 subjects aged 18-24 years), compared to 659 cases (0.10%) retrieved in the PSUR #2.
  - Country of incidence: Australia (135), France (79), UK (73), Germany (44), Italy (33), New Zealand (19), Japan (14), Netherlands, Sweden (12 each), Norway (11), US (6). The remaining 41 cases were distributed among 16 countries.
  - Subjects' age in years: n = 479, range: 18 -24, mean: 21.2, median: 21.0.
  - Medical history (n = 120): the medical conditions reported more than twice included Asthma (21), Immunodeficiency, Pericarditis (6 each), Attention deficit hyperactivity disorder, Mite allergy, Non-tobacco user, Obesity, Overweight, Tobacco user (5 each), Food allergy, Irritable bowel syndrome (4 each), Disease risk factor, Drug hypersensitivity, Endometriosis, Hospitalisation, Hypersensitivity, Hypothyroidism, Migraine, Seasonal allergy, and Substance use (3 each).
  - COVID-19 Medical history (n = 37): COVID-19 (24), Suspected COVID-19 (12), SARS-CoV-2 test positive (1).
  - Co suspects (n= 8 cases): COVID-19 vaccine MRNA (MRNA 1273) (2), COVID-19 vaccine, dupilumab, Influenza vaccine INACT SPLIT 4V, insulin, levothyroxine, salbutamol, zuclopenthixol (1 each).
  - Most frequently co-reported PTs (≥2%): Dyspnoea (141), Myocarditis (112), Palpitations (95), Fatigue (83), Chest discomfort (75), Pyrexia (66), Tachycardia (65), Headache, Pericardial effusion (35 each), Dizziness (33), Inappropriate schedule of product administration (26), Electrocardiogram abnormal (24), Pain (23), Immunisation, Myalgia (20 each), Malaise, Off label use (19 each), Interchange of vaccine products, Syncope (18 each), Asthenia (17), Pain in extremity (16), Nausea (15), Angina pectoris, Chills, Vomiting (14 each), Cough (13), C-reactive protein increased, Dyspnoea exertional, Hyperhidrosis, Lethargy (12 each), Anxiety, Sinus tachycardia (10 each), Arthralgia, Heart rate increased (9 each), Back pain, Electrocardiogram ST segment elevation, Paraesthesia, Troponin increased (8 each).
  - Pericarditis events with fatal outcome (1).

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=479)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	120	169	6
	No	72	110	2
Relevant PT[a]	Pericarditis	192	279	8
Hospitalisation required/prolonged	Yes	46	96	3
	No	146	183	5
Relevant suspect dose	Dose 1	79	102	4
	Dose 2	52	96	0
	Dose 3	49	60	0
	Dose 4	1	2	0
	Unknown	11	19	4
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=479	≤ 24 hours	27	18	0
	1-5 days	66	93	1
	6-13 days	22	34	2
	14-21 days	5	16	0
	22-31 days	5	9	0
	32-60 days	1	12	1
	61-180 days	7	10	0
	181-375 days	0	1	0
	Unknown	59	86	4
Event Outcome	Fatal	0	1	0
	Not resolved	74	97	2
	Resolved	20	33	2
	Resolved with sequelae	7	7	1
	Resolving	47	65	0
	Unknown	44	76	3
Duration of event[b] n=18, median: 21	Up to 3 days	1	2	0
	4-6 days	0	2	0
	7-10 days	0	3	0
	11-26 days	0	2	0
	27-57 days	3	3	1
	58-180 days	0	1	0

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

Fatal pericarditis cases in adult (18-24 years of age) (1 case, medically confirmed):

- A 22-year-old male subject from [redacted]:
  - Medical history: Unknown.
  - Co-suspect medications: None.
  - PTs with fatal outcome: Cardiac tamponade, Multiple organ dysfunction syndrome, Pericardial effusion, Pericardial mass, Pericardial mesothelioma malignant, Pericarditis, Right ventricular dysfunction, Right ventricular failure.
  - Time to onset (pericarditis): 31 days after dose 2.
  - Causes of death: all the above events.

Rapporteur assessment comment:

During the current reporting period, there were 479 cases reporting pericarditis in persons aged 18-24 years compared to 659 pericarditis cases reported in the previous 2nd PSUR. There was 1 fatal case compared to no fatal cases in the previous reporting period.

The MAH only briefly presented the fatal case and did not provide an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and no WHO causality assessment for the case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal case with pericarditis in persons aged 18-24 years and perform an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 25 - 29 years

- Clinical Trial Data
  - Number of cases: none; no cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 417 (0.08 % of 507,683 cases of the total PM dataset, 1.0 % of the 43,518 subjects aged 25-29 years), compared to 614 cases (0.09%) retrieved in the PSUR #2.
  - Country of incidence: Australia (136), UK (75), France (71), Germany (21), Italy, Netherlands (18 each), New Zealand (16), Sweden (8), Japan, Spain (7 each), Denmark (6), Canada (5). The remaining 29 cases were distributed among 17 countries.
  - Subjects' age in years: n = 417, range: 25 -29, mean: 27.0, median: 27.0.
  - Medical history (n = 87): the medical conditions reported more than twice included Asthma (10), Tobacco user (7), Obesity (6), Disease risk factor, Drug hypersensitivity, Non-tobacco user, Pericarditis (4 each), Abstains from alcohol, Contraception, Gastritis, Steroid therapy (3 each).
  - COVID-19 Medical history (n = 31): Suspected COVID-19 (17), COVID-19 (14), Post acute COVID-19 syndrome (3), Exposure to SARS-CoV-2 (1).
  - Co suspects (n= 3 cases): COVID-19 vaccine (2), and Methylphenidate (1).
  - Most frequently co-reported PTs (≥2%): Dyspnoea (137), Palpitations (101), Fatigue (94), Myocarditis (87), Tachycardia (67), Chest discomfort (60), Pyrexia (49), Headache (40), Dizziness, Immunisation (33 each), Nausea (22), Pain (21), Off label use (20), Interchange of vaccine products (19), Malaise, Pericardial effusion (17 each), Syncope (16), Electrocardiogram abnormal, Myalgia (14 each), Angina pectoris (13), Arthralgia, Asthenia, Heart rate increased (12 each), Dyspnoea exertional, Pain in extremity, Paraesthesia, Vaccination site pain (11 each), Lethargy, Lymphadenopathy (10 each), Inappropriate schedule of product administration (9), Troponin increased (8), Cardiac flutter, Diarrhoea, Vomiting (7 each).
  - Pericarditis events with fatal outcome (1).

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=417)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	102	146	2
	No	71	91	5
Relevant PT[a]	Pericarditis	171	237	7
	Pleuropericarditis	2	0	0
Hospitalisation required/prolonged	Yes	41	47	2
	No	132	190	5
Relevant suspect dose	Dose 1	68	100	4
	Dose 2	40	61	1
	Dose 3	50	58	2
	Dose 4	0	1	0
	Unknown	15	17	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=418	≤ 24 hours	15	21	0
	1-5 days	42	76	1
	6-13 days	23	21	0
	14-21 days	15	20	1
	22-31 days	6	7	0
	32-60 days	8	8	0
	61-180 days	11	12	1
	181-375 days	1	0	0
	Unknown	52	73	4
Event Outcome	Fatal	0	1	0
	Not resolved	78	84	1
	Resolved	12	37	2
	Resolved with sequelae	2	3	0
	Resolving	34	47	1
	Unknown	47	65	3
Duration of event[b] n=13, median: 13	Up to 3 days	0	3	0
	7-10 days	1	2	0
	11-26 days	1	2	1
	27-57 days	2	0	0
	58-180 days	0	1	0

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

Fatal pericarditis cases in adult (25-29 years of age) (1 case, medically confirmed)

- A 29-year-old male subject from [redacted]:
  - Medical history: Hypoventilation, Obesity, Pulmonary fibrosis, Sleep apnoea syndrome, Still's disease
  - Co-suspect medications: None
  - PTs with fatal outcome: Acute kidney injury, Aortic dissection, Chest pain, Hypoventilation, Inflammatory marker increased, Multiple organ dysfunction syndrome, Pericardial disease, Pericarditis, Respiratory failure, Sepsis.
  - Time to onset (pericarditis): 6 days after dose 3.

Causes of death: Multiple organ dysfunction syndrome; Sepsis; Still's disease.

Rapporteur assessment comment:

During the current reporting period, there were 417 cases reporting pericarditis in persons aged 25-29 years compared to 614 pericarditis cases reported in the previous 2nd PSUR. There was 1 fatal case compared to no fatal cases in the previous reporting period.

The MAH only briefly presented the fatal case and did not provide an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and no WHO causality

assessment for the case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal case with pericarditis in persons aged 18-24 years and perform an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects aged 30 - 39 years

- Clinical Trial Data
  - Number of cases: none. No cases were retrieved in the PSUR #2.
- Post-Authorisation Data
  - Number of cases: 940 (0.2 % of 507,683 cases of the total PM dataset; 1.0 % of the 97,870 subjects aged 30-39), compared to 1222 cases (0.2%) retrieved in the PSUR #2.
  - Country/region of incidence: Australia (356), UK (217), France (114), Germany (46), Italy (39), New Zealand (26), Netherlands (21), Canada (18), Norway (16), Sweden (13), Belgium (9), Greece, US (8 each), Denmark, Japan (6 each), Austria, and Hong Kong (5 each). The remaining 27 cases were distributed among 17 different countries.
  - Subjects' age in years: n = 940, range: 30 -39, mean: 34.3, median: 34.0.
  - Medical history (n = 217): the medical conditions reported more than 5 times included the PTs Pericarditis (27), Asthma (20), Drug hypersensitivity (18), Seasonal allergy (13), Mite allergy, Non-tobacco user, Pregnancy, Tobacco user (11 each), Migraine (10), Chest pain, Hypothyroidism (8 each), Anxiety, Clinical trial participant, Immunodeficiency (7 each), Alcohol use, Eczema, Obesity (6 each).
  - COVID-19 Medical history (n = 70): COVID-19 (43), Suspected COVID-19 (24), SARS-CoV-2 test positive (3).
  - Co suspect vaccines/medications (n=6): colchicine (2), amoxicillin, interferon Beta-1A, iron isomaltoside 1000, propranolol (1 each).
  - Most frequently co-reported PTs (≥2%): Chest pain (547), Dyspnoea (345), Palpitations (260), Fatigue (239), Myocarditis (236), Tachycardia (179), Chest discomfort (125), Pyrexia (113), Headache (93), Dizziness (75), Immunisation (74), Malaise, Pain in extremity (54 each), Nausea, Paraesthesia (48 each), Arthralgia, Pain (46 each), Off label use (45), Myalgia (44), Inappropriate schedule of product administration (40), Heart rate increased, Interchange of vaccine products (39 each), Hypoaesthesia, Pericardial effusion (38 each), Asthenia (32), Hyperhidrosis, Syncope (29 each), Electrocardiogram abnormal, Influenza like illness (25 each), Cardiac flutter (24), Arrhythmia (23), Chills, Lethargy (21 each), Feeling abnormal, Vaccination site pain (20 each), Diarrhoea, Exercise tolerance decreased, Vomiting (18 each), Cough (17), Anxiety, Back pain, Dyspnoea exertional, Lymphadenopathy, Neck pain (16 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=940)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	277	284	5
	No	193	179	2
Relevant PT[a]	Pericarditis	470	462	7
	Pleuropericarditis	0	2	0
Hospitalisation required/prolonged	Yes	68	96	0
	No	402	367	7
Relevant suspect dose	Dose 1	223	243	3
	Dose 2	119	111	2
	Dose 3	108	85	2
	Unknown	20	24	0
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=941	≤ 24 hours	37	35	0
	1-5 days	105	120	0
	6-13 days	47	52	1
	14-21 days	27	20	0
	22-31 days	17	17	0
	32-60 days	17	20	0
	61-180 days	21	12	1
	181-375 days	5	1	0
	Unknown	194	187	5
Event Outcome	Fatal	0	0	0
	Not resolved	181	189	3
	Resolved	37	63	1
	Resolved with sequelae	6	3	0
	Resolving	80	65	0
	Unknown	166	144	3
Duration of event[b] n=27, median: 15	Up to 3 days	0	5	0
	4-6 days	1	2	0
	7-10 days	1	1	0
	11-26 days	5	4	0
	27-57 days	4	2	0
	58-180 days	1	1	0

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

Rapporteur assessment comment:

During the current reporting period, there were 940 cases reporting pericarditis in persons aged 30-39 years compared to 1222 pericarditis cases reported in the previous 2nd PSUR. There were no fatal cases compared to 1 fatal case in the previous reporting period.

Subjects aged ≥40 years

- Clinical Trial Data
  - Number of cases: none. One (1) case (0.14%) retrieved in the PSUR #2. Please see above the "Overall – All Ages" subsection.
- Post-Authorisation Data
  - Number of cases: 1756 (0.3 % of 507,683 cases of the total PM dataset, 0.7% of the 236,404 subjects ≥ 40 years), compared to 2059 cases (0.3%) retrieved in the PSUR #2.
  - Country of incidence: UK (375), Australia (333), France (288), Italy (169), Germany (137), Canada (61), New Zealand (44), Netherlands (41), Greece (40), Sweden (35),

Austria, Norway (28 each), Japan (25), Denmark (20). The remaining 132 cases were distributed among 25 different countries.

- Subjects' age in years: n = 1756, range: 40-98, mean: 54.6, median: 52.0.
- Medical history (n = 738): the medical conditions reported more than 10 times included PTs Hypertension (133), Pericarditis (47), Asthma (43), Immunodeficiency, Seasonal allergy (36 each), Hypothyroidism (34), Hypersensitivity (29), Obesity, Tobacco user, Type 2 diabetes mellitus (28 each), Diabetes mellitus (27), Drug hypersensitivity, Gastrooesophageal reflux disease (25 each), Depression (20), Atrial fibrillation (19), Dyslipidaemia, Rheumatoid arthritis (18 each), Anxiety (17), Breast cancer, Dyspnoea, Hypercholesterolaemia, Myocardial ischaemia, Non-tobacco user (16 each), Chronic kidney disease (15), Myocardial infarction (14), Chronic obstructive pulmonary disease, Food allergy, Gastritis (13 each), Autoimmune thyroiditis, Chest pain, Systemic lupus erythematosus (12 each), Overweight, Palpitations, Psoriasis, Steroid therapy (11 each).
- COVID-19 Medical history (n = 142): COVID-19 (89), Suspected COVID-19 (56), Post acute COVID-19 syndrome (3), COVID-19 pneumonia (2), Exposure to SARS CoV-2 (1).
- Co suspect vaccines/medications (n= 24): Influenza vaccine (7), COVID-19 vaccine MRNA (MRNA 1273), Influenza vaccine INACT SAG 3V (3 each), Adalimumab, Apixaban, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Etanercept, Glyceryl trinitrate, Influenza vaccine INACT SPLIT 4V, Levetiracetam, Peginterferon alfa-2A, Pembrolizumab, Rivaroxaban, Sotrovimab (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (787), Dyspnoea (567), Fatigue (455), Myocarditis (396), Palpitations (372), Tachycardia (286), Off label use (272), Interchange of vaccine products (246), Immunisation (243), Pyrexia (223), Chest discomfort (199), Pericardial effusion (167), Headache (157), Dizziness (131), Malaise (87), Pain in extremity (83), Asthenia (82), Arthralgia (74), Nausea (73), Pain (71), Inappropriate schedule of product administration (70), Syncope (69), Myalgia (67), Angina pectoris, Paraesthesia (60 each), Arrhythmia, Cough (57 each), Lymphadenopathy (50), Heart rate increased (49), Chills (46), Hyperhidrosis (44), Electrocardiogram abnormal (43), Back pain (42), Hypertension (41), Lethargy (40), Pleural effusion, Vaccination site pain (39 each), Atrial fibrillation, Diarrhoea (38 each), Dyspnoea exertional (37), Influenza like illness (36), Myocardial infarction (33), Neck pain (32), Cardiac flutter, Condition aggravated (31 each), C-reactive protein increased, Vomiting (29 each).
- Pericarditis events with fatal outcome (17) occurred in subjects aged ≥40 years (n=17, ranged between 41 to 92 years of age).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 51 below.

Table 51. Pericarditis in Subjects aged ≥ 40 years (N=1756)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	538	388	8
	No	474	338	10
Relevant PT[a]	Pericarditis	1001	720	17
	Pericarditis constrictive	2	3	0
	Pleuropericarditis	15	4	1
Hospitalisation required/prolonged	Yes	225	264	2
	No	789	462	16
Relevant suspect dose	Dose 1	296	224	5
	Dose 2	295	210	4
	Dose 3	348	241	6
	Dose 4	15	8	1
	Unknown	58	43	2
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=1763	≤ 24 hours	53	33	0
	1-5 days	190	122	2
	6-13 days	119	99	0
	14-21 days	77	74	0
	22-31 days	57	45	3
	32-60 days	64	44	0
	61-180 days	67	48	0
	181-375 days	17	5	0
	Unknown	374	257	13
Event Outcome[b]	Fatal	5	12	0
	Not resolved	355	207	2
	Resolved	114	121	2
	Resolved with sequelae	26	21	1
	Resolving	215	148	0
	Unknown	304	218	13
Duration of event[c] n= 87, median: 28	Up to 3 days	1	7	0
	4-6 days	6	2	0
	7-10 days	2	2	0
	11-26 days	11	11	0
	27-57 days	6	12	0
	58-180 days	16	8	0
	181-265 days	3	0	0

a. All serious occurrences.
b. Multiple episodes of the same PT event were reported with a different clinical outcome in one case hence the sum of the events outcome exceeds the total number of PT events.
c. For those cases where the event resolved or resolved with sequelae.

Fatal Pericarditis cases in adult (40-50 years of age) (4 cases; 2 cases medically confirmed and 2 non-medically confirmed):

- 2 cases medically confirmed:
  - A 43-year-old male subject from [redacted].
    - Medical history: Diabetes mellitus, Obesity.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Myocarditis, Pericarditis, Sudden death.
    - Time to onset (pericarditis and myocarditis): On the same day of receiving dose 3, the patient died.
    - Cause of death: Myocarditis, Pericarditis, Sudden death.
  - A 48-year-old male subject from [redacted].
    - Medical history: Unknown.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Brain stem haemorrhage, Pericarditis.

        - Time to onset (pericarditis): 17 days after dose 2.
        - Cause of death: Both the above events.

- 2 cases non-medically confirmed:
    - A 41-year-old male subject from [redacted].
        - Medical history: Congestive cardiomyopathy, Huntington's disease, Positive airway pressure therapy, Sleep apnoea syndrome, Type 2 diabetes mellitus.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Interchange of vaccine products, Myocarditis, Off label use, Pericarditis, Sudden death.
        - Time to onset (pericarditis and myocarditis): 11.5 hours after dose 3, the patient died.
        - Cause of death: Myocarditis; Pericarditis; Sudden death.
    - A 49-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Aortic rupture, Back pain, Cardiomegaly, Internal haemorrhage, Myocarditis, Pericarditis, Pyrexia, Syncope, Vomiting.
        - Time to onset (pericarditis): ~50 days after dose 1, the patient died due to the above events.
        - Cause of death: Cardiomegaly.

Fatal Pericarditis cases in adult (51-64 years of age) (7 cases; 5 cases medically confirmed and 2 non-medically confirmed)

- 5 cases medically confirmed:
    - A 56-year-old male subject from [redacted]
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Malaise, Pericarditis.
        - Time to onset (pericarditis): On the same day of receiving dose 1.
        - Cause of death: Both the above events.
    - A 57-year-old female subject from [redacted].
        - Medical history: Thyroid cancer.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Pericarditis.
        - Time to onset (pericarditis): Unspecified days after dose 3.
        - Cause of death: Pericarditis.
    - A 59-year-old female subject from [redacted]
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Atrial fibrillation, Atrioventricular block complete, Cardiac arrest, Chest pain, Electrocardiogram ST segment depression, Myocarditis, Pericarditis, Troponin increased.
        - Time to onset (pericarditis): 67 days after dose 3.
        - Cause of death: All the above events.
    - A 61-year-old female subject from [redacted].
        - Medical history: Cerebrovascular accident, Syncope, Thymic carcinoma, Thymoma.
        - Co-suspect medications: None.

        - PTs with fatal outcome: Cardio-respiratory arrest, Coronary artery stenosis, Endocarditis, Myocarditis, Pericarditis, Right ventricular failure, Sudden death.
        - Time to onset (pericarditis): 11 days after dose 3.
        - Cause of death: All the above events.
    - A 62-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Cardiac failure, Pericarditis.
        - Time to onset (pericarditis): 14 days after dose 2.
        - Cause of death: Both the above events.
- 2 cases non-medically confirmed:
    - A 53-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Pericarditis.
        - Time to onset (pericarditis): Within 7 days after dose 1.
        - Cause of death: Pericarditis.
    - A 62-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Abdominal pain upper, Cardiac arrest, Chest pain, Dizziness, Dyspnoea, Fatigue, Immunisation, Myocarditis, Pain in extremity, Palpitations, Pericarditis, Thrombosis.
        - Time to onset (pericarditis): 6 days after dose 3.
        - Cause of death: All the above clinical events.

Fatal Pericarditis cases in elderly (65-74 years of age) (2 cases, both non-medically confirmed)

- A 69-year-old female subject from [redacted].
    - Medical history: Arthralgia, Brain neoplasm, Hypertension.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Amnesia, Death, Interchange of vaccine products, Memory impairment, Myocarditis, Off label use, Pericarditis.
    - Time to onset (pericarditis and myocarditis): Unspecified days after the dose 3.
    - Causes of death: Brain neoplasm.
- A 71-year-old male subject from [redacted].
    - Medical history: Unknown.
    - Co-suspect medications: None.
    - PTs with fatal outcome: Chest pain, Death, Dyspnoea, Fatigue, Myocarditis, Palpitations, Pericarditis, Pulmonary embolism, Thrombosis.
    - Time to onset (pericarditis and myocarditis): Unspecified days after the dose 2.
    - Causes of death: Death; Thrombosis.

Fatal Pericarditis cases in elderly (> 75 years of age –4 cases; 2 cases medically confirmed and 2 cases non-medically confirmed)

- 2 cases medically confirmed:
    - An 89-year-old female subject from [redacted].
        - Medical history: Anaemia megaloblastic, Aphasia, Arthropathy, Atrial fibrillation, Benign tumour excision, Cardiac assistance device user, Cerebrovascular accident, Chronic gastritis, Cognitive disorder, Diverticulum,

Dyslipidaemia, Hypertension, Neoplasm, Oropharyngeal surgery, Parotitis, Salivary gland neoplasm, Sinus node dysfunction, Type 2 diabetes mellitus.
        - Co-suspect medications: Influenza vaccine INACT SAG 3V.
        - PTs with fatal outcome: Pericarditis.
        - Time to onset (pericarditis): 2 days after dose 3.
        - Causes of death: Pericarditis
    - A 92-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Aortic dissection, Cardiac failure, Cardiac tamponade, Pericarditis.
        - Time to onset (pericarditis): Unspecified days after dose 3.
        - Causes of death: All the above events.
- 2 cases not medically confirmed:
    - An 81-year-old male subject, from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Pericarditis.
        - Time to onset (pericarditis): 60 days after dose 3.
        - Causes of death: Pericarditis.
    - A 78-year-old male subject from [redacted].
        - Medical history: Unknown.
        - Co-suspect medications: None.
        - PTs with fatal outcome: Multiple organ dysfunction syndrome, Myocardial infarction, Pericarditis.
        - Time to onset (pericarditis): 8 days after dose 3.
        - Causes of death: Due to all the above events.

Rapporteur assessment comment:

During the current reporting period, there were 1756 cases reporting pericarditis in persons aged ≥40 years compared to 2059 pericarditis cases reported in the previous 2nd PSUR. There were 17 fatal cases compared to 8 fatal cases in the previous reporting period.

The MAH only briefly presented the 17 fatal cases and did not provide an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and no WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases with pericarditis in persons aged ≥ 40 years and perform per case an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, and a WHO causality assessment. **Request for supplementary information**

Subjects with booster dose

- Clinical Trial Data
    - Number of cases: none; one (1) case was retrieved in the PSUR #2.
- Post-Authorisation Data
- Number of cases: 1216 (0.2% of 507,683 cases of the total PM dataset, 1.0% of the 117,750 subjects who received a booster dose), compared to 283 cases (0.04%) in the PSUR #2.

- Country of incidence: UK (474), France (202), Germany (94), Italy (93), Netherlands (46), New Zealand (38), Norway (32), Japan (30), Israel, Sweden (21 each); the remaining 165 cases were distributed among 24 countries.
- MC (500), NMC (716).
- Subjects' gender: female (661), male (531), and unknown (24).
- Subjects' age in year: n = 1130, range: 13 -93, mean: 45.1, median: 44.0
- Medical history (n = 566): the medical conditions reported more or equal to 10 times included the PTs Hypertension (79), Pericarditis (40), Asthma (38), Immunodeficiency (32), Hypothyroidism (29), Obesity (22), Diabetes mellitus, Drug hypersensitivity (19 each), Seasonal allergy (18), Depression, Steroid therapy, Tobacco user (15 each), Atrial fibrillation, Non-tobacco user, Type 2 diabetes mellitus (14 each), Anxiety, Dyslipidaemia, Gastrooesophageal reflux disease (13 each), Clinical trial participant, Disease risk factor, Migraine (12 each), Myocardial infarction, Rheumatoid arthritis (11 each), Chronic kidney disease, Food allergy (10 each).
- COVID-19 Medical history (n = 114): Suspected COVID-19 (60), COVID-19 (55), Post acute COVID-19 syndrome (3), Exposure to SARS-CoV-2, SARS-CoV-2 test positive (1 each).
- Co suspects (n=20 cases): Influenza vaccine (6), Influenza vaccine INACT SAG 3V (3), Adalimumab, amoxicillin, Apixaban, Colchicine, COVID-19 vaccine, COVID-19 vaccine MRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Etanercept, Propranolol, Salbutamol, Zuclopenthixol (1 each).
- Number of relevant events: 1220.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Pericarditis (1212), Pleuropericarditis (8)
- Relevant event outcome: fatal (12), resolved/resolving (414), resolved with sequelae (21), not resolved (296), unknown (478).
- Most frequently co-reported PTs (>3%): Chest pain (620), Myocarditis (461), Dyspnoea (448), Fatigue (427), Immunisation (418), Off label use (365), Palpitations (363), Interchange of vaccine products (332), Tachycardia (291), Pyrexia (218), Chest discomfort (151), Headache (124), Pericardial effusion (88), Malaise (87), Pain (82), Dizziness (74), Pain in extremity (66), Syncope (61), Arthralgia (58), Heart rate increased (57), Angina pectoris, Nausea (50 each), Asthenia (48), Arrhythmia (41), Chills, Lymphadenopathy, Myalgia (40 each), Back pain, Vaccination site pain (34 each), Cough (33).

The number of pericarditis cases occurred after a booster dose in each age group is reported in the below Table 53 by gender.

Table 53. Pericarditis in Subjects who Received a Booster Dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases			Unknown dose No. of cases		
		F	M	U	F	M	U	F	M	U
Age group	0 to 17 years	1	0	0	2	9	0	2	9	0
	18 to 24 years	4	13	0	24	32	0	25	22	0
	25 to 29 years	8	10	0	25	35	0	22	20	2
	30 to 39 years	23	15	0	62	50	2	32	24	0
	40 years and older	140	94	4	143	85	2	100	87	2
	Unknown	26	8	5	16	12	5	6	6	2
	Total	*202*	*140*	*9*	*272*	*223*	*9*	*187*	*168*	*6*

F=female; M=male; U=unknown

Rapporteur assessment comment:

During the current reporting period, there were 1216 cases reporting pericarditis in persons who received a booster dose compared to 283 pericarditis cases reported in the previous 2nd PSUR. There were 12 fatal cases compared to 1 fatal case in the previous reporting period.

The 12 fatal cases are assumed to be imbedded in the fatal cases stated in the age categories above, which are subject for a request for supplementary information.

During the reporting period, of the 4156 cases reported, there were 1319 cases of medically confirmed pericarditis with a latency 21 days or less, of which in 975 cases pericarditis occurred within 1 week post vaccine administration. The majority (1255) of the cases were assessed as serious due to hospitalisation and/or medically significant. In 58 other cases, the seriousness criterion was reported as disability or life threatening, and in 6 cases, a fatal outcome was reported, which are reviewed above in the age-stratified sections.

Rapporteur assessment comment:

During the current reporting period, there were 1,319 cases reporting medically confirmed pericarditis with a TTO 21 days or less compared to 1,461 medically confirmed pericarditis cases reported in the previous 2nd PSUR.

Observed versus Expected analyses

The MAH conducted analyses for myocarditis and myocarditis/pericarditis stratified by age and sex, and by dose. Since background incidence rates stratified by age and sex were not available for pericarditis alone, analyses performed for a combined myocarditis/pericarditis (table 17 and 18).

Spontaneously reported cases of myocarditis and myocarditis/pericarditis were limited to those occurring in EEA countries or the United States. Cases were also limited to those with time to onsets occurring within the 14-day (results not reproduced here) or 21-day risk windows (table 15 and 16) to increase the sensitivity for signal detection for these events.

Table 15. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a],[33]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a],[44]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a],[21]	Exp Cases	O/E Ratio	95% CI
Males ≤11 years	513,444	14	0.48	2.5	5.681	3.106, 9.531	4.40	22.6	0.620	0.339, 1.040	8.26	42.4	0.330	0.180, 0.554
Males 12-17 years	918,902	604	0.48	4.4	136.939	126.234, 148.30	4.40	40.4	14.939	13.771, 16.179	8.26	75.9	7.958	7.336, 8.618
Males 18-24 years	1,344,972	990	2.77	37.3	26.573	24.943, 28.281	4.40	59.2	16.729	15.703, 17.804	20.20	271.7	3.644	3.420, 3.878
Males 25-49 years	5,884,467	1,271	2.48	145.9	8.709	8.237, 9.202	4.40	258.9	4.909	4.643, 5.186	14.97	880.9	1.443	1.365, 1.524
Males 50-59 years	2,797,358	279	1.66	46.4	6.008	5.324, 6.756	4.40	123.1	2.267	2.009, 2.549	8.48	237.2	1.176	1.042, 1.323
Males 60-69 years	2,371,600	137	2.37	56.2	2.437	2.046, 2.881	4.40	104.4	1.313	1.102, 1.552	4.80	113.8	1.203	1.010, 1.423
Males 70+ years	3,690,412	106	2.47	91.2	1.163	0.952, 1.406	4.40	162.4	0.653	0.534, 0.790	4.31	159.1	0.666	0.546, 0.806
Females ≤11 years	578,990	4	0.08	0.5	8.636	2.353, 22.111	4.40	25.5	0.157	0.043, 0.402	1.42	8.2	0.487	0.133, 1.246
Females 12-17 years	1,036,208	92	0.08	0.8	110.982	89.467, 136.109	4.40	45.6	2.018	1.627, 2.475	1.42	14.7	6.252	5.040, 7.668
Females 18-24 years	1,516,671	202	0.74	11.2	17.998	15.602, 20.659	4.40	66.7	3.027	2.624, 3.474	4.55	69.0	2.927	2.537, 3.360
Females 25-49 years	6,635,676	694	0.72	47.8	14.526	13.465, 15.648	4.40	292.0	2.377	2.203, 2.561	3.97	263.4	2.634	2.442, 2.838
Females 50-59 years	3,154,468	247	0.97	30.6	8.072	7.097, 9.144	4.40	138.8	1.780	1.565, 2.016	3.46	109.1	2.263	1.990, 2.564
Females 60-69 years	2,674,357	108	1.48	39.6	2.729	2.238, 3.294	4.40	117.7	0.918	0.753, 1.108	4.20	112.3	0.962	0.789, 1.161
Females 70+ years	4,161,528	105	0.76	31.6	3.320	2.715, 4.019	4.40	183.1	0.573	0.469, 0.694	3.84	159.8	0.657	0.537, 0.795
Overall, dose 1	14,052,564	1,293	1.34	188.3	6.867	6.497, 7.251	4.40	618.3	2.091	1.979, 2.208	6.27	881.1	1.467	1.389, 1.550
Overall, dose 2	13,838,666	2,667	1.34	185.4	14.382	13.841, 14.939	4.40	608.9	4.380	4.215, 4.549	6.27	867.7	3.074	2.958, 3.193
Overall, dose 3	9,387,821	893	1.34	125.8	7.099	6.641, 7.580	4.40	413.1	2.162	2.022, 2.308	6.27	588.6	1.517	1.419, 1.620

a. Background rate per 100,000 person years

Table 16. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a, 33]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a, 44]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,21]	Exp Cases	O/E Ratio	95% CI
Males ≤11 years	387,938	2	0.48	1.9	1.074	0.130, 3.880	4.40	17.1	0.117	0.014, 0.423	8.26	32.0	0.062	0.008, 0.225
Males 12-17 years	643,410	63	0.48	3.1	20.399	15.675, 26.099	4.40	28.3	2.225	1.710, 2.847	8.26	53.1	1.185	0.911, 1.517
Males 18-24 years	879,957	80	2.77	24.4	3.282	2.602, 4.085	4.40	38.7	2.066	1.638, 2.572	20.20	177.8	0.450	0.357, 0.560
Males 25-49 years	3,302,205	83	2.48	81.9	1.013	0.807, 1.256	4.40	145.3	0.571	0.455, 0.708	14.97	494.3	0.168	0.134, 0.208
Males 50-59 years	1,444,518	13	1.66	24.0	0.542	0.289, 0.927	4.40	63.6	0.205	0.109, 0.350	8.48	122.5	0.106	0.057, 0.181
Males 60-69 years	1,342,014	11	2.37	31.8	0.346	0.173, 0.619	4.40	59.0	0.186	0.093, 0.333	4.80	64.4	0.171	0.085, 0.306
Males 70+ years	1,461,865	17	2.47	36.1	0.471	0.274, 0.754	4.40	64.3	0.264	0.154, 0.423	4.31	63.0	0.270	0.157, 0.432
Females ≤11 years	437,462	2	0.08	0.3	5.715	0.692, 20.644	4.40	19.2	0.104	0.013, 0.375	1.42	6.2	0.322	0.039, 1.163
Females 12-17 years	725,547	14	0.08	0.6	24.120	13.186, 40.469	4.40	31.9	0.439	0.240, 0.736	1.42	10.3	1.359	0.743, 2.280
Females 18-24 years	992,292	8	0.74	7.3	1.089	0.470, 2.147	4.40	43.7	0.183	0.079, 0.361	4.55	45.1	0.177	0.076, 0.349
Females 25-49 years	3,723,763	47	0.72	26.8	1.753	1.288, 2.331	4.40	163.8	0.287	0.211, 0.381	3.97	147.8	0.318	0.234, 0.423
Females 50-59 years	1,628,924	19	0.97	15.8	1.202	0.724, 1.878	4.40	71.7	0.265	0.160, 0.414	3.46	56.4	0.337	0.203, 0.526
Females 60-69 years	1,513,335	13	1.48	22.4	0.580	0.309, 0.993	4.40	66.6	0.195	0.104, 0.334	4.20	63.6	0.205	0.109, 0.350
Females 70+ years	1,648,486	13	0.76	12.5	1.038	0.552, 1.774	4.40	72.5	0.179	0.095, 0.306	3.84	63.3	0.205	0.109, 0.351
Overall, dose 1	8,864,722	121	1.34	118.8	1.019	0.845, 1.217	4.40	390.0	0.310	0.257, 0.371	6.27	555.8	0.218	0.181, 0.260
Overall, dose 2	7,441,337	228	1.34	99.7	2.287	1.999, 2.603	4.40	327.4	0.696	0.609, 0.793	6.27	466.6	0.489	0.427, 0.556
Overall, dose 3	3,825,656	36	1.34	51.3	0.702	0.492, 0.972	4.40	168.3	0.214	0.150, 0.296	6.27	239.9	0.150	0.105, 0.208

a. Background rate per 100,000 person years

Table 17. Observed to Expected (O/E) Analysis of Myocarditis/Pericarditis in European Economic Area Countries, Cumulative Period

		14-Day Risk Window					21-Day Risk Window				
Stratification	Bkgd rate[a34]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	16.77	15	342,453	57.4	0.261	0.146, 0.431	16	513,444	86.1	0.186	0.106, 0.302
Males 12-17 years	16.77	636	612,811	102.8	6.189	5.717, 6.689	679	918,902	154.1	4.406	4.081, 4.750
Males 18-24 years	54.88	1,081	897,033	492.3	2.196	2.067, 2.331	1,162	1,344,972	738.1	1.574	1.485, 1.667
Males 25-49 years	43.53	1,620	3,924,413	1,708.3	0.948	0.903, 0.996	1,831	5,884,467	2,561.5	0.715	0.682, 0.748
Males 50-59 years	25.25	368	1,865,492	471.0	0.781	0.703, 0.865	431	2,797,358	706.3	0.610	0.554, 0.671
Males 60-69 years	26.50	195	1,581,950	419.2	0.465	0.402, 0.535	230	2,371,600	628.5	0.366	0.320, 0.416
Males 70+ years	21.45	176	2,462,707	528.3	0.333	0.286, 0.386	217	3,690,412	791.6	0.274	0.239, 0.313
Females ≤11 years	1.39	4	386,171	5.4	0.745	0.203, 1.908	4	578,990	8.0	0.497	0.135, 1.273
Females 12-17 years	1.39	135	691,042	9.6	14.054	11.784, 16.635	149	1,036,208	14.4	10.345	8.751, 12.146
Females 18-24 years	6.42	323	1,011,548	64.9	4.974	4.446, 5.547	354	1,516,671	97.4	3.636	3.267, 4.035
Females 25-49 years	7.61	1,281	4,425,402	336.8	3.804	3.598, 4.018	1,429	6,635,676	505.0	2.830	2.685, 2.980
Females 50-59 years	10.23	460	2,103,640	215.2	2.138	1.947, 2.342	524	3,154,468	322.7	1.624	1.488, 1.769
Females 60-69 years	13.38	204	1,783,901	238.7	0.855	0.741, 0.980	239	2,674,357	357.8	0.668	0.586, 0.758
Females 70+ years	11.04	174	2,777,095	306.6	0.568	0.486, 0.658	202	4,161,528	459.4	0.440	0.381, 0.505
Overall, dose 1	18.68	1,996	9,368,805	1,750.1	1.141	1.091, 1.192	2,300	14,052,564	2,625.0	0.876	0.841, 0.913
Overall, dose 2	18.68	3,419	9,226,601	1,723.5	1.984	1.918, 2.051	3,793	13,838,666	2,585.1	1.467	1.421, 1.515
Overall, dose 3	18.68	1,257	6,270,252	1,171.3	1.073	1.015, 1.134	1,374	9,387,821	1,753.6	0.784	0.743, 0.826

a. Background rate per 100,000 person years (PY)

Table 18. Observed to Expected (O/E) Analysis of Myocarditis/Pericarditis in the United States, Cumulative Period

		14-Day Risk Window					21-Day Risk Window				
Stratification	Bkgd rate[a34]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	16.77	3	259,088	43.4	0.069	0.014, 0.202	3	387,938	65.1	0.046	0.010, 0.135
Males 12-17 years	16.77	69	429,707	72.1	0.958	0.745, 1.212	72	643,410	107.9	0.667	0.522, 0.840
Males 18-24 years	54.88	88	587,687	322.5	0.273	0.219, 0.336	92	879,957	482.9	0.191	0.154, 0.234
Males 25-49 years	43.53	92	2,205,406	960.0	0.096	0.077, 0.118	98	3,302,205	1,437.4	0.068	0.055, 0.083
Males 50-59 years	25.25	19	964,734	243.6	0.078	0.047, 0.122	22	1,444,518	364.7	0.060	0.038, 0.091
Males 60-69 years	26.50	12	896,275	237.5	0.051	0.026, 0.088	16	1,342,014	355.6	0.045	0.026, 0.073
Males 70+ years	21.45	21	976,319	209.4	0.100	0.062, 0.153	24	1,461,865	313.6	0.077	0.049, 0.114
Females ≤11 years	1.39	2	292,163	4.1	0.492	0.060, 1.779	2	437,462	6.1	0.329	0.040, 1.188
Females 12-17 years	1.39	14	484,563	6.7	2.079	1.136, 3.487	16	725,547	10.1	1.586	0.907, 2.576
Females 18-24 years	6.42	13	662,711	42.5	0.306	0.163, 0.523	14	992,292	63.7	0.220	0.120, 0.369
Females 25-49 years	7.61	65	2,486,947	189.3	0.343	0.265, 0.438	74	3,723,763	283.4	0.261	0.205, 0.328
Females 50-59 years	10.23	24	1,087,891	111.3	0.216	0.138, 0.321	27	1,628,924	166.6	0.162	0.107, 0.236
Females 60-69 years	13.38	24	1,010,693	135.2	0.177	0.114, 0.264	28	1,513,335	202.5	0.138	0.092, 0.200
Females 70+ years	11.04	18	1,100,955	121.5	0.148	0.088, 0.234	19	1,648,486	182.0	0.104	0.063, 0.163
Overall, dose 1	18.68	153	5,915,701	1,105.1	0.138	0.117, 0.162	170	8,864,722	1,655.9	0.103	0.088, 0.119
Overall, dose 2	18.68	259	4,966,389	927.7	0.279	0.246, 0.315	282	7,441,337	1,390.0	0.203	0.180, 0.228
Overall, dose 3	18.68	52	2,563,048	478.8	0.109	0.081, 0.142	55	3,825,656	714.6	0.077	0.058, 0.100

a. Background rate per 100,000 person years (PY)

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

For myocarditis in the US, O/E ratios were above 1 for all stratifications except males 50+, females 60-69 years, and dose 3 using the low background rate, for males 12-24 years using the mid background rate, and for males and females 12-17 years using the high background rate.

Recent increases in O/E ratios for the younger age groups may have been influenced by increased reporting of cases after the release of a Dear Healthcare Provider letter in late July 2021.

For myocarditis/pericarditis, the O/E ratios were above 1 for the 12-24 years age groups in males, the 12-59 years age groups in females, and dose 1, 2, and 3 in the EEA. All O/E ratios were below 1 for myocarditis/pericarditis in the US except for females 12-17 years.

Rapporteur assessment comment:

Myocarditis in EEA

Cumulatively using 21-days risk window and the low background rate, all O/E ratios were above 1 across age groups, genders, and doses.

Myocarditis/pericarditis in EEA

Cumulatively using 14-days or 21-days or risk window, the O/E ratios were above 1 for males aged 12-24 years, females aged 12-59 years, and dose 1, 2, and 3.

Rapporteur assessment comment:

In general, the MAH should focus the analysis of pericarditis cases on aspects of these ADRs not fully known or addressed in the Comirnaty PI (pericarditis is already an ADR stated in section 4.8), and if the warning in section 4.4 regarding pericarditis is still in line with current knowledge. Therefore, the analysis should focus more on information concerning the course, outcome, and possible risk factors of the pericarditis cases following Comirnaty exposure. **Request for next PSUR**

Pericarditis

Clinical trial data

During the reporting period, no cases were retrieved.

Post-marketing

- Aged 5-11 years: There were 30 cases reporting pericarditis (no fatal cases) compared to 4 pericarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 12-15 years: There were 118 cases reporting pericarditis (no fatal cases) compared to 215 pericarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 16-17 years: There were 106 cases reporting pericarditis (no fatal cases) compared to 174 pericarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 18-24 years: There were 479 cases reporting pericarditis (1 fatal case) compared to 659 pericarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 25-29 years: There were 417 cases reporting pericarditis (1 fatal case) compared to 614 pericarditis cases (no fatal cases) reported in the previous 2nd PSUR.
- Aged 30-39 years: There were 940 cases reporting pericarditis (no fatal cases) compared to 1222 pericarditis cases (1 fatal case) reported in the previous 2nd PSUR.

- Aged ≥40 years: There were 1756 cases reporting pericarditis (17 fatal cases) compared to 2059 pericarditis cases (8 fatal cases) reported in the previous 2nd PSUR.

The MAH is requested to provide detailed information concerning the fatal cases with pericarditis in persons aged 18-24 years, 25-29 years, and ≥40 years and perform per case an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, a WHO causality assessment,and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable. **Request for supplementary information**

Rapporteur assessment comment:

In spite of the recent risk communication and routine risk minimisation measures concerning myocarditis and pericarditis fatal cases continue to be reported, which is worrisome. Upon analysis of the requested details of the fatal myocarditis/pericarditis cases the MAH is expected to discuss whether the current risk minimisation measures is still adequate. **Request for supplementary information**

Evaluation of important potential risks

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

Search criteria:

1 - PTs Vaccine associated enhanced respiratory disease OR Vaccine associated enhanced disease

OR

2 - Standard Decreased Therapeutic Response Search (Drug ineffective OR Vaccination failure) AND 1 among the following PTs: Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory failure; Acute respiratory distress syndrome; Cardiac failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.

Clinical trial data

- There were no cases reporting COVID-19 infection associated to one of the PTs utilised to identify potential severe or atypical cases of COVID-19.

Post-Authorisation Data

- Number of cases: 1268 (0.2% of 507,683 cases, the total PM dataset), compared to 1490 (0.2%) retrieved in the PSUR # 2. All cases are serious.
- MC cases (878), NMC cases (390).
- Country of incidence: France (346), Spain (142), UK (139), US (117), Italy (105), Estonia (94), Germany (66), Philippines (45), Australia, Canada (19 each), Switzerland (18), Portugal,

(17), Netherlands (14), Austria (10); the remaining 117 cases originated from 117 different countries.

- Gender: female (636), male (604), and unknown (28).
- Age in years (n = 1215), range: 5 – 102, mean: 61.4, median: 65.0.
- Relevant event seriousness: 1295 serious, 406 non-serious.
- Reported relevant PTs by organ system:
    - Respiratory system PTs (1631): COVID-19 pneumonia (524), Dyspnoea (398), Respiratory failure (48), Acute respiratory distress syndrome (42), Pulmonary embolism (40), Hypoxia (28), and Tachypnoea (27).
    - Gastrointestinal/Hepatic system PTs (288): Diarrhoea (139), Vomiting (88), Abdominal pain (54), and Jaundice (7).
    - Cardiovascular system PTs (143): Myocarditis (85), Arrhythmia (32), Cardiac failure (18), Acute myocardial infarction (6), and Cardiogenic shock (2).
    - Renal and urinary system PTs (39): Acute kidney injury (27), and Renal failure (12).
    - Nervous system PTs (47): Seizure (21), Cerebrovascular accident (18), Encephalopathy (6), and Altered state of consciousness (2).
    - Vascular system PTs (23): Deep vein thrombosis (12), Shock (6), Vasculitis (3), and Peripheral ischaemia (2).
    - Blood and lymphatic system PTs (14): Thrombocytopenia (12), and Disseminated intravascular coagulation (2).
    - Immune system PTs (30): Vaccine associated enhanced disease (12), and Multisystem inflammatory syndrome in children (9), and Vaccine associated enhanced respiratory disease (9 each).
    - Other PTs (24): Multiple organ dysfunction syndrome (13), Chillblains (5), Meningitis (4), and Erythema multiforme (2).
- Case outcome: fatal (184), not resolved (329), resolved/resolving (582), resolved with sequelae (31), and unknown (142).

MAH's conclusion

The nature of spontaneously reported data provides a challenge because of the lack of a comparison group. Further, the background rate of VAED is not known. Considering the limitations of the review, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.

Rapporteur assessment comment:
No new important safety concern could be identified regarding VAED/VAERD.

Evaluation of Other Risks (not categorised as important)

Adverse events of special interest (AESIs)

Anaphylactic AESIs

Rapporteur assessment comment:

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

Cardiovascular AESIs

Search criteria: *PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia*

Clinical trial data

- Number of cases: 27 (blinded therapy [6], and BNT162b2 [21]) (4.0 % of 668 cases, the total CT dataset) compared to 35 cases (4.9%) retrieved in the PSUR #2. None of the events were related BNT162b2 or blinded therapy.

Post-authorization data

- Number of cases: 32,712 (6.4 % of 507,683 cases, the total PM dataset), compared to 29,486 (4.5%) cases retrieved in the PSUR #2.
- MC cases (11,952), NMC cases (20760).
- Country of incidence (>16 occurrences): Germany (11,180), Australia (4456), UK (3049), France (2612), Taiwan Province of China (1393), Italy (1334), Netherlands (810), Austria (677), Malaysia (591), Philippines (475), US (422), Japan (397), New Zealand (396), Norway (369), Finland (338), Sweden (333), Belgium (328), Canada (317), Poland (307), Iraq (298), Greece (275), Spain (271), Ireland (237), Romania (217), Czech Republic (198), Denmark (125), Switzerland (119), Brazil (118), Lithuania (110), Croatia (92), Estonia (88), Portugal (82), Egypt (77), Israel (74), Slovenia (70), Mexico (62), Iceland (52), Slovakia (51), Hungary (50), Singapore (35), South Africa (30), Georgia (24), Latvia (24), Luxembourg (22), Turkey (20), Bulgaria (18), Cyprus (17); the remaining 72 cases were distributed among 31 countries.
- Subjects' gender: female (19,730), male (12,424) and unknown (558).
- Subjects' age in years (n = 31,124), range: 2 months-99, mean: 40.3, median: 39.
- Medical history (n = 9348): the most frequently (>2%) reported relevant medical conditions included Hypertension (1349), Seasonal allergy (1121), Asthma (839), Drug hypersensitivity (758), Hypersensitivity (511), Food allergy (502), Mite allergy (387), Hypothyroidism (365), Tobacco user (290), Allergy to animal (285), Autoimmune thyroiditis (280), Diabetes mellitus (274), Obesity (253), Atrial fibrillation (232), Non-tobacco user (232), Arrhythmia (220), Allergy to metals (216), Migraine (214).
- COVID-19 Medical history (n = 1546): the medical conditions reported included COVID-19 (1021), Suspected COVID-19 (492), Post-acute COVID-19 syndrome (40), COVID-19 pneumonia (16), SARS-CoV-2 test positive (14), Coronavirus infection (7), Asymptomatic COVID-19 (6), Exposure to SARS-CoV-2 (4), and Coronavirus pneumonia (1).
- Co suspects (n = 295 cases): the frequently (>12 occurrences) reported relevant co-suspect medications were COVID-19 vaccine mRNA (MRNA 1273) (66), COVID-19 vaccine (34), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (20), INFLUENZA VACCINE (19), adalimumab (13).
- Number of relevant events: 36,790.
- Relevant event seriousness: serious (16,539), non-serious (20,268).

- Relevant PTs: Chest pain (17,945), Tachycardia (10,914), Arrhythmia (5627), Myocardial infarction (921), Cardiac failure (583), Acute myocardial infarction (364), Postural orthostatic tachycardia syndrome (149), Coronary artery disease (114), Cardiogenic shock (72), Cardiac failure acute (57), Stress cardiomyopathy (44).
- Time to event onset (n = 26,744 occurrences), range: <24 hours to 382 days, median: 1 day.
- Duration of relevant events (n = 8262 out of 8906 occurrences with outcome of resolved and resolved with sequalae), range: <24 hours to 430 days, median: 4 days.
- Relevant event outcome: fatal (496), resolved/resolving (13,937), resolved with sequelae (1321), not resolved (12,839), unknown (8437).
    - In 449 cases (reporting 496 relevant events with fatal outcome), the reported causes of death (>10 occurrences) were coded to the PTs Myocardial infarction (147), Cardiac failure (94), Chest pain (55), Acute myocardial infarction (54), Dyspnoea (43), Cardiac arrest (42), Arrhythmia (34), Cardiac failure acute (26), Myocarditis (22), Cardiogenic shock, Cardio-respiratory arrest (20 each), Thrombosis (15), Malaise (13), Loss of consciousness, Pulmonary embolism, Pulmonary oedema, Tachycardia (12 each), Pneumonia, Respiratory failure (11 each). Of note, in 16 cases limited information regarding the cause of death was provided (PT Death [11]; PT Sudden death [1]; Unknown [4]). Most (250 of 449 cases) of the fatal cases involved elderly subjects. When the medical history was provided (253 cases), the most frequently (≥ 9 occurrences) relevant medical conditions included events coded to the PTs Hypertension (91), Diabetes mellitus (32), Atrial fibrillation (28), Obesity (24), Cardiac failure (23), Type 2 diabetes mellitus (16), Coronary artery disease (15), Dyslipidaemia, Myocardial infarction (13 each), Chronic kidney disease, Chronic obstructive pulmonary disease (12 each), Cardiac disorder, Tobacco user (11 each), Cardiac failure chronic, Hyperlipidaemia (10 each), Arteriosclerosis, Asthma, Cerebral infarction, Myocardial ischaemia (9 each).

<u>Analysis by age group</u>

- Clinical trials: Paediatric (1), Adults (14), and Elderly (12). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (2808), Adults (25850), Elderly (2996) and Unknown (1058).
    - Higher reporting proportion of events coded to the PTs Arrhythmia [4.6% in paediatrics vs 18.2% in adults vs 24.3% in elderly], Cardiac failure [0.5% in paediatrics vs 0.8% in adults vs 11.5% in elderly], Myocardial infarction [0.3% in paediatrics vs 2.2% in adults vs 9.0% in elderly], Cardiogenic shock [0.1% in paediatrics vs 0.2% in adults vs 0.8% in elderly], Acute myocardial infarction [0.1% in paediatrics vs 0.8% in adults vs 4.8% in elderly], Cardiac failure acute [0.1% in paediatrics vs 0.1% in adults vs 0.8% in elderly], Stress cardiomyopathy [0.04% in paediatrics vs 0.1% in adults vs 0.7% in elderly], and Coronary artery disease [0% in paediatrics vs 0.3% in adults vs 1.5% in elderly] and was reported in elderly population when compared to adult and paediatric population.

      Higher reporting proportion of PT Chest pain [81.6% in paediatrics vs 53.5% in adults vs 36.3% in elderly] was reported in paediatrics compared to adults and elderly subjects.

Higher reporting proportion of PT Tachycardia [19.6% in paediatrics vs 36.5% in adults vs 22.7% in elderly] was reported in adults compared to paediatrics and elderly subjects.

The PT Postural orthostatic tachycardia syndrome was reported among the paediatric and adult subjects only (0.4% each).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3726 (0.7% of 507,683 cases, the total dataset).
- No significant difference was observed in the reporting proportion of cardiovascular AESIs with fatal outcome in individuals with comorbid conditions (0.4% of events with fatal outcome) when compared to the reporting proportion observed in the individuals without comorbidities (0.9 % of events with fatal outcome).

O/E analysis

- O/E analysis was performed for Acute myocardial infarction/Myocardial infarction; Arrhythmia; Coronary artery disease; Heart failure; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy. All O/E ratios were <1.

MAH's conclusion

No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

During the interval period, post-marketing there were retrieved 32,712 cases (6.4 % of 507,683 cases, the total PM dataset) reporting cardiovascular AESIs which is an increase compared to 29,486 (4.5%) cases retrieved in the previous 2nd PSUR. Of note, during the current interval period the overall (all ages) exposure decreased compared to the previous interval period: 843 Mio doses versus 1.4 billion doses. However, the paediatric exposure increased from 47 Mio paediatric Tris/Sucrose doses shipped worldwide in the previous interval period to 182 Mio paediatric Tris/Sucrose doses in current interval period.

The O/E analysis showed that all O/E ratios were below 1 and age stratified O/E ratios were also <1, when available.

No new important safety concern could be identified for cardiovascular AESIs. For future PSURs in the section 'Evaluation of AESIs', the cardiovascular 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**

Haematological AESIs

Search Criteria: *Leukopenias NEC; Neutropenias OR SMQ Haemorrhage terms (excl laboratory terms) OR PT Acquired haemophilia.*

Clinical trial data

- Number of cases: 15 (BNT162b2 [12] and blinded therapy [3]) (2.2 % of 668 cases, the total CT dataset) compared to 19 cases (2.4%) retrieved in the PSUR #2. None of these SAEs were assessed as related to BNT162b2/blinded therapy.

Post-authorisation data

- Number of cases: 30,302 (5.9% of 507,683 cases, the total PM dataset), compared to 37,327 cases (5.7%) retrieved in the PSUR #2.
- MC cases (4952), NMC cases (25,350).
- Country of incidence: Germany (7802), Netherlands (6166), UK (3266), Norway (2930), France (2905), Australia (1010), Spain (626), Italy (579), Sweden (557), Belgium (438); the remaining 4023 cases were distributed among 63 countries.
- Subjects' age in years (n = 28,488), range: 5 months-100 years, mean: 38.9, median: 37.0.
- Medical history (n = 10,294): the most frequently (≥200 occurrences) reported relevant medical conditions were coded to the PTs Disease risk factor (957), Hypertension (648), Menopause (620), Asthma (508), Seasonal allergy (427), Drug hypersensitivity (419), Amenorrhoea (404), Hypersensitivity (379), Hypothyroidism (295), Endometriosis (225), Food allergy (223), Migraine (213), and Contraception (200).
- COVID-19 Medical history (n = 2397): Medical conditions reported more than once were coded to the PTs COVID-19 (1636), Suspected COVID-19 (730), Post-acute COVID-19 syndrome (12), SARS CoV 2 test positive (8), COVID-19 pneumonia (5), Coronavirus infection, Exposure to SARS CoV 2 (2 each), Asymptomatic COVID-19, and Coronavirus test positive (1 each).
- Co-suspects: the most frequently (≥10 occurrences) reported relevant co suspect vaccines/medications were COVID-19 vaccine MRNA (97), adalimumab (43), Influenza vaccine (36), COVID-19 vaccine NRVV (31), levonorgestrel (24), and COVID-19 vaccine (19).
- Number of relevant events: 33,677.
- Relevant event seriousness: serious (8090) and non-serious (25,587).
- Most frequently reported relevant PTs (≥2%): Heavy menstrual bleeding (12,905), Intermenstrual bleeding (6088), Vaginal haemorrhage (1759), Epistaxis (1645), Contusion (1450), Vaccination site haematoma (1137), Postmenopausal haemorrhage (1137), Haematoma (944), and Haemorrhage (677).
- Time to event onset (n = 24,005 events), range: <24 hours to 7337 days, median: 3 days.
- Duration of relevant events (n = 240 out of 572 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 21,170 days.
- Relevant event outcome: fatal (146), resolved/resolving (11,605), resolved with sequelae (571), not resolved (13,999), and unknown (7480).
    - In the 174 fatal cases (including 146 relevant events with fatal outcome, reported in 114 cases), the reported causes of death (>8 occurrences) were coded to the PTs Haemorrhage (12), Gastrointestinal haemorrhage, Haematemesis, and Pericardial haemorrhage (9 each). Of note, in 19 cases limited information regarding the cause of death was provided (PT Death). Most (122 of 174 cases) of the fatal cases involved elderly subjects. When the medical history was provided (114 cases), the most frequently (≥ 10 occurrences) relevant medical conditions included the PTs Hypertension (44), Cardiac arrest (16), Myocardial infarction (14), Cardiac failure, Cardio-respiratory arrest, Haemorrhage, and Myocardial ischaemia (10 each).

Analysis by age group

- Clinical trials: Adults (9) and Elderly (5). A meaningful comparison between the different age groups is not possible due to the low number of cases.

- Post-marketing: Paediatric (1044), Adults (26,592), Elderly (1731) and Unknown (935).
    - A significantly higher reporting proportion of events coded to the PTs Heavy menstrual bleeding and Intermenstrual bleeding was observed in paediatric and adult population when compared to elderly population (Heavy menstrual bleeding [33.9 % in paediatrics vs 45.7% in adults vs 0.2 % in elderly] and Intermenstrual bleeding [8.3% in paediatrics vs 22.1 % in adults vs 1.2 % in elderly]).

      The reporting proportion of the PT Epistaxis was significantly higher in paediatric and elderly population when compared to adult population (21.3 % in paediatrics vs 14.3 % in elderly vs 4.2 % in adults).

      The reporting proportion of PT Haematoma was higher in elderly population (12.1 %) when compared to paediatrics (1.2 %) and adult (2.0 %) population.

      The comparative differences in reporting proportions are not unexpected given the generally expected medical issues affecting each age group (paediatrics, adults, elderly).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2542 (8.4% of the CT and PM cases reporting haematological AESIs).
- The reporting proportion of haematological AESIs with fatal outcome (1.6%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.3%).

O/E analysis

- O/E analysis was performed for Acquired haemophilia and Haemorrhage. All O/E ratios below 1.

MAH's conclusion

Acquired haemophilia was evaluated during this reporting period. No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Please refer regarding Heavy menstrual bleeding to the separate signal procedure (EMEA/H/C/005735/SDA/053- EPITT 19783), in which PRAC concluded that heavy menstrual bleeding should be listed as an ADR in the Comirnaty PI.

Please refer regarding the assessment of acquired haemophilia to section 2.2 Signal evaluation of this AR.

Haematological AESIs were continuously monitored in the 13th and 14th SSRs (through 15 Apr 2022) for Comirnaty during the reporting period.

No new important safety concern could be identified for haematological AESIs. For future PSURs in the section 'Evaluation of AESIs', the haematological 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**

COVID-19 AESIs

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

Clinical trial data

- Number of cases: 7 (blinded therapy [3] and BNT162b2 [4]) (1.0 % of 668 cases, the total CT dataset) compared to 3 cases (0.4%) retrieved in the PSUR #2. None of the events were related to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of relevant cases: 54,335 (10.7% of 507,683 cases, the total PM dataset), compared to 25,453 cases (3.9%) retrieved in the PSUR #2. The increase in the number of cases reported during the current PSUR is attributed to the increase in cases reported from Austria (9068 cases in the PSUR #2 vs 31,769 cases in the current PSUR #3) due to active solicitation of LOE cases from the Austrian BoH.
- MC cases (40,416); NMC cases (13,919).
- Country of incidence (≥ 2%): Austria (31,769), US (4874), UK (2725), Germany (2386), France (1934), Netherlands (1495); the remaining 9152 cases were distributed among 77 countries.
- Subjects' gender: female (29,370), male (22,867) and unknown (2098).
- Subjects' age in years: (n = 51,267), range: 6 months – 107 years, mean: 47.1, median: 46.0.
- Medical history (n = 8328): the most frequently (≥2%) reported relevant medical conditions included Hypertension (1429), Asthma (766), Drug hypersensitivity (617).
- COVID-19 Medical history: COVID-19 (1018), Suspected COVID-19 (361), Exposure to SARS-CoV-2 (49), Post-acute COVID-19 syndrome (48), COVID-19 pneumonia (10), SARS-CoV-2 test positive (9), Asymptomatic COVID-19, Coronavirus infection (3 each), Coronavirus test positive, Occupational exposure to SARS-CoV-2 (2 each).
- Co-suspects (n = 3995 cases): the most frequently (≥10) reported relevant co-suspect vaccines/medications were COVID-19 vaccine (1861), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (798), COVID-19 vaccine MRNA (MRNA 1273) (768), Adalimumab (256), JNJ 78436735 (100), Ocrelizumab (35), Influenza vaccine (34), Upadacitinib (31), COVID-19 vaccine INACT (VERO) CZ02 (25), Risankizumab (21), Prednisone (18), Casirivimab/Imdevimab, Rituximab (13 each), Mycophenolate (10).
- Number of relevant events: 55,437.
- Relevant event seriousness: serious (52,185), non-serious (3254).
- Most frequently reported relevant PTs (≥2%): COVID-19 (47,981) Suspected COVID-19 (3002), and Ageusia (1094).
- Time to event onset (n = 46,269), range: <24 hours to 564 days, median: 117 days.
- Duration of relevant events (n = 1968 out of 4800 occurrences with outcome of resolved/resolved with sequelae), range: 24 hours to 373 days, median: 9 days.
- Relevant event outcome: fatal (506), resolved/resolving (7289), resolved with sequelae (296), not resolved (3281), unknown (44071).

- In 493 cases (reporting 543 relevant events of which 506 relevant events reported a fatal outcome), the reported causes of death (>20 occurrences) were coded to the PTs COVID-19 (297), Vaccination failure (143), Drug ineffective (131), COVID-19 pneumonia (127), Death (46), Dyspnoea (21). Of note, in 39 cases limited information regarding the cause of death was provided (PT Death [38] and Sudden death [1]). Most (406 of 493 cases) of the fatal cases involved elderly subjects. When the medical history was provided (272 cases), the most frequently (≥ 20 occurrences) relevant medical conditions included the PTs Hypertension (117), Atrial fibrillation (53), Chronic kidney disease, Dyslipidaemia (33 each), Type 2 diabetes mellitus (29), Myocardial ischaemia (25), Cardiac failure (24), COVID-19 (22), and Diabetes mellitus (21).

Analysis by age group

- Clinical trials: Paediatric (1), Adults (5), Elderly (1). Due to low volume of paediatric cases, a meaningful comparison of the same with the other age groups is not possible.
- Post-marketing: Paediatric (2158), Adults (39,726), Elderly (9566). No significant difference was observed in the reporting proportion of the most frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3846 (0.8% of 507,683 cases, the total dataset).
- The reporting proportion of COVID-19 AESIs with fatal outcome (5.6% [230 of 4093 events]) is higher in subjects with comorbid conditions, compared to the reporting proportion observed in the individuals without comorbidities (0.5% [276 of 51,344 cases] of fatal events).

Long COVID

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

Clinical trial data

- No cases.

Post-authorization data

- Number of relevant cases: 200 (0.04% of 507,683 cases, the total PM dataset), compared to 72 cases (0.3% of 25,453 cases) retrieved in the PSUR #2.
- MC cases (62); NMC cases (138).
- Country of incidence: Germany (106), France (15), UK (14), Austria (13), Sweden (9), Australia, Finland (8 each), Netherlands (6), Italy (4), Ireland, US (3 each), Belgium, Hungary, New Zealand, Spain (2 each), Brazil, Greece and Luxembourg (1 each).
- Subjects' gender: female (151), male (46) and unknown (3).
- Subjects' age in years: (n = 174), range: 9 – 85 years, mean: 43.6, median: 45.0. Of these 174 subjects, there were 10 paediatric, 156 adults, and 8 elderly subjects.
- Medical history (n = 104): the most frequently (≥2%) reported medical conditions included Asthma, Drug hypersensitivity (8 each), and Seasonal allergy (7).
- COVID-19 Medical history: COVID-19 (38), Post-acute COVID-19 syndrome (33), Suspected COVID-19 (10).

O/E analysis

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

MAH's conclusion

Loss of/Altered Taste and Smell was evaluated as signal during the reporting period and determined not to be a risk.

No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

During the interval period, there was an increased number of cases reporting COVID-19 AESIs (54,335 [10.7% of the total PM dataset] compared to 25,453 cases (3.9%) retrieved in the 2nd PSUR which is attributed to the increase in cases reported from Austria (9,068 cases in the 2nd PSUR versus 31,769 cases in the current 3rd PSUR) due to active solicitation of lack of efficacy cases from the Austrian board of health.

Please refer regarding the closed signal 'Loss of/altered taste and smell' to section 2.2.2. Evaluation of closed signals of this AR (PRAC concluded that the data provided did not support a causal relationship between Comirnaty exposure and the loss of/altered taste and smell).

COVID-19 AESIs were continuously monitored in the 13th and 14th SSRs (through 15 Apr 2022) for Comirnaty during the reporting period.

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

Dermatological AESIs

Search criteria: *PTs Chillblains; Erythema multiforme.*

Clinical trial data

- No cases, and no cases were retrieved in the PSUR #2.

Post-authorization data

- Number of cases: 284 (0.06% of 507,683 cases, the total PM dataset), compared to 339 (0.05%) cases retrieved in the PSUR #2.
- MC cases (158), NMC cases (126).
- Country of incidence: France (72), Germany (38), UK (25), Italy (24), Singapore (18), Japan, Poland (11 each), the Netherlands, US (9 each), Australia (8), Belgium (7), Canada, New Zealand, Spain (6 each); the remaining 34 cases were distributed among 18 countries.
- Subjects' gender: female (182), male (93) and unknown (9).
- Subjects' age in years: (n = 269), range: 7-89, mean: 46.4, median: 46.
- Medical history (n = 102): the most frequently (≥ 4 occurrences) reported relevant medical conditions included Hypertension (16), COVID-19 (12), Asthma (8), Drug hypersensitivity, Suspected COVID-19 (6 each), Diabetes mellitus (5), Cerebrovascular accident, Food allergy, Herpes simplex, Hypothyroidism, Type 2 diabetes mellitus (4 each).
- COVID-19 Medical history (n = 17): COVID-19 (12), Suspected COVID-19 (6), and Post-acute COVID-19 syndrome (1).

- Co-suspects (n = 4 cases): Acetylcysteine/benzalkoniumchloride/tuaminoheptane sulfate, Albendazole, Dextromethorphan, Ibuprofen, Ketoprofen, Ocrelizumab, Prednisolone metasulfobenzoate sodium, Sulfasalazine (1 each).
- Number of events: 284.
- Relevant event seriousness: serious (206), non-serious (78).
- Reported relevant PTs: Erythema multiforme (181), Chillblains (103).
- Time to event onset (n = 72), range: <24 hours to 262 days, median: 4 days.
- Duration of relevant events (n = 14 out of 53 occurrences with outcome of resolved/resolved with sequelae), range: 0 days to 67 days, median: 20.5 days:
- Relevant event outcome: resolved/resolving (108), resolved with sequelae (8), not resolved (118), unknown (50). No fatal events were reported.

Analysis by age group

- Post-marketing: Paediatric (31), Adults (183), Elderly (60) and Unknown (10).
    - Due to low volume of paediatric cases a meaningful comparison of the same with the other age groups is not possible. No significant difference observed in the reporting proportion of events chillblains and erythema multiforme between adult and elderly population.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 53 (18.7 % of the cases reporting dermatological AESIs). A higher reporting proportion of dermatological AESIs was reported in subjects without significant comorbidities (81.3 %) when compared to subjects with significant comorbidities.

O/E analysis

- O/E analysis was performed for Chillblains and Erythema multiforme: all O/E ratios <1.

MAH's conclusion

No other safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

No new important safety concern could be identified for dermatological AESIs. For future PSURs in the section 'Evaluation of AESIs', the dermatological 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**

Please refer regarding Pemphigus and Pemphigoid to the separate ongoing signal procedure (EPITT 19859).

Facial paralysis

Search Criteria: *PTs Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis.*

Clinical trial data

- Number of cases: 1 (BNT162b2 [1]) (0.1% of 668 cases, the total CT dataset) compared to no cases retrieved in the PSUR #2. Not related to BNT162b2.

Post-authorization data

- Number of cases: 2589 (0.5% of 507,683 cases, the total PM dataset), compared to 4515 cases (0.7%) retrieved in the PSUR #2.
- MC cases (1105), NMC cases (1484).
- Country/region of incidence: Germany (714), France (387), UK (229), Australia (184), Italy (112), Austria (97), Sweden (87), Hong Kong (70), Taiwan, Province of China (69), US (54); the remaining 586 cases were distributed among 40 countries.
- Subjects' gender: female (1487), male (1060), and unknown (42).
- Subjects' age in years: (n = 2473), range: 1.42 – 99, mean 47.3, median 47.0.
- Medical history (n = 934): the most frequently (>2%) reported relevant medical conditions were coded to the PTs Hypertension (185), Asthma (89), Seasonal allergy (85), Drug hypersensitivity (63), Hypersensitivity (57), Diabetes mellitus (55), Type 2 diabetes mellitus (40), Obesity (35), Food allergy (34), Hypothyroidism (32), Facial paralysis, Mite allergy (28 each), Allergy to animal (26), Bell's palsy (25), Hypercholesterolaemia (24), Chronic obstructive pulmonary disease, Tobacco user (23 each), Migraine (20), and Coronary artery disease (19).
- COVID-19 Medical history (n = 133): reported medical conditions were coded to the PTs COVID-19 (100), Suspected COVID-19 (31), Post-acute COVID-19 syndrome (4), SARS CoV 2 test positive (2), Asymptomatic COVID-19, Coronavirus infection, and COVID-19 pneumonia (1 each).
- Co-suspects (n = 33): the relevant co suspect vaccines/medications were diphtheria vaccine toxoid/ polio vaccine inact 3V (vero)/ tetanus vaccine toxoid and meningococcal group C tetanus toxoid conjugate vaccine (1 each).
- Number of relevant events: 2706.
- Relevant event seriousness: serious (2431) and non-serious (543).
- Reported relevant PTs: Facial paralysis (1428), Bell's palsy (733), Facial paresis (543), and Oculofacial paralysis (2).
- Time to event onset (n = 2152 events), range: <24 hours to 389 days, median 7 days.
- Duration of relevant events (n = 286 out of 613 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 246 days, median: 6 days.
- Relevant event outcome: fatal (6), resolved/resolving (999), resolved with sequelae (111), not resolved at the time of reporting (1063), and unknown (534).
    - In 6 cases (reporting 6 relevant events with a fatal outcome), the causes of death (≥2 occurrences) were coded to the PTs Facial paralysis (3), Cerebrovascular accident and Death (2 each). Of note, in 2 cases limited information regarding the cause of death was provided (PT Death). All of the patients were >60 years of age (range 61 to 99 years). When the medical history was provided (4 cases), significant medical conditions reported Arthralgia, Cerebral infarction, Diverticulitis, Lung adenocarcinoma, Neoplasm malignant, Pemphigoid, and Pulmonary embolism (1 each).

Analysis by age group

- Paediatric (146), Adults (1914), Elderly (420), and Unknown (109).

- There was no significant difference observed in the reporting proportion of facial paralysis events between age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 407 (15.7% of the CT and PM cases reporting facial paralysis).
    - The reporting proportion of cases reporting a facial paralysis events with a fatal outcome is higher in subjects with comorbid conditions (0.74%) when compared to the reporting proportion observed in the subjects without comorbidities (0.14%).

O/E analysis

- O/E analysis was performed for Bell's palsy (PTs: Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis): all O/E ratios <1.

MAH's conclusion

No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

No new important safety concern could be identified for facial paralysis. For future PSURs in the section 'Evaluation of AESIs', the facial paralysis 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**

Hepatic AESIs

Search Criteria: *SMQ Liver related investigations, signs and symptoms (Narrow and Broad) OR PTs Autoimmune hepatitis , Liver injury*.

Clinical trial data

- No cases compared to 2 cases (0.28%) retrieved in the PSUR #2.

Post-authorization data

- Number of relevant cases: 1091 (0.2 % of 507,683 cases, the total PM dataset), compared to 1393 cases (0.2%) retrieved in the PSUR #2.
- MC cases (560), NMC cases (531).
- Country of incidence: Germany (276), Japan (157), France (152), UK (71), Australia (66), US (55), Italy (44), Austria (35), Spain (29), Taiwan, province of China (26), Netherlands (17), Sweden (15), Belgium, Finland (14 each), New Zealand (13), Greece (11), Canada (10), Denmark (9), Czech Republic (8), Norway, Poland (6 each), Croatia, Ireland, Romania (5 each), Switzerland (4), Brazil, Latvia, Philippines, Portugal, Slovakia, Slovenia (3 each), Estonia, Hungary, Lithuania, Malaysia, Mexico (2 each); the remaining 10 cases were distributed among 10 countries.
- Subjects' gender: female (661), male (406) and unknown (24).
- Subjects' age in years (n = 1017), range: 5 - 94, mean: 49.3, median: 51.0.
- Medical history (n = 518): the most frequently reported relevant medical conditions (≥ 5 occurrences) included Hypertension (80), Drug hypersensitivity (38), Hypothyroidism,

Seasonal allergy (33), Asthma (32), Food allergy (23), Autoimmune thyroiditis, Type 2 diabetes mellitus (21 each), Allergy to animal (20), Allergy to metals, Dyslipidaemia (19 each), Mite allergy (17), Atrial fibrillation (16), Diabetes mellitus, Hepatic steatosis, Tobacco user (15 each), Obesity (14), Hypercholesterolaemia, Hypersensitivity (13 each), Gastro-oesophageal reflux disease, Rheumatoid arthritis (12 each), Breast cancer, Mycotic allergy, Non-tobacco user, Tonsillectomy (11 each), Autoimmune hepatitis, Depression, Ovarian cystectomy (10 each), Interchange of vaccine products, Osteoporosis, Salivary gland operation (9 each), Cardiac failure, Cholecystectomy, Liver disorder, Migraine (8 each), Abstains from alcohol, Alcohol use, Allergy to plants, Anxiety, Arrhythmia, Epstein-Barr virus infection, Headache, Hysterectomy, Pyrexia, Type 1 diabetes mellitus (7 each), Coeliac disease, Disease risk factor, Hepatic cirrhosis, Hyperuricaemia, Thyroid disorder, Weight decreased (6 each), Colon cancer, Dermatitis contact, Diverticulum intestinal, Epilepsy, Hepatic function abnormal, Hepatitis, Hyperlipidaemia, Immunodeficiency, Insomnia, Nephrolithiasis, Neuropathy peripheral, Pericarditis, Primary biliary cholangitis, Sinus operation, Sjogren's syndrome, Sleep apnoea syndrome, and Thyroid cancer (5 each).

- COVID-19 Medical history (n = 46): the medical conditions reported included COVID-19 (34), Post-acute COVID-19 syndrome, Suspected COVID-19, (5 each), Asymptomatic COVID-19, and COVID-19 pneumonia (1 each).
- Co-suspects (n = 58): the relevant co suspect medications reported were adalimumab (10), upadacitinib (3), atorvastatin, hepatitis A vaccine, methotrexate, paracetamol (2 each), amlodipine, amoxicillin, cabozantinib, cefuroxime, certolizumab, clopidogrel, clozapine, colchicine, drospirenone ethinylestradiol, ebastine, ethinylestradiol gestodene, exemestane, fingolimod, ibuprofen, ipilimumab, lanreotide, nitrofurantoin, nivolumab, paclitaxel, ribociclib, rosuvastatin, sorafenib, spironolactone, teriflunomide, torasemide, and valsartan (1 each).
- Number of relevant events: 1422.
- Relevant event seriousness: serious (676) and non-serious (746).
- Most frequently reported relevant PTs (≥50 occurrences): Hepatic enzyme increased (131), Alanine aminotransferase increased (126), Hepatic function abnormal (124), Liver function test abnormal (119), Aspartate aminotransferase increased (110), Autoimmune hepatitis (99), Hepatic pain (98), Gamma-glutamyltransferase increased (86), Liver function test increased (79), Transaminases increased (72), Ascites (60).
- Time to event onset (n = 876 events) , range: <24 hours to 177 days, median: 7 days.
- Duration of relevant events (n = 120 out of 1425 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 210 days, median: 23 days.
- Relevant event outcome: fatal (23), resolved/resolving (426), resolved with sequelae (46), not resolved at the time of reporting (343), and unknown (586).
    - In 22 cases with fatal outcome (reporting 23 relevant events with fatal outcome), the reported causes of death were coded to Ascites (5), Congestive hepatopathy, Hepatic function abnormal, Hepatic pain, Hypertransaminasaemia (2 each), Alanine aminotransferase increased, Autoimmune hepatitis, Blood bilirubin increased, Hepatic enzyme increased, Hepatic mass, Hepatomegaly, Hepatosplenomegaly, Hypoalbuminaemia, Liver function test abnormal, and Liver injury (1 each). Of note, in 6 cases limited information regarding the cause of death was provided (Alanine aminotransferase increased, Ascites, Hepatic mass, Hepatic pain,

Hypertransaminasaemia, Liver injury (1 each). Most (13 of 22 cases) of the fatal cases involved subjects who were ≥60 years of age.

When the medical history was provided (13 cases), the relevant medical conditions included Hepatic steatosis, Type 2 diabetes mellitus (3 each), Diabetes mellitus (2), Autoimmune hepatitis, and Hepatic function abnormal (1 each).

Analysis by age group

- Post-marketing: Paediatric (66), Adults (712), Elderly (243) and No data (70).
    - Among the frequently (≥2%) reported relevant hepatic events, Hepatic pain was reported significantly higher in the adult population when compared to elderly population (25.5% in adult vs 6.3% in elderly). Upon further review, the majority of the events of hepatic pain were assessed as non-serious in the adult population (63 of 84 events).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 265 (24.3% of the CT and PM cases reporting hepatic AESIs).
    - The reporting proportion of hepatic AESIs with fatal outcome (2.1%) is slightly higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (1.4%).

O/E analysis

- O/E analysis was performed for Acute liver injury/Liver injury and Autoimmune hepatitis. All O/E ratios were <1.

MAH's conclusion

A cumulative review of Autoimmune hepatitis has been performed. No other safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Please refer regarding autoimmune hepatitis to section 2.2 Signal evaluation of this AR (a causal association between Comirnaty and autoimmune hepatitis cannot be concluded based on the available information).

No new important safety concern could be identified for hepatic AESIs. For future PSURs in the section 'Evaluation of AESIs', the hepatic 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**

Immune-mediated/autoimmune AESIs

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

Clinical Trial Data

- Number of cases: 19 (BNT162b2 [17] and blinded therapy [2] (2.8% of 668 cases, the total CT dataset) compared to 20 cases (2.8%) retrieved in the PSUR #2. All SAEs were assessed as not related to BNT162b2 or blinded therapy.

Post-authorization data

- Number of cases: 11,726 (2.3% of 507,683 cases of the total PM dataset), compared to 21,994 cases (3.3%) retrieved in the PSUR #2.
- MC cases (4822), NMC cases (6904).
- Country of incidence: Germany (3094), France (1474), UK (1038), US (718), Italy (582), Japan (490), Australia (461), Netherlands (370), Austria (362), Sweden (250), Belgium (237), Norway (230), Greece (229), Finland (216), Poland, Spain (184 each), Taiwan, Province of China (156), Canada (145), New Zealand (125); the remaining 1181 cases were distributed among 64 countries.
- Subjects' gender: female (7678), male (3661), and unknown (387).
- Subjects' age in years (n = 10,827), range: 5 – 98, mean: 47.5, median: 47.0.
- Medical history (n = 4887): the most frequently (≥150 occurrences) reported relevant medical conditions were coded to the PTs Seasonal allergy (400), Asthma (378), Drug hypersensitivity (317), Hypersensitivity (306), Psoriasis (269), Hypothyroidism (252), Autoimmune thyroiditis (237), Food allergy (235), Diabetes mellitus (186), and Colitis ulcerative (158).
- COVID-19 Medical history (n = 507): the reported medical conditions were coded to the PTs COVID-19 (382), Suspected COVID-19 (115), COVID-19 pneumonia (11), Post-acute COVID-19 syndrome (6), Coronavirus infection (4), SARS-CoV-2 test positive (3), and Asymptomatic COVID-19 (2).
- Co-suspects (n = 460): the most frequently (≥10 occurrences) reported relevant co suspects were adalimumab (168), COVID-19 vaccine MRNA (MRNA 1273) (36), influenza vaccine (26), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (19), influenza vaccine inact split 4V, and Risankizumab (13 each).
- Number of relevant events: 12,795.
- Relevant event seriousness: serious (8445) and non-serious (4356).
- Most frequently reported relevant PTs (≥2%): Hypersensitivity (2393), Psoriasis (660), Thrombocytopenia (487), Polymyalgia rheumatica (431), Dermatitis (305), Rheumatic disorder (286), and Alopecia areata (281).
- Time to event onset (n = 7591), range: □24 hours to 499 days, median: 6 days.
- Duration of relevant events (n = 969 out of 2334 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 419 days, median 14 days.
- Relevant event outcome: fatal (133), resolved/resolving (3786), resolved with sequelae (664), not resolved at the time of reporting (4934), and unknown (3304).
    - In 112 cases (reporting 133 relevant events with a fatal outcome), the reported causes of death (≥5 occurrences) were coded to the PTs Thrombocytopenia (19), Death, Interstitial lung disease (13 each), Haemophagocytic lymphohistiocytosis, Immune thrombocytopenia (8 each), Cerebral haemorrhage, Encephalitis, Multiple organ dysfunction syndrome, Renal failure (7 each), Pneumonia, Respiratory failure (6 each), and Pulmonary embolism (5). Of note, in 13 cases limited information regarding the cause of death was provided (PT Death). Most (78 of 104 cases that provided age) of the fatal cases involved elderly subjects. When the medical history was provided (67 cases), significant medical conditions reported in more than 3 cases included

Hypertension (23), Atrial fibrillation (9), Osteoporosis (7), Dyslipidaemia (6), Diabetes mellitus, Hyperlipidemia, Type 2 diabetes mellitus (5 each), Hypothyroidism, Myocardial infarction, Radiotherapy, and Thrombocytopenia (4 each).

Analysis by age group

- Clinical trial: Paediatric (5), Adults (11), and Elderly (3). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (591), Adults (8319), Elderly (2125) and Unknown (691).
    - Among the frequently (>2%) reported immune mediated/autoimmune AESIs, a higher reporting proportion of events coded to the PT Polymyalgia rheumatica were observed in the elderly population when compared to paediatric and adult populations (none in paediatrics vs 1.7% in adults vs 12.9% in elderly).

      A higher reporting proportion of events coded to the PTs Hypersensitivity and Alopecia areata were observed in the paediatric and adult populations when compared to the elderly population (Hypersensitivity [24.2% in paediatrics vs 20.8% in adults vs 11.8% in elderly], Alopecia areata [3.6% in paediatrics vs 2.7% in adults vs 0.9% in elderly]).

      A higher reporting proportion of events coded to the PTs Psoriasis and Rheumatic disorder were observed in the adult and elderly populations when compared to the paediatric population (Psoriasis [2.2% in paediatrics vs 5.8% in adults vs 5.9% in elderly], Rheumatic disorder [0.5% in paediatrics vs 2.3% in adults vs 3.4% in elderly]).

      A higher reporting proportion of events coded to the PT Thrombocytopenia were observed in the paediatric and elderly populations when compared to the adult population (8.8% in paediatrics vs 3.3% in adults vs 6.3% in elderly).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3199 (27.2% of the CT and PM cases reporting immune mediated/autoimmune AESIs).
    - The reporting proportion of immune mediated/autoimmune AESIs with a fatal outcome (2.6%) is higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (0.6% of events with fatal outcome).

O/E analysis

- O/E analysis was performed for Acute disseminated encephalomyelitis (ADEM), ADEM and encephalitis, Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus. All O/E ratios were <1.

MAH's conclusion

Polymyalgia rheumatica, Uveitis and Subacute Thyroiditis (SAT) were evaluated as signals in the reporting period and determined not to be risks. No new safety signals have emerged based on a review of the remaining events and on O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Please refer regarding polymyalgia rheumatica, uveitis and subacute thyroiditis to section 2.2 Signal evaluation of this AR.

Immune-mediated/autoimmune AESIs were continuously monitored in the 13th and 14th SSRs (through 15 Apr 2022) for Comirnaty during the reporting period.

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

Multisystem Inflammatory Syndrome in Children / Adults

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

Rapporteur assessment comment:

The amended the search strategy since the initial signal evaluation was considered acceptable by PRAC (13th SSR; EMEA/H/C/005735/MEA/002.12), because no additional MIS-C/A cases were identified using the extended search strategy.

Clinical Trial Data

- No serious cases from the CT dataset were reported. For comparison, 2 cases (0.3%) were retrieved in the PSUR #2.

Post-authorization data

- Number of relevant cases: 207 (0.04% of 507,683 cases in the total PM dataset), compared to 438 (0.07%) retrieved in PSUR #2.
- MC cases (170), NMC cases (37).
- Country of incidence (≥5 occurrences): France (55), Germany (27), UK (18), Australia (15), US (14), Japan (12), Norway (6), Spain (5); the remaining 55 cases were distributed among 30 countries.
- Subjects' gender: female (92), male (109), unknown (6).
- Subjects' age in years (n = 196), range: 3 – 95, mean: 46.6, median: 50.
- Medical history (n = 132): the most frequently (≥5 occurrences) reported medical conditions included the PTs Hypertension (40), Obesity (11), Diabetes mellitus (9), Ex-tobacco user, Hypothyroidism (8 each), Atrial fibrillation, Tobacco user, Type 2 diabetes mellitus (7 each), Alcohol use, Osteoporosis, Pyrexia, Sleep apnoea syndrome (6 each), Asthma, Non-tobacco user, Prostate cancer, and Rheumatoid arthritis (5 each).
- COVID-19 medical history (n = 19): PTs COVID-19 (15), Suspected COVID-19 (3), Asymptomatic COVID-19 (1).
- Co-suspects (n = 16 cases): COVID-19 vaccine mRNA (mRNA 1273) (2), carboplatin, cefotaxime, ciclosporin, colchicine, COVID-19 vaccine, eltrombopag, enoxaparin, everolimus, mesalazine, methotrexate, pembrolizumab, pemetrexed, rituximab, treprostinil (1 each).
- Number of relevant events: 210.
- Relevant event seriousness: serious (210).
- Relevant PTs: Multiple organ dysfunction syndrome (82), Multisystem inflammatory syndrome (43), Multisystem inflammatory syndrome in children (38), Systemic inflammatory response

syndrome (32), Multisystem inflammatory syndrome in adults (10), Cytokine release syndrome (5).

- Time to event onset (n = 115), range: <24 hours to 234 days, median: 15 days.
- Duration of relevant events (n = 12 out of 39 occurrences with outcome of resolved or resolved with sequelae), range: 3 days to 57 days, median: 16 days.
- Relevant event outcome: fatal (57), resolved/resolving (61), resolved with sequelae (3), not resolved (20), unknown (72).
    - In 56 cases (reporting 57 relevant events with fatal outcome), the reported causes of death (≥5 occurrences) were coded to Multiple organ dysfunction syndrome (55), Septic shock (10), Renal failure (9), Immunisation, Sepsis (8 each), Pneumonia (7), Acute respiratory distress syndrome (6), Acute kidney injury, Cardiac arrest, COVID-19, COVID-19 pneumonia, Drug ineffective, Hepatic failure, Respiratory failure, and Vaccination failure (5 each).

      Most (35 of 56 cases) of the fatal cases involved elderly subjects. When the medical history was provided (43 cases), the most frequently (≥3 occurrences) medical conditions included Hypertension (19), Diabetes mellitus, Obesity (6 each), COVID-19 (5), Atrial fibrillation, Ex-tobacco user, Hypothyroidism, Osteoarthritis, Renal transplant, and Tobacco user (3 each).

Analysis by age group

- Post-marketing: Paediatric (46 [16 Child, 30 Adolescent]), Adult (84), Elderly (69), Unknown (8).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 73 (35.3% of the 207 cases reporting Multisystem Inflammatory Syndrome AESIs).
    - Of the PM cases that reported medical histories, the percentage of cases with a fatal Multisystem Inflammatory Syndrome AESI is higher in subjects with comorbid conditions (60.5%) when compared to the percentage of cases with a fatal Multisystem Inflammatory Syndrome AESI in subjects without comorbidities (39.5%).
    - Upon review of the relevant events in PM cases that recorded medical histories, no Multisystem Inflammatory Syndrome AESIs had a significant proportional reporting ratio of >3:1 in subjects with comorbidities compared to subjects without comorbidities.

O/E analysis

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

Table 10. 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,53]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Age											
≤11 years	2.77	12	1,917,834	53.1	0.226	0.117, 0.395	12	2,779,982	77.0	0.156	0.081, 0.272
12-17 years	2.77	31	3,324,066	92.1	0.337	0.229, 0.478	40	5,127,186	142.0	0.282	0.201, 0.384
18-20 years	1.50	7	2,028,811	30.4	0.230	0.092, 0.474	9	3,204,508	48.1	0.187	0.086, 0.355
21-24 years	0.23	7	2,705,081	6.2	1.125	0.452, 2.318	8	4,272,677	9.8	0.814	0.351, 1.604
25-49 years	0.58	54	19,546,111	113.4	0.476	0.358, 0.622	57	30,991,113	179.7	0.317	0.240, 0.411
50-59 years	1.47	29	9,025,268	132.7	0.219	0.146, 0.314	34	14,461,569	212.6	0.160	0.111, 0.223
60-69 years	3.38	36	7,901,305	267.1	0.135	0.094, 0.187	46	12,856,855	434.6	0.106	0.077, 0.141
70+ years	7.42	107	10,962,290	813.4	0.132	0.108, 0.159	142	17,896,776	1,327.9	0.107	0.090, 0.126
Gender											
Males	2.36	147	26,983,060	636.8	0.231	0.195, 0.271	179	43,047,613	1,015.9	0.176	0.151, 0.204
Females	2.36	136	30,427,706	718.1	0.189	0.159, 0.224	169	48,543,053	1,145.6	0.148	0.126, 0.172

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

- As in the most recent SBSR #3, the 21-24 years age group using the 21-day risk window meets the signal criteria with an O/E ratio >1, however, the result if not statistically significant as the 95% CI includes 1.

  MIS is a condition known to be associated with COVID-19. The MAH's COVID-19 vaccine requires the first two doses to be spaced 21 days apart before achieving optimal effectiveness. It is possible that COVID-19 may occur within the 21-day window between doses. Additionally, general awareness of MIS is currently increased because of COVID-19, leading to possible stimulated reporting. The ACCESS background rates used for the MIS analysis are primarily based on codes for Kawasaki disease and may mis-charaterize background rates of true MIS cases in the presence of COVID-19 infections.

MAH's conclusion

Cases of potential MIS in adults (MIS-A) and children (MIS-C) reported during this interval period are assessed in Appendix 6A.4 of the PSUR.

During the reporting period, an article including important safety information on MIS-C was reviewed.

No new safety signals have emerged based on a review of these cases, literature or of the O/E analysis. The MAH will continue to monitor MIS

Rapporteur assessment comment:

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

During the interval period, the MAH reported post-marketing 207 relevant MIS-C/ -A cases. However, in Appendix 6A.4 of the PSUR the MAH reported 199 MIS-C/ -A cases during the interval period. The MAH is requested to explain this discrepancy in the numbers of retrieved MIS-C/ -A cases. **Request for supplementary information**

The study of Ouldali et al. was discussed in the 13th (2nd bi-monthly) SSR (procedure EMEA/H/C/005735/MEA/002.12). No new safety concern was identified.

In the O/E analyses for multisystem inflammatory syndrome, the O/E ratio was elevated (O/E ratio 1.1, 95% CI 0.5;2.3) for the 21-day risk window in the 21-24 years age group.

Provided MAH's response regarding the Requests for supplementary information for MIS-C/ -A, no new important safety concern could be identified for multisystem inflammatory syndrome in children / adults.

Musculoskeletal AESIs

Search Criteria: *PTs Arthralgia; Arthritis; Chronic fatigue syndrome; Juvenile idiopathic arthritis ; Polyarthritis; Post viral fatigue syndrome; Rhabdomyolysis; Rheumatoid arthritis*.

Clinical Trial Data

- Number of cases: 6 (BNT162b2) (0.9% of 668 cases, the total CT dataset) compared to 4 cases (0.6%) retrieved in the PSUR #2. Not related to BNT162b2.

Post-authorization data

- Number of relevant cases: 31,012 (6.1% of 507,683 cases, the total PM dataset), compared to 58,250 cases (8.9 %) retrieved in the PSUR #2.
- Relevant PTs: Arthralgia (29,429), Arthritis (996), Rheumatoid arthritis (660), Chronic fatigue syndrome (219), Polyarthritis (145), Post viral fatigue syndrome (92), Rhabdomyolysis (78), Juvenile idiopathic arthritis (14).

Analysis by age group

- Clinical trial: Adult (1) and Elderly (5).
- Post-marketing: Paediatric (664), Adult (25,307), Elderly (3469), Unknown (1572).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 3193 (10.3% of the cases reporting musculoskeletal AESIs).

O/E analysis

- O/E analysis was performed for Chronic fatigue syndrome/ME/PVFS, Rhabdomyolysis, Rheumatoid arthritis, polyarthritis, juvenile idiopathic arthritis. All O/E ratios were <1.

MAH's conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. The majority of the events reported in this category are arthralgia which is considered to be an adverse reaction for the vaccine and is labelled as such. Arthralgia will be removed from the search strategy in the next PSUR. Safety surveillance will continue.

Rapporteur assessment comment:

MAH's proposal to remove arthralgia from the search strategy for musculoskeletal AESIs in the next PSUR is endorsed because the majority of the musculoskeletal events reported are arthralgia which is labelled in the ADR table in section 4.8 of the Comirnaty SmPC (frequency very common).

Musculoskeletal AESIs were continuously monitored in the 13th and 14th Comirnaty SSRs (through 15 Apr 2022) during the reporting period.

No new important safety concern could be identified for musculoskeletal AESIs. For future PSURs in the section 'Evaluation of AESIs', the musculoskeletal 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**

Myocarditis and Pericarditis AESIs

Rapporteur assessment comment:

Please refer to the section 2.3 'Evaluation of important Identified Risks' of this assessment report.

Neurological AESIs (including demyelination)

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

Clinical Trial Data

- Number of cases: 15 cases (BNT162b2 [11], blinded therapy [4]; 2.2% of 668 cases in the total CT dataset) compared to 7 cases (0.97%) retrieved in the PSUR #2. None of these SAEs were assessed as related to BNT162b2/blinded therapy.

Post-authorization data

- Number of relevant cases: 5111 (1.0% of 507,683 cases in the total PM dataset), compared to 7197 cases (1.1%) retrieved in the PSUR #2.

Analysis by age group

- Clinical trial: Paediatric (Infant [2], Child [4]), Adult (6), Elderly (3).
- Post-marketing: Paediatric (523 [162 Child, 361 Adolescent]), Adult (3574), Elderly (787), Unknown (227).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 1201 (23.5% of the 5111 cases reporting Neurological AESIs).

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.

MAH's conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Neurological AESIs were continuously monitored in the 13th and 14th Comirnaty SSRs (through 15 Apr 2022) during the reporting period.

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

Other AESIs

Search Criteria: *HLT (All Path) Herpes viral infections OR PTs Adverse event following immunisation; Appendicectomy; Appendicitis; Appendiceal abscess; Appendicitis perforated; Complicated appendicitis; Deafness; Deafness bilateral; Deafness neurosensory; Deafness permanent; Deafness transitory; Deafness unilateral; Hypoacusis; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Occupational exposure to communicable disease; Patient isolation;*

Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive; Sudden hearing loss.

Clinical Trial Data

- Number of cases: 26 (BNT162b2 [22], blinded therapy [3] and placebo [1]) (3.9% of 668 cases, the total CT dataset) compared to 2 cases (0.28%) retrieved in the PSUR #2. None of the SAEs were assessed as related to BNT162b2 or blinded therapy or placebo.

Post-authorization data

- Number of relevant cases: 68,548 (13.5% of 507,683 cases, the total PM dataset), compared to 118,843 cases (18.1%) retrieved in the PSUR #2.
- Most frequently reported relevant PTs (≥ 50 occurrences): Pyrexia (57,474), Herpes zoster (6216), Inflammation (1585), Oral herpes (794), Hypoacusis (744), Deafness (488), Sudden hearing loss (370), Herpes virus infection (297), Appendicitis (254), Deafness unilateral, Ophthalmic herpes zoster (222 each), Herpes simplex (206), Adverse event following immunisation (188), Genital herpes (163), Herpes ophthalmic (70), Deafness neurosensory (63), Herpes zoster oticus (61), Herpes zoster reactivation, and Varicella (59 each).

Analysis by age group

- Clinical trial: Adult (14), Paediatric (10), Elderly (2).
- Post-marketing: Paediatric (5092), Adult (53,918), Elderly (6771), and Unknown (2767).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 5215 (7.6 % of the cases reporting other AESI).

O/E analysis

- O/E analysis was performed on Appendicitis, Herpes zoster and Sudden hearing loss. All O/E ratios were <1.

MAH's conclusion

Hearing loss and Appendicitis was evaluated as a signal during the reporting period. No other safety signals than those mentioned have emerged based on the review of these cases, or from the O/E analysis. No risks have been identified following the evaluations of appendicitis and hearing loss. Safety surveillance will continue.

Rapporteur assessment comment:

Regarding hearing loss please refer to the assessment in section 2.2.1.1 Post-approval regulatory requests of this AR above.

Regarding Appendicitis please refer to the assessment in section 2.2.2.1 Signals determined not to be risks of this AR above.

Other AESIs were continuously monitored in the 13th and 14th Comirnaty SSRs (through 15 Apr 2022) during the reporting period.

No new important safety concern could be identified for other AESIs. For future PSURs in the section 'Evaluation of AESIs', the other 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**

Pregnancy related AESIs

Rapporteur assessment comment: Please refer to the assessment in section 'Use in pregnant/lactating women' in this AR below.

Glomerulonephritis and Nephrotic Syndrome AESIs

Search Criteria: *HLT Glomerulonephritis and nephrotic syndrome*.

The PTs Acute kidney injury and Renal failure have been removed from the search criteria and replaced with a more focused search of glomerulonephritis and nephrotic syndrome based on the evolving pharmacovigilance and medical literature. An evaluation of IgA nephropathy, as requested by EMA in the PSUR 2 assessment report is ongoing and will be provided to EMA under separate cover from the PSUR.

Clinical Trial Data

- No serious cases from the CT dataset were reported. No comparison with PSUR #2 is possible due to the change in the search criteria.

Post-authorization data

- Number of cases: 276 (0.05% of 507,683 cases, the total PM dataset). No comparison with PSUR #2 is possible.
- MC cases (172), NMC cases (104).
- Country of incidence: Germany (74), Japan (50), France (29), Australia (13), Italy, UK (11 each); the remaining 88 cases were distributed among 28 countries.
- Subjects' gender: female (150), male (124) and unknown (2).
- Subjects' age in years (n = 270), range: 5 – 88, mean: 44.2, median: 43.0.
- Medical history (n = 148): the most frequently (≥5 occurrences) reported relevant medical conditions included Hypertension (25), Nephrotic syndrome (12), Hypercholesterolaemia (8), Dyslipidaemia, Glomerulonephritis, Haematuria, IgA nephropathy (7 each), Proteinuria (6).
- COVID-19 Medical history (n = 10): COVID-19 (7), Suspected COVID-19 (2), COVID-19 pneumonia (1).
- Co-suspects (n = 3 cases): the reported relevant co-suspect medications included Hepatitis A vaccine, Influenza vaccine, and Tocilizumab (1 each).
- Number of relevant events: 323.
- Relevant event seriousness: serious (318), non-serious (5).
- Most frequently reported relevant PTs: Nephrotic syndrome (99), IgA nephropathy (47), Glomerulonephritis (46), Glomerulonephritis minimal lesion (25), Granulomatosis with polyangiitis (22), Microscopic polyangiitis (14), Glomerulonephritis membranous (12), Focal segmental glomerulosclerosis, and Glomerulonephritis rapidly progressive (10 each).
- Time to event onset (n = 172), range: <24 hours to 172 days, median: 12 days.
- Duration of relevant events (n = 12 out of 323 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 137 days, median 48 days.

- Relevant event outcome: fatal (2), resolved/resolving (95), resolved with sequelae (23), not resolved (111), unknown (92).

  In 2 cases (reporting 2 relevant events with fatal outcome), the reported causes of death were coded to Glomerulonephritis and Granulomatosis with polyangiitis (1 each). Both fatal cases involved elderly subjects. Medical history was provided in both cases and included Autoimmune hypothyroidism, Hypertension and Obesity (1 each).

Analysis by age group

- Post-marketing: Paediatric (33), Adult (177), Elderly (62) and Unknown (4).
- Among the frequently (≥2%) reported relevant events Glomerulonephritis and Nephrotic Syndrome AESIs, the PT Renal failure was reported significantly higher in elderly population when compared to adult population (2.8% in adults vs 8.4% in elderly). A higher reporting proportion of events coded to the PTs Haematuria and IgA nephropathy were observed in the adult population when compared to the elderly population (Haematuria [10.4% in adults vs 2.1% in elderly] and IgA nephropathy [11.1% in adults vs 1.1% in elderly]). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 14 (5.1% of the cases reporting Glomerulonephritis and nephrotic syndrome AESIs).
- The reporting proportion of Glomerulonephritis and nephrotic syndrome AESIs with fatal outcome is 0.4 % in subjects without comorbid conditions. There were no fatal outcomes in the subjects with comorbidities.

O/E analysis

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

MAH's conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. The ongoing evaluation of IgA nephropathy will be submitted separately from the PSUR. Safety surveillance will continue.

Rapporteur assessment comment:

Regarding the assessment of the cumulative review IgA nephropathy please refer to section 2.2 'Signal evaluation' of this AR above.

During the reporting interval, retrieved were 46 glomerulonephritis cases which is considered an increase compared with the 27 glomerulonephritis cases from the previous reporting period. Therefore, the MAH is requested to provide detailed information concerning the 46 cases with glomerulonephritis in the interval period and perform an WHO-UMC causality assessment per case, and to provide an updated review with DLP 14 Nov 2022 of cases reporting glomerulonephritis from their safety database including a WHO-UMC causality assessment per case regarding Comirnaty exposure. **Request for supplementary information**

Respiratory AESIs

Search Criteria: *HLTs (All Path) Lower respiratory tract infections NEC; Respiratory failures (excl. neonatal); Viral lower respiratory tract infections OR PTs Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Respiratory disorder.*

Clinical trial data

- Number of cases: 33 (Blinded therapy [10], BNT162b2 [23]) (4.9 % of 668 cases, the total CT dataset) compared to 38 cases (5.3%) retrieved in the PSUR #2. All were assessed as not related to BNT162B2 or blinded therapy.

Post-authorisation data

- Number of cases: 2188 (0.4% of 507,683 cases, the total PM dataset), compared to 3356 cases (0.51%) retrieved in the PSUR #2.
- Most frequently reported relevant PTs (≥ 100 occurrences): Pneumonia (809), Respiratory disorder (325), Bronchitis (303), Respiratory failure (213), Lower respiratory tract infection (175), Cardio-respiratory arrest (140), and Hypoxia (133).

Analysis by age group

- Clinical trial: Paediatric (8), Adult (12) and Elderly (13).
- Post-marketing: Paediatric (83), Adult (1168), Elderly (836) and Unknown (101).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 113 (5.16 % of the cases reporting respiratory AESIs).

O/E analysis

O/E analysis was performed for Acute respiratory distress syndrome: all O/E ratios were below 1.

MAH's conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue. Respiratory events were originally included in the AESI list in order to capture potential cases of respiratory failure that may occur in cases of severe COVID-19. The search strategy will be amended to focus on acute respiratory distress syndrome and respiratory failure for the next PSUR.

Rapporteur assessment comment:

No new important safety concern could be identified for respiratory AESIs. For future PSURs in the section 'Evaluation of AESIs', the respiratory 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**

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: 19 cases (BNT162b2 [18], blinded therapy [1]; 2.8% of 668 cases in the total CT dataset) compared to 19 cases (2.6%) retrieved in the PSUR #2. None of the SAEs were assessed as related to BNT162b2/blinded therapy.

Post-authorisation data

- Number of cases: 3091 (0.6% of 507,683 cases in the total PM dataset), compared to 4834 cases (0.7%) retrieved in the PSUR #2.
- Most frequently (>25 occurrences) reported relevant PTs: Cerebrovascular accident (1363), Cerebral infarction (416), Ischaemic stroke (367), Cerebral haemorrhage (306), Cerebral venous sinus thrombosis (166), Cerebral thrombosis (93), Cerebral ischaemia (76), Subarachnoid haemorrhage (72), Cerebral venous thrombosis (68), Cerebellar infarction (42), Brain stem infarction, Haemorrhage intracranial (35 each), Ischaemic cerebral infarction (33), Embolic stroke (31), Haemorrhagic stroke (29), Thalamic infarction (26).

Analysis by age group

- Clinical trial: Adult (6), Elderly (13).
- Post-marketing: Paediatric (33 [9 Child, 24 Adolescent]), Adult (1575), Elderly (1352), Unknown (131).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 719 (23.3% of the 3091 cases reporting stroke-related events).

O/E analysis

- O/E analysis was performed for Cerebral venous sinus thrombosis, Ischemic stroke and Hemorrhagic stroke. For the CVST analysis, males and females 18-24 years, males and females 25-49 years, females 60-69 years, and overall dose 2 using the low background rate meet the signal criteria with an O/E ratio greater than 1 in either the 21-day 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, all stratifications have an O/E ratio less than 1. The O/E were similar to the most recent SBSR #3.

MAH's conclusion

Cerebral venous sinus thrombosis (CVST) and Cerebrovascular Accident (CVA)/Stroke were evaluated as signals during the reporting period and were not determined to be risks causally associated with the vaccine. No additional safety signals other than those mentioned above have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Regarding cerebral venous sinus thrombosis (CVST) please refer to section 2.2. 'Evaluation of closed signals' of this AR above.

Stroke was continuously monitored in the 13th and 14th Comirnaty SSRs (through 15 Apr 2022) during the reporting period, and concerning cerebrovascular accident (CVA)/stroke/ cerebral venous sinus thrombosis (CVST) no new important safety information could be identified.

In the age-stratified analysis, some of the O/E ratios (incl. 95% CI) were >1 (not in paediatric persons), this was only seen when applying the low background rates. Using the mid-range background rate all O/E ratios were below 1 and similar to the O/E analyses results provided in the 14th Comirnaty SSR.

No new important safety concern could be identified for stroke.

Sudden Death

Rapporteur assessment comment:

Please refer to 'Death' in section 'Evaluation of special situations' of this AR below.

Thromboembolic AESIs

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

Clinical trial data

- Number of cases: 17 (BNT162b2 [16], blinded therapy [1]; 2.5% of 668 cases in the total CT dataset) compared to 15 cases (2.1%) retrieved in the PSUR #2. None of these SAEs were assessed as related to BNT162b2/blinded therapy.

Post-authorisation data

- Number of cases: 6102 (1.2 % of 507,683 cases in the total PM dataset), compared to 6507 cases (1.0%) retrieved in the PSUR #2.
- Most frequently (≥50 occurrences) reported relevant PTs: Pulmonary embolism (2068), Thrombosis (1461), Deep vein thrombosis (1321), Thrombophlebitis (285), Venous thrombosis limb (276), Superficial vein thrombosis (258), Venous thrombosis (173), Coagulopathy (164), Retinal vein occlusion (127), Embolism (103), Pulmonary thrombosis (77), Ophthalmic vein thrombosis (74), Retinal vein thrombosis (54), Retinal artery occlusion (52), Portal vein thrombosis (50).

Analysis by age group

- Clinical trial: Adults (12), Elderly (5).
- Post-marketing: Paediatric (79 [7 Child, 72 Adolescent]), Adults (3833), Elderly (1966), Unknown (224). The reporting proportion of the PT Coagulopathy was significantly higher in the paediatric population (11.4%) when compared to the adult and elderly populations (2.7% and 2.1%, respectively).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1356 (22.2% of the 6102 cases reporting thromboembolic AESIs).

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 safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Thromboembolic AESIs were continuously monitored in the 13th and 14th Comirnaty SSRs (through 15 Apr 2022) during the reporting period.

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

Vasculitic events

Search criteria: *HLT (All Path) Vasculitides OR PTs Microangiopathy; Peripheral ischaemia*.

Clinical trial data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 612 (0.12% of 507,683 cases, the total PM dataset), compared to 854 cases (0.13%) retrieved in the PSUR #2.
- Most frequently reported relevant PTs (≥20 occurrences): Vasculitis (267), Giant cell arteritis (102), Henoch-Schonlein purpura (66), Peripheral ischaemia (60).

Analysis by age group

- Post-marketing: Paediatric (62), Adults (317), Elderly (208) and Unknown (25).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 224 (36.6 % of the PM cases reporting vasculitic events).

O/E analysis

- O/E analysis was performed for Behcet's syndrome, Giant cell arteritis, Henoch-Schonlein purpura, Limb ischaemia, and Vasculitis.

MAH's conclusion

Vasculitis was evaluated as signal during the reporting period and was determined to not be a risk. No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

An updated cumulative review of vasculitis (through 15 Apr 2022) was assessed in the 14th (3rd bi-monthly) SSR (reporting period 16 Feb 2022 – 15 Apr 2022; procedure EMEA/H/C/005735/MEA/002.13). The MAH had provided an updated review of vasculitis and included WHO-UMC causality assessments for the relevant vasculitis cases. Given that the O/E ratios are <1, only two probable cases were identified and no relevant literature was available, PRAC agreed that based on the data provided no safety concern was identified.

No new important safety concern could be identified for vasculitic events. For future PSURs in the section 'Evaluation of AESIs', the vasculitic events 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**

AESIs in subjects with Malnutrition; HIV infection

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.

Search criteria - *PT Decode (History): Acute HIV infection; Asymptomatic HIV infection; Congenital HIV infection; HIV infection; HIV infection CDC Group I; HIV infection CDC Group II; HIV infection CDC Group III; HIV infection CDC Group IV subgroup A; HIV infection CDC Group IV subgroup B; HIV infection CDC Group IV subgroup C1; HIV infection CDC Group IV subgroup C2; HIV infection CDC Group IV subgroup D; HIV infection CDC Group IV subgroup E; HIV infection CDC category A; HIV infection CDC category B; HIV infection CDC category C; HIV infection CDC group IV; HIV infection WHO clinical stage I; HIV infection WHO clinical stage II; HIV infection WHO clinical stage III; HIV infection WHO clinical stage IV; Malnutrition; Perinatal HIV infection; Prophylaxis against HIV infection; Tuberculosis*.

Clinical trial data

- Number of cases: 11 (blinded therapy [2], BNT162b2 [9]) (1.6% of 668 cases, the total CT dataset, compared to 7 cases (1.0%) retrieved in the PSUR #2.
- Reported PTs (16): Condition aggravated, Maternal exposure during pregnancy , Mental disorder (2 each), Atrial fibrillation, Cephalo-pelvic disproportion, Constipation, Craniocerebral injury, Failed trial of labour, Headache, Intestinal obstruction, Lumbar spinal stenosis, Prostate cancer, and Spinal claudication (1 each). None of the events were related to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 197 (0.04% of 507,683 cases, the total PM dataset), compared to 393 cases (0.06%) retrieved in the PSUR #2.

  Patients with pre-existing HIV Infection:

  - 107 cases (0.02% of 507,683 cases, the total PM dataset).

  Patients with pre-existing tuberculosis:

  - 67 cases (0.01% of 507,683 cases, the total PM dataset).

  Patients with pre-existing malnutrition:

  - 23 cases (<0.01% of 507,683 cases, the total PM dataset).

MAH's conclusion

No safety signals have emerged based on the review of these cases. Safety surveillance will continue.

Rapporteur assessment comment:

Based on the data presented concerning individuals with pre-existing HIV infection, with pre-existing tuberculosis, or with pre-existing malnutrition, no new important safety concern could be identified.

Clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2

Data are available from 3 analyses: children 2 to <5 years and children 6 months to <2 years receiving up to 3 primary doses of BNT162b2 3 µg, and adults 18-55 years receiving a fourth dose booster of either the current vaccine or a monovalent Omicron-modified vaccine.

Children 6 months to <2 years (from C4591007)

- Subgroups of Phase 2/3 pediatric participants 6 months to <2 years of age had similar reactogenicity, with regard to **local reactions** and **systemic events**, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution.
- There were no meaningful differences in the overall patterns of local reactions and of systemic events across these subgroups.

Children 2 to <5 years (from C4591007)

Subgroups of Phase 2/3 pediatric participants 2 to <5 years of age had similar reactogenicity, with regard to **local reactions** and **systemic events**, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution.

There were no meaningful differences in the overall patterns of local reactions and of systemic events across these subgroups.

Adults 18 through 55 years (from C4591031 Substudy D)

- Any local reactions reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI (78.6%) and BNT162b2 (79.4%) groups, and most events were mild or moderate in severity. No Grade 4 local reactions were reported.
- Any systemic events reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI (77.6%) and BNT162b2 (72.9%) groups, and most events were mild or moderate in severity. No Grade 4 systemic events were reported.
- The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the local reactions and of the systemic events by SARS-CoV-2 baseline status were not considered clinically meaningful.

Rapporteur assessment comment:

No new important safety concern could be identified based on the data presented regarding reactogenicity on individuals previously exposed or not to SARS-COV-2.

Local adverse reactions

Search criteria: *PTs Erythema; Injection site erythema; Injection site pain; Injection site swelling; Swelling.*

Clinical trial data

- No serious clinical trial cases of local reactions reported during the reporting interval; no cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 8,597 (1.7% of 507,683 cases, the total PM dataset), compared to 21,240 cases (3.2%) retrieved in the PSUR #2.
- Most frequently reported relevant PTs (≥2%): Erythema (4137), Swelling (4036), Injection site pain (690), and Injection site swelling (212).
- Time to event onset (n = 5683) range: range: <24 hours to 366 days, median: 1 day.
- Duration of relevant events (n = 1328 out of 9440 occurrences with outcome of resolved/resolved with sequelae), range = <24 hours to 233 days, median 3 days.
- Relevant event outcome: fatal (6), resolved/resolving (4065), resolved with sequelae (99), not resolved (2582), unknown (2524).
    - There were 6 cases reporting fatal events of interest (Erythema [4 cases] and Swelling [2 case]) in elderly (4 cases) and adult (2 cases) patients. Time to onset of fatal events were < 24 hours (1 event), 1 day (1 event), 3 days (1 event), 4 days (1 event), and unknown days (2 events). Review of these cases identified additional fatal adverse events reported in these cases and the local adverse reactions were not the primary cause of death in these cases.

Analysis by age group

- Post-marketing: Paediatric (512), Adults (6972), Elderly (373) and Unknown (740). In general, the events of interest were similar by percentage across age group.

Analysis by presence of comorbidities

- Post-marketing:
    - Number of subjects with comorbidities: 38,787 (7.6% of 507,683 cases, the total PM dataset). Subjects with comorbidities were reported in (902/10.5 %) of the Local Adverse Reactions dataset. There were no differences between the group with comorbidities and the one without comorbidities.

Analysis by dose

- Post-marketing: Number of post-authorisation vaccine doses administered at the time of the event onset: Dose 1 in 2140 cases, Dose 2 in 1874 cases, Dose 3 in 2627 cases, Dose 4 in 77 case, Dose 5 in 1 case, and the dose number was not specified in 2039 cases. The majority of post-authorisation events reported across doses were similar with the exception of injection site pain being reported more frequently in the unspecified dose group.

MAH's conclusion

Local adverse reactions were reported in 8597 relevant cases representing 1.7% of the cases in the reporting period. The majority of events (79.8 %) were non-serious events with 44.9% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 9 fatal cases describing fatal local adverse reactions in 6 cases; two were in adult and 4 were elderly subjects. Three of the 9 fatal cases did not report fatal local adverse reaction events. Review of these cases indicated that there were additional fatal adverse events reported and the event of interests (Erythema, Swelling) were not the primary cause of death in these subjects. When reported, the majority onset of events occurred within to <24 hours, with durations lasting <24 hours to 7 days.

The PM data appears to differ from the clinical trial data where injection site pain is generally the most frequently reported local reactogenicity event in adults and children. However, this is considered to be an effect of coding conventions given that commonly co-reported PTs in the cases are: Pain, Pain in

extremity and Vaccination site pain. Evaluation of local adverse reaction cases did not reveal any significant new safety information. Local adverse reactions are appropriately described in the RSI. Surveillance of local adverse reactions will continue.

Rapporteur assessment comment:

During the interval period, a significant decreased number of 8,597 cases (1.7% of 507,683 cases, the total PM dataset) reporting local adverse reactions were retrieved compared to 21,240 cases (3.2% of the total PM dataset) retrieved in the previous 2nd PSUR.

Local adverse reactions are stated in the ADR table of section 4.8 of the Comirnaty SmPC. No new important safety concern could be identified for local adverse reactions. For future PSURs in the section 'Evaluation of AESIs', the local adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Systemic adverse reactions

Search criteria: *PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia*.

Clinical trial data

- Number of cases: 11 (BNT162b2 [10], and blinded therapy [1]) (1.6% of 668 cases, the total CT dataset) compared to 4 cases (0.6%) retrieved in the PSUR #2.
- Relevant PTs: Pyrexia (6), Arthralgia (3), Headache, and Myalgia (1 each), none of which were assessed as related to BNT162b2 by the investigator and Sponsor.

Post-authorisation data

- Number of cases: 167,760 (33% of 507,683 cases in the total PM dataset), compared to 279,184 (42.5% retrieved in the PSUR #2).
- Relevant event seriousness: serious (36801), non-serious (273,863).
- Relevant PTs: Headache (77,970), Fatigue (67,855), Pyrexia (57,671), Myalgia (43,916), Chills (33,541), and Arthralgia (29,430).
- Time to event onset (n = 253,501) range: <24 hours to 3654 days, median: 1 day.
- Duration of relevant events (n = 76,627 , out of which 76,067 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 1 year, 2 months 8 days, median 2 days.
- Relevant event outcome78: fatal (300), resolved/resolving (175,756), resolved with sequelae (3756), not resolved (86,147), unknown (45,676).
    - In 233 cases, the following relevant events (300) were reported as fatal: PTs Pyrexia (119), Fatigue (63), Headache (55), Chills (29), Myalgia (20), and Arthralgia (14). More than half (124 of 233 cases, 53.2%) of the cases with a fatal outcome involved elderly subjects

Analysis by age group

- Clinical trial: Paediatric (5, PTs Pyrexia [4], Myalgia [1]), Adults (1, PT Headache), Elderly (5, PTs Arthralgia [3], Pyrexia [2]). A meaningful comparison between the different age groups is not possible due to the low number of cases.

- Post-marketing: In the current reporting interval, the most frequent systemic adverse reactions in subjects 16 years of age and older (in order from highest to lowest frequencies) were PTs Headache (69,392), Fatigue (61,567), Pyrexia (48,928), Myalgia (40,707), Chills (30,837) and Arthralgia (27,333); the most frequent systemic adverse reactions in adolescents 12 through 15 years of age were PTs Headache (4485), Pyrexia (4727), Fatigue (2381), Myalgia (1164), Chills (1121), Arthralgia (614). Across the age groups in the table below, the greatest number of events were reported in the adult population, followed by the elderly. In general, relevant events were more likely to be assessed as non-serious and/or associated with a resolving outcome with increasing age. Generally, there were less relevant events associated with a worse outcome (not resolved/fatal).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 13,030 (2.6% of 508,351 cases in the total dataset and 7.8% of 167,771 [11 CT and 167,760 PM] cases reporting systemic adverse reactions).
- Clinical trial: None of the CT cases reported selected comorbidities.
- Post-marketing: The total proportion of relevant events were generally evenly distributed among subjects that reported selected comorbidities and subjects that did not report selected comorbidities. In subjects with selected comorbidities, the relevant event was more likely to be assessed as non-serious and/or with a resolved or resolving event outcome. Of note, subjects that reported comorbidities were more likely to be of advanced age, polypharmacy users, report more AEs on average (e.g., concurrent conditions) and/or prone to hospitalisation; therefore, assessment of the contributory role of BNT162b2 on the seriousness and outcome of these relevant events is confounded.

Analysis by dose

- Number of vaccine doses administered: 1 dose in 47,268 cases, 2 doses in 49,553 cases; 3 doses in 44,738 cases, 4 doses in 893 cases, and in 25,515 cases the dose was either not specified or reported as others.
- Clinical trial: Vaccination dose number: 2 doses (3), 3 doses (7) and 4 doses (1). A meaningful comparison by dose is not possible due to the low number of CT cases.
- Post-marketing: In general, the total proportion of relevant events, event seriousness, and event outcome were highest in those subjects who had received three doses of the vaccine; following this, most events were reported in those who had received two doses of the vaccine.

MAH's conclusion

Systemic adverse reactions were reported in 167,771 (11 CT and 167,760 PM) cases representing 33.0 % of the cases in the total dataset for the reporting period. The majority of events (88.2%) were non-serious events with 57.8% of the events resolved, resolved with sequelae or resolving at the time of reporting. Evaluation of systemic adverse reaction cases did not reveal any significant new safety information based on analysis by age group, by presence of comorbidities or by dose. Systemic adverse reactions are appropriately described in the RSI. Surveillance of systemic adverse reactions will continue.

Rapporteur assessment comment:

During the interval period, a decreased number of 167,760, (33% of 507,683 cases in the total PM dataset) reporting systemic adverse reactions were retrieved compared to 279,184 cases (42.5% of the total PM dataset) retrieved in the previous 2nd PSUR.

Systemic adverse reactions are stated in the ADR table of section 4.8 of the Comirnaty SmPC. No new important safety concern could be identified for systemic adverse reactions. For future PSURs in the section 'Evaluation of AESIs', the systemic adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Severe reactogenicity

Search criteria: *PT Extensive swelling of vaccinated limb*.

Clinical trial data

- There were no serious CT cases indicative of extensive swelling of vaccinated limb; no cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 1613 (0.32% of 507,683 cases, the total PM dataset), compared to 1558 cases (0.24%) retrieved in the PSUR #2.
- MC cases (196), NMC cases (1417).
- Country of incidence: Netherlands (921), Belgium (590), Iraq (26), Australia (24), UK (12), France, Germany (8 each), Philippines (5); the remaining 19 cases were distributed among 10 countries.
- Subjects' gender: female (1310), male (300) and unknown (3).
- Subjects' age in years (n = 1536), range: 7 – 94, mean: 38.3, median: 36.0.
- Medical history (n = 497): the relevant reported medical conditions included Drug hypersensitivity (24), Hypersensitivity (8), Allergic reaction to excipient, Allergy to vaccine, Reaction to preservatives (1 each).
- COVID-19 Medical history (n = 219): medical conditions reported included COVID-19 (162), Suspected COVID-19 (54), Post-acute COVID-19 syndrome (2), and SARS-CoV-2 test positive (1).
- Co-suspects (n= 17 cases): Influenza vaccine (6), Pneumococcal vaccine polysacch 23V (2).
- Number of relevant events: 1613
- Relevant event seriousness: serious (202), non-serious (1,411).
- Time to event onset (n = 1450) , range: range:<24 hours to 175 days, median: 1 day.
- Duration of relevant events (n = 375 out of 1,615 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 157 days, median 4 days.
- The reported relevant PT included Extensive swelling of vaccinated limb (1613).
- Relevant event outcome: fatal (1), resolved/resolving (910), resolved with sequelae (8), not resolved (583), unknown (112).
    - During the reporting period, 1 case was received from a Health Authority, reporting the relevant PT Extensive swelling of vaccinated limb with a fatal outcome. This case described a 14-year-old male patient who received BNT162b2 intramuscularly for COVID-19 immunisation and experienced swelling of limb. The patient also experienced

difficulty breathing (PT Dyspnoea), cyanosis (PT Cyanosis) and oedematous lower extremities (PT Oedema), all of which were reported as non-serious events. The reported cause of death was peripheral swelling. Limited information was provided in this case precluding a meaningful medical assessment, including a lack of event onset dates, event details, test results, medical history, and concomitant medications.

- A majority of the cases did not describe the type or extent of swelling and reported (verbatim) terms such as, "extensive swelling of the arm, reaction at or around the injection site, swelling limb, or extended swelling of the arm: extensive swelling of vaccinated limb". Many cases also reported additional events related to pain, warmth, or erythema at the injection site, with no additional relevant details. Most cases described localized redness or swelling limited to the injection site and/or reports of lymph node swelling with no evidence in the case detail regarding any additional extensive swelling. For those cases reporting details of swelling, most appeared limited to the area surrounding the injection site with little evidence of additional extensive swelling of the rest of the limb. In a majority of the cases reporting swelling associated with the injection site, it was not reported if treatment was required, and no case reported long lasting or permanent sequelae following the event.

Analysis by age group

- Post-marketing: Paediatric (25), Adult (1506), Elderly (65), Unknown (17). A higher reporting proportion of events coded to the PT Extensive swelling of vaccinated limb was observed in elderly versus adult population (26.5% in elderly vs 20.3% in adults). 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 by presence of comorbidities

- 51 (3.2% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (96.9%) when compared to patients with significant comorbidities. The reporting proportion of the event severe reactogenicity with the outcome of resolved/resolving (58.8%) is slightly higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (56.3% of events with resolved/resolving).

MAH's conclusion

There was a total of 1613 cases in the safety database reporting the PT Extensive swelling of vaccinated limb with the use of BNT162b2 which were mostly reported from the Netherlands (921) and Belgium (590). A majority of the cases involved females (1310, 81.2%) and were reported in subjects aged 31-50 years (793, 49.2%). Two-hundred and two (202; 12.5%) of the events were assessed as serious due to meeting medically significant criteria (there were 6 hospitalisations due to reported events). There was 1 case reporting a fatal outcome. One thousand two hundred and thirty-seven (1237) cases reported time to onset of the event as the same day or the day following vaccination. The majority of cases reporting swelling associated with the injection site, did not report that treatment was required, and no case reported long lasting or permanent sequelae following the event. Injection site swelling and lymphadenopathy are listed adverse drug reactions in the RSI for BNT162b2, and based on the data reviewed, there is insufficient evidence from reported cases to date that would warrant a change to the existing product information.

Rapporteur assessment comment:

The ADRs 'Extensive swelling of vaccinated limb', 'Injection site swelling' and 'Lymphadenopathy' are stated in section 4.8 of the Comirnaty SmPC.

No new important safety concern could be identified for severe reactogenicity. For future PSURs in the section 'Evaluation of AESIs', the severe reactogenicity should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Age-related adverse reactions

Clinical trial data

- Number of cases: 668.
- Time to event onset (n = 793), range: <24 hours to 558 days, median: 116 days.
- Relevant event outcome: fatal (50), resolved/resolving (663), resolved with sequelae (49), not resolved (115), unknown (3).

Post-authorisation data

- Number of cases: 507,683.
- Time to event onset (n = 1,196,069), range: <24 hours to 7337 days, median: 1 day.
- Relevant event outcome: fatal (8526), resolved/resolving (595,395), resolved with sequelae (26,518), not resolved (434,513), unknown (536,733).

Analysis by age group

- Clinical trial: Paediatric (103), Adults (336), Elderly (211) and Unknown (1).
    - The 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented are Table 57, Table 58 and Table 59 (not reproduced here). Of note, 139 cases reported 151 events pertaining the Infections and infestations SOC, which was included among the SOCs of the most frequently reported AEs in all 3 age groups.
    - There were 59 cases reporting 65 events in the Cardiac disorders SOC for the adult and elderly age group. Forty-five (45) cases reported relevant medical history (e.g., coronary artery disease, atrial fibrillation, congestive cardiac failure, cardiovascular disorder), which may have contributed to the relevant events. The most frequently reported events (≥3 occurrences) in the Cardiac disorders SOC for the adult and elderly age group were Atrial fibrillation (16), Myocardial infarction (9), Cardiac failure congestive, Coronary artery disease (5 each), Acute coronary syndrome, Acute myocardial infarction (4 each), Angina pectoris and Angina unstable (3).
    - There were 96 cases reporting 98 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Twenty-eight (28) cases reported pre-existing medical history of cancer (e.g., basal cell carcinoma, neoplasm malignant, pituitary tumour benign, prostate cancer). The most frequently reported events (≥3 occurrences) in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group were Prostate cancer (13), Adenocarcinoma of colon, Breast cancer, Pancreatic carcinoma (5 each), Brain neoplasm (4), Invasive ductal breast carcinoma, and Oesophageal carcinoma (3 each). When reported, latency ranged from 1 day to 437 days with a

median of 104 days. Of the 78 events reporting latency, the majority of the relevant event latency (65 events) was reported between 1 day to 6 months.

- There were 7 cases reporting 9 events in the Psychiatric disorders SOC for the paediatric age group. The 9 events reported were Depression, Suicidal ideation, Suicide attempt (2 each), Depression suicidal, Major depression and Mental status changes (1 each). The events were assessed as unrelated to BNT162b2/Blinded therapy by the investigator and the Sponsor.

- Post-marketing: Paediatric (31,832), Adults (361,138), Elderly (56,588) and Unknown (56,647).
- The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group are presented in Table 60, Table 61, and Table 62 (not reproduced here). The top 5 SOCs were generally comparable for all age groups except Reproductive system and breast disorders in the adult age group, Skin and subcutaneous tissue disorders in the paediatric age group and Infections and infestations in the elderly age group.
- In the Reproductive system and breast disorders SOC for adult age group, event seriousness was assessed as serious (8609) and non-serious (61,891). Event outcome was reported as resolved/resolving (19,328), not resolved (33,732), resolved with sequelae (1,390), unknown (16,268), and fatal (6). The most commonly reported PTs (>1000 occurrences) in Reproductive system and breast disorders for the adult age group were Heavy menstrual bleeding (11,691), Menstrual disorder (11,655), Menstruation irregular (6481), Dysmenorrhoea (5824), Intermenstrual bleeding (5650), Amenorrhoea (5267), Polymenorrhoea (4522), Menstruation delayed (4500), Oligomenorrhoea (1818), Breast pain (1816), Vaginal haemorrhage (1588), and Postmenopausal haemorrhage (1028). It is not unexpected for these events of reproductive system and breast disorders to be reported more frequently in adult subjects compared to elderly and paediatric subjects (males or females of non-puberty age).
- In the Skin and subcutaneous tissue disorders SOC for paediatric age group, event seriousness was assessed as serious (966) and non-serious (4194). Event outcome was reported as resolved/resolving (2903), not resolved (1161), resolved with sequelae (20), unknown (1085), and fatal (3). The fatal cases are reviewed in Section 16.3.4.1 Death of the PSUR. The most commonly reported PTs (≥110 occurrences) in Skin and subcutaneous tissue disorders for the paediatric age group were Rash (1538), Pruritus (718), Urticaria (681), Erythema (326), Hyperhidrosis (270), Rash pruritic (198), Cold sweat (131), and Sensitive skin (110). Most of these events are listed or consistent with listed events as per the current RSI.
- In the Infections and infestations SOC for elderly age group, event seriousness was assessed as serious (11,447) and non-serious (2756). Event outcome was reported as resolved/resolving (3096), not resolved (2014), resolved with sequelae (157), unknown (8305), and fatal (649). The fatal cases are reviewed in Section 16.3.4.1 Death of the PSUR. The most commonly reported PTs (>250 occurrences) in Infections and infestations for the elderly age group were coded to the PTs COVID-19 (8394), Herpes zoster (1771), Suspected COVID-19 (462), COVID-19 pneumonia (408), Influenza (407), Pneumonia (346), and Nasopharyngitis (251). It is not unexpected for these events to be reported more frequently in elderly subjects compared to adult and paediatric subjects.

MAH's conclusion

The most frequently reported SOCs and overall PTs with the COVID-19 vaccine across the age groups were listed or consistent with listed events as per the current RSI. The analysis of age-related AEs did not identify any new significant safety information.

Rapporteur assessment comment: No new important safety concern could be identified for age-related adverse reactions.

Vaccination stress/anxiety related ADRs

Search criteria: *PTs Anxiety; Blood pressure decreased; Blood pressure increased; Dizziness; Dyspnoea; Hyperhidrosis; Loss of consciousness; Palpitations; Paraesthesia; Paraesthesia oral; Syncope; Tachycardia (reported in very close temporal proximity to vaccination, e.g., when time to event onset for the relevant PTs is same day or 1 day after vaccination).*

Clinical trial data

- Number of cases: 2, both involving BNT162b2 (0.3 % of 668 cases in the total CT dataset) compared to no cases retrieved in the PSUR #2.
- Country of incidence: Israel, Poland (1 each).
- Subjects' gender: male (2).
- Subjects' age in years (n = 2), 10 years and 73 years.
- Medical history: Hypertension, Hypercholesterolaemia, Myocardial ischaemia and Glucose-6-phosphate dehydrogenase deficiency (1 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PTs: Dyspnoea and Syncope (1 each).
- Time to event onset: 1 days for both the relevant events.
- Duration of relevant events: 1 day for the event Syncope, 5 days for the event Dyspnoea.
- Relevant event outcome: resolved (2).

Post-authorisation data

- Number of relevant cases: 39,800 (7.8% of 507,683 cases, the total PM dataset), compared to 56,230 cases (8.6%) retrieved in the PSUR #2.
- Most frequently reported relevant PTs (≥2%): Dizziness (16,611), Dyspnoea (7875), Paraesthesia (6846), Tachycardia (4757), Palpitations (4754), Blood pressure increased (2539), Hyperhidrosis (2339), Syncope (2294) and Loss of consciousness (1037).
- Relevant event outcome: fatal (81), resolved/resolving (26,704), resolved with sequelae (1170), not resolved (16,695), unknown (5789).

Analysis by age group

- Clinical data: Paediatric (1) and Adults (1). A meaningful comparison between the different age groups is not possible due to the low number of cases.

- Post-marketing: Paediatric (3681), Adults (31,950), Elderly (2921) and Unknown (1248). No significant difference was observed in the reporting proportion of frequently (≥2%) reported relevant events between the adult and elderly populations. A higher reporting proportion of relevant PT Syncope was observed in the paediatric population when compared to the adult or elderly population (15.2% in paediatric vs 4.6% in adult vs 6.1% in elderly subjects). This is consistent with expectations based on age-related event reports from other vaccines.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3277 (0.8 % of the cases reporting stress/anxiety ADRs). Upon review, no significant difference in the occurrence of the most frequently reported AEs related to vaccination stress/anxiety and in relevant AEs with fatal outcome in the subjects with comorbidities compared to the population without underlying diseases was identified, apart from the event syncope that was reported with higher proportion (6.3%) in subjects with comorbidities with respect to subjects without comorbidities (0.6%). The subjects' underlying conditions are likely to be contributory to the occurrence of syncope in these cases.

MAH's conclusion

No new significant safety information was identified based on a review of these cases.

Rapporteur assessment comment:

Anxiety and stress-related adverse events (e.g., dizziness, paraesthesia, hypoesthesia, hyperhidrosis) are stated in section 4.4 and 4.8 of the Comirnaty SmPC. No new important safety concern could be identified for vaccination stress/anxiety related ADRs.

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

Evaluation of special situations

Death

Search criteria - *Death cases are identified based on the following criteria: If the case or event outcome is "Fatal"; If the date of death field has a value; If any of the history type values is "Death" or "Autopsy"; If the death field is set to "Yes"; If the case contains one of the following terms: High Level Group Term: Fatal outcomes; Preferred Terms: Assisted suicide, Completed suicide.*

Clinical trial data

- Number of cases: 34 (blinded therapy [4] and BNT162b2 [30]) (5.1 % of 668 cases, the total CT dataset) compared to 44 cases (6.1%) retrieved in the PSUR #2.
- Causes of death most frequently reported (>2 occurrences): Death (6), Disease progression (5), and Completed suicide (4). None of the fatal events are considered related to blinded therapy/BNT162b2.

Post-authorisation data

- Number of cases: 3163 (0.6% of 507,683 cases, the total PM dataset) compared to 5215 (0.8%) analysed in the PSUR #2.
- MC cases (2061), NMC cases (1102).

- Country of incidence (≥107 occurrences): Germany (655), France (304), Japan (252), Philippines (205), Austria (194), the UK (164), Malaysia (151), the US (138), Australia (122), and Italy (107).
- Subjects' gender: female (1304), male (1722), unknown (137).
- Subjects' age in years (n = 2901), range: 5.0 – 107.0 years, mean: 68.0 years, median: 73.0 years.
- Medical history (n = 1631) : The most frequently reported (>70 occurrences) medical conditions included cardiac and vascular disorders [e.g., Hypertension (588), Atrial fibrillation (171), Cardiac failure (113), Dyslipidaemia (80), and Myocardial ischaemia (72)]. Other most frequently reported (>70 occurrences) medical conditions included Diabetes mellitus (169), Type 2 diabetes mellitus (117), Obesity (102), Chronic obstructive pulmonary disease (95), Dementia (83), and Chronic kidney disease (72).
- COVID-19 Medical history (n = 98): COVID-19 (86), Suspected COVID-19 (9), COVID-19 pneumonia (8), Coronavirus infection, Post-acute COVID-19 syndrome, and SARS-CoV-2 antibody test positive (1 each).
- Causes of death most frequently reported (>100 occurrences): Death (739), COVID-19 (301), Cardiac arrest (215), Dyspnoea (185), Myocardial infarction (154), Vaccination failure (144), Drug ineffective (131), COVID-19 pneumonia (129), Sudden death (110), Pulmonary embolism (105), Cardio-respiratory arrest (102), and Cardiac failure (101).
- Autopsy results were provided in 165 cases and the most commonly reported (≥7 occurrences) were: Pulmonary embolism (22), Myocarditis (18), Pulmonary oedema (12), Arteriosclerosis coronary artery, Myocardial infarction, Myocardial ischaemia (10 each), Acute myocardial infarction, Arteriosclerosis (9 each), Arrhythmia, Death (8 each), Cardiac failure (7).
- Co-suspect vaccines/medications (n = 144): the most frequently reported (>3 occurrences) were COVID-19 vaccine (25), influenza vaccine (16), COVID-19 vaccine MRNA (MRNA 1273) (15), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (14), influenza vaccine INACT SPLIT 4V (8), influenza vaccine INACT SAG 4V (6), casirivimab/imdevimab (5), apixaban, furosemide, and lenalidomide (4 each).
- Cases with confounders and risk factors: 1726 fatal cases included one or more contributing factors, which precluded a meaningful causality assessment: co-suspect (144 cases), concomitant drugs (638 cases) and/or underlying medical history/risk factors (1652 cases).
- Events with a fatal outcome (n = 8335): The most frequently reported (>100 occurrences) fatal events were coded to the PTs: Death (652), COVID-19 (340), Immunisation (240), Cardiac arrest (222), Vaccination failure (218), Dyspnoea (217), Drug ineffective (209), Off label use (193), Myocardial infarction (155), Interchange of vaccine products (144), Sudden death (140), COVID-19 pneumonia (137), Pyrexia (119), Pulmonary embolism (116), and Cardiac failure (102).
- Time to fatal event onset (n = 5580), range: <24 hours to 365 days, median: 8 days

Analysis by age group

- Clinical trial: Adults (18-64) (17) and Elderly (65 years and older) (17). A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.

- Post-marketing: Paediatric (17 years and under) (82), Adults (18-64 years) (932), Elderly (65 years and older) (1946), and Unknown (203).
    - There is a significant difference observed in the reporting proportion for the majority of the frequently reported fatal events (>100 occurrences) in the elderly population when compared to the adult population due to a higher proportion of fatal cases reported in subjects over 64 years of age (61.5% vs 29.5%, respectively). There is no meaningful comparison between elderly vs paediatric population possible due to the low number of paediatric fatal cases reported (2.6% vs 61.5%, respectively).
    - Most of the cases reporting a fatal outcome (42.1%) were in subjects over 75 years of age. The elderly population is generally considered a priority group targeted for vaccination by many regions and countries, including Europe and the US (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1094 (0.2 % of 508,351, the total dataset) when compared to 2090 (0.3% of 658,249 cases) in the PSUR #2. Upon review, there were no significant differences observed in the patterns of the most frequently reported fatal events (>100 occurrences) between the group with comorbidities and the one without comorbidities.

Analysis by dose

- Number of vaccine doses administered at the time of the subjects' death:
    - First dose (378 cases).
    - Second dose (934 cases). Of the 934 cases, 163 cases (17.5 %) reported a latency of same day to 3 days after vaccination. There were 2477 fatal events. The most frequently reported (>100 occurrences) fatal events were coded to the PTs COVID-19 (178), Death (154), Drug ineffective (113), Vaccination failure (111).
    - Third dose (1084 cases). Majority of these cases (>50 occurrences) originated from Germany (240), Japan (151), France (139), the UK (78), and Austria (56). There were 3267 fatal events. The most frequently reported (>100 occurrences) fatal events were coded to the PTs Death (206) Immunisation (188), Off label use (117), COVID-19 (112), Interchange of vaccine products (107), and Vaccination failure (101).
    - Fourth dose (71 cases). Majority of these cases (>10 occurrences) originated from Germany (23), France, and the UK (11 each). There were 254 fatal events. The most frequently reported (>20 occurrences) fatal events were coded to the PTs Off label use (42) Immunisation43 (39), and Death (22).
    - Fifth dose (1 case). This is a spontaneous case reported by a consumer. In this case, a 66-year-old male subject received BNT162b2, as dose 5 (booster), for COVID-19 immunisation (Off label use). Relevant medical history included interchange of vaccine products (first 2 doses with Coronavac; third and fourth doses with BNT162b2) and hospitalisation for the drop in oxygen saturation. The subject's condition worsened after receiving the fifth dose and he experienced immunisation reaction such as low oxygen saturation, lung oedema, abnormal lung function and shortness of breath, and he died 3 days later. Oxygen deficiency and failure of the lungs to function were cited as the cause of death. It was unknown if an autopsy was performed.

- In the remaining cases (695), dose number was not specified at the time of the subject's death.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

Observed versus expected analysis

O/E analysis was performed for events with a fatal outcome. All O/E ratios were below 1.

MAH's conclusion

No new risks were identified following review of fatal cases.

Rapporteur assessment comment: No new important safety concern could be identified for cases reporting fatal outcome.

Overdose

Search criteria: *HLT Overdoses NEC OR PT Accidental overdose.*

Clinical trial data

- No serious clinical trial cases of overdose of the vaccine reported during the current interval period, similar to no cases in the PSUR #2.

Post-authorisation data

- Number of cases: 1595 (0.3% of 507,683 cases, the total PM dataset), compared to 1985 cases (0.3%) retrieved in the PSUR #2.
- Relevant PTs: Overdose (1510), Accidental overdose (81), and Intentional overdose (4).
- Relevant event outcome: resolved/resolving (68), not resolved (12), fatal (3), resolved with sequelae (2), unknown (1510).

Analysis by age group

- Paediatric (630), Adults (420), Elderly (89) and Unknown (456). Upon review, no significant differences in the reporting proportion of the most frequently co-reported AEs were noted between the different age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 63 (4.0% of the total cases reporting overdose). Upon review, no significant differences in the occurrence of the most frequently co-reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

Literature

- Review of the literature did not identify any significant new information regarding overdoses of BNT162b2.

MAH's conclusion

The most frequently reported reasons (≥ 2%) for overdose were:

- administration of incorrect dose of diluted vaccine, different from the recommended 0.3 ml for the subjects aged ≥ 12 years and 0.2 ml for the paediatric subjects aged 5 through 11 years (411; 25.8% of the total cases reporting overdose);
- administration of undiluted vaccine (582; 36.5% of the total cases reporting overdose);
- dilution with a volume of sodium chloride different from the recommended 1.8 ml for the subjects aged ≥ 12 years and 1.3 ml for the paediatric subjects aged 5 through 11 years (170; 10.7% of the total cases reporting overdose);
- administration of more than 1 dose of vaccine (39; 2.4% of the total cases reporting overdose);
- incorrect vaccine formulation administered to paediatric subjects aged 5 through 11 years instead of the recommended 10 mcg dosage (71; 4.4% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 218 cases, the reason for overdose was not reported or unclear, 2 of which reported the PT Intentional overdose. In the remaining 2 cases reporting intentional overdose, an administration of 30 mcg in children (aged 9 and 10 years old) was reported.

No new significant safety information was identified based on the review of these cases. The majority of the most frequently co-reported AEs other than overdose and medication error PTs were events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS.

Rapporteur assessment comment:

No new important safety concern could be identified for overdose. For future PSURs in the section 'Evaluation of special situations', the overdose 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**

Abuse, misuse, and drug dependency

Abuse Search Criteria: *PTs Alcohol use disorder; Dependence; Disturbance in social behaviour; Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug detoxification; Drug diversion; Drug level above therapeutic; Drug level increased; Drug rehabilitation; Drug screen; Drug screen positive; Drug tolerance; Drug tolerance decreased; Drug tolerance increased; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal; Maternal use of illicit drugs; Needle track marks; Neonatal complications of substance abuse; Pharmaceutical nomadism ; Substance abuse; Substance abuser; Substance dependence; Substance use; Substance use disorder; Toxicity to various agents; Withdrawal syndrome.*

Misuse Search Criteria: *Intentional product misuses; Intentional device use issue; Intentional dose omission; Intentional medical device removal by patient; Intentional product use issue; Intentional removal of drug delivery system by patient; Intentional underdose; Performance enhancing product use; Prescription drug used without a prescription; Treatment noncompliance.*

Of the 55 cases, 44 cases were determined to be non-contributory and were not included in the discussion.

Clinical trial data

- No serious clinical trial cases of abuse or misuse of the vaccine reported during the reporting period; no cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 11 (0.002% of 507,683 cases, the total PM dataset), compared to 45 cases (0.01%) retrieved in the PSUR #2.
- Relevant PTs: Intentional product misuse, Intentional product use issue (4 each), Intentional underdose (3).
- Relevant event outcome: fatal (1), not resolved (3), unknown (7).

  In the case involving the fatal outcome, a female subject (age unknown) received three vaccines COVID-19 (BNT162b2), pneumonia vaccine (unspecified) and the flu vaccine at one time. The patient experienced a myocardial infarction and died. Onset date of myocardial infarction was not reported.

Analysis by age group

- Post-marketing: Paediatric (2), Adults (5), Elderly (2), and Unknown (2). There was no meaningful difference between different age groups.

Analysis by dose

- Post-marketing: Number of vaccine doses administered at the time of the event onset: dose 1 in 1 case, dose 2 in 1 case, dose 3 in 1 case, and number of doses was not specified in 8 cases. There are no differences between the AEs that occurred after the first, the second and the booster dose.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and abuse, dependence or misuse.

MAH's conclusion

Overall, there were 11 cases representing 0.002% of the overall post-marketing dataset, that reported events indicative of misuse. These cases involved either improper storage, improper dilution of vaccine, administration of vaccine to unapproved age groups or administration of vaccine at a dose lower than the recommended dose. In general, the most frequently co-reported events observed in these cases were consistent with those observed in the overall population. No safety signals have emerged that would be considered specific to this population.

Rapporteur assessment comment:

No new important safety concern could be identified for abuse, misuse, and drug dependency. For future PSURs in the section 'Evaluation of special situations', the abuse, misuse, and drug dependency 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**

Occupational exposure

Search criteria: *PTs Exposure to contaminated device; Occupational exposure to product; Occupational exposure to radiation; Occupational exposure to toxic agent*.

Clinical trial data

- No serious clinical trial cases indicative of occupational exposure during the reporting period; no cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 20 (0.004% of 507,683 cases, the total PM dataset), compared to 41 cases (0.01%) retrieved in the PSUR #2.
- Relevant PTs: Occupational exposure to product (20).
- Relevant event outcome: resolved/resolving (2), resolved with sequelae (1), unknown (17).

Analysis by age group

- Post-marketing: Paediatric (2), Adults (5), Elderly (0) and Unknown (13). A meaningful comparison between the different age groups is not possible due to the low number of cases.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and occupational exposure.

MAH's conclusion

Overall, there were 20 cases representing 0.004% of the overall post-marketing dataset, that reported events indicative of occupational exposure. Review of the cases did not identify any significant new information regarding the use of BNT162b2 and occupational exposure. No safety signals have emerged that would be considered specific to this population.

Rapporteur assessment comment:

No new important safety concern could be identified for occupational exposure. For future PSURs in the section 'Evaluation of special situations', the occupational exposure should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal. **Request for next PSUR**

Lack of therapeutic efficacy

Search Criteria: PTs Drug ineffective, Vaccination failure.

Clinical trial data

- No lack of efficacy cases in the clinical trial dataset for this reporting period or for the reporting period of PSUR #2.

Post-authorization data

- Number of cases: 51,028 (10.1% of 507,683 cases, the total PM dataset), compared to 21,457 cases (3.3%) in PSUR #2. The increase in the reporting proportion of LOE cases was multifactorial. A high number of cases were reported from Austria (31,629 cases in the current PSUR), as compared to the previous PSURs (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. In addition, the epidemiology of the virus has changed since December 2021 in that the Omicron variant has become predominant in most regions. BNT162b2 efficacy against Omicron variants is less than against the previous dominant variants of concern.
- MC cases (39,368), NMC cases (11,660).

- Relevant lack of efficacy events : 51,028 (Vaccination failure [24,762] and Drug ineffective [26,266]).
- Country of incidence (≥2%): Austria (31,629), US (4734), UK (2316), Germany (1856), France (1478), Netherlands (1291); the remaining 7724 cases were distributed among 71 countries.
- Subjects' gender: female (27,177), male (21,802) and unknown (2049).
- Subjects' age in years (n = 48,297), range: 1.5 – 107.0 years, mean: 47.3 years, median: 47.0 years.
- Relevant event seriousness: all serious.

Confirmed vaccination failure (24,077 cases)

- Age groups: Child (40), Adolescent (1053), Adult (18,337), Elderly (4475) and Unknown (172).
- Time to event onset was known for 23,013 cases:
    - Time to onset reported after the second dose ranged from 7 – 501 days.
    - Time to onset reported after the third dose ranged from 1 – 293 days.
    - Time to onset reported after the fourth dose ranged from 1 – 213 days.
- Reported COVID-19 infection related events (>5 occurrences) : COVID-19 (23,679), COVID-19 pneumonia (285), SARS-CoV-2 test positive, Suspected COVID-19 (107 each), Vaccine breakthrough infection (21), Breakthrough COVID-19 (8), and Post-acute COVID-19 syndrome (6).
- Outcome of COVID-19 infection related events: resolved/resolving (2187), resolved with sequelae (29), not resolved (673), unknown (21,115), and fatal (221).
- Of the 24,077 subjects with confirmed vaccination failure, in 880 cases, the COVID-19 events were severe, resulting in: Hospitalisation (non-fatal/non-life threatening) (623), Disability (13), Life threatening (40), Death (204).

Suspected vaccination failure (1402 cases)

Not a vaccination failure case (25,549 cases)

SARS-CoV-2 Variants (11,901 cases)

In 11,901 of the 51,028 cases, information on SARS-CoV-2 variants was provided:

- Delta (India) variant (11,274 cases)
    - Country of incidence (>3 occurrences): Austria (11,164), France (84), Germany (16), and US (4).
    - Lack of efficacy events: Vaccination failure (6591) and Drug ineffective (4683).
    - Outcome of COVID-19 infection related events160: resolved/resolving (50), resolved with sequelae (2), not resolved (23), unknown (11,156), and fatal (51).
- Omicron variant (606 cases)
    - Country/region of incidence (>2 occurrences): Hong Kong (391), France (79), Germany (40), US (39), Japan (12), Spain (6), Austria (4), Belgium, Brazil, Mexico, and Norway (3 each).

- Lack of efficacy events: Vaccination failure (404) and Drug ineffective (202).
- Outcome of COVID-19 infection related events160: resolved/resolving (81), not resolved (11), unknown (503), and fatal (18).

- Alpha (UK) variant (19 cases)
  - Country of incidence: Austria, Germany (5 each), France, Italy (4 each), and Poland (1).
  - Lack of efficacy events: Vaccination failure (16) and Drug ineffective (3).
  - Outcome of COVID-19 infection related events160: resolved/resolving (8), not resolved (1), unknown (10), and fatal (1).
- Others (2 cases)
  - In 2 other cases, variant was reported as Beta (South Africa162) and South African or Brazilian (as reported), respectively.

Literature

- Review of the literature identified significant new information with regards to the use of BNT162b2 and lack of therapeutic efficacy.

MAH's conclusion

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

Rapporteur assessment comment:

During the interval period, a substantial increase of cases reporting lack of efficacy was retrieved by the MAH (51,028 [10.1% of total PM dataset] compared to 21,457 cases (3.3%) in the previous 2nd PSUR. The MAH stated as reasons for this increase that a high number of cases were reported from Austria due to the active solicitation of lack of efficacy cases (including retrospective cases), and that Comirnaty efficacy against current Omicron variants is less than against the previous dominant variants.

In view of the 843,724,061 administered Comirnaty doses during the current interval period, a total of 24,077 (0.003%) confirmed vaccination failures cases is not considered a safety signal.

No new important safety concern could be identified for lack of therapeutic efficacy.

Off-label use

Search criteria: *PTs Contraindicated product administered; Contraindicated product prescribed; Drug effective for unapproved indication; Drug ineffective for unapproved indication; Intentional device use issue; Intentional product use issue; Intentional underdose; Off label use; Off label use of device; Prescribed underdose; Product administered to patient of inappropriate age; Product use in unapproved indication; Product use issue; Therapeutic product effective for unapproved indication; Therapeutic product ineffective for unapproved indication*.

Post-authorisation data

- Number of cases: 29,805 (5.9% of 507,683 cases, the total PM dataset), compared to: 22,533 (3.4%) cases retrieved in the PSUR #2. A general increase in cases reporting Interchange of

vaccine products was noted (54.0% of PM cases from PSUR #2 versus 83.3% of PM cases retrieved during this reporting period).

- MC cases (6091), NMC cases (23,714).
- Country of incidence (≥2%): UK (10,172), Netherlands (6230), Germany (4368), France (1516), Poland (602)
- Subjects' gender: female (20,994), male (7831) and unknown (980).
- Subjects' age in years (n = 26,283), range: 0.01– 104 years, mean: 45.8 years, median: 44.0 years.
- Medical history (n = 12,399): the most frequently (≥2%) reported medical conditions include PT Disease risk factor (1663), COVID-19 (1591), Suspected COVID-19 (1448), Hypertension (1089), Breast feeding (1061), Asthma (746), Immunodeficiency (581), Hypothyroidism (340), Diabetes mellitus (319), Hypersensitivity (296), Steroid therapy (293), Depression (281), Drug hypersensitivity (279), Seasonal allergy (271).
- COVID-19 Medical history (n = 3001): the most frequently (≥2%) reported medical conditions included COVID-19 (1591) and Suspected COVID-19 (1448).
- Co-suspects (n = 1745 cases): the most frequently (≥2%) reported co-suspect vaccines/medications included COVID-19 vaccine MRNA (MRNA 1273) (681), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (420), Influenza vaccine (188), Influenza vaccine inact SAG 4V (80), Influenza vaccine inact SPLIT 4V (64), JNJ 78436735 (51), COVID-19 vaccine (50).
- Number of events: 174,381 (of which 32,211 were events of interest).
- Relevant event seriousness:42 serious (10,382), non-serious (21,845).
- Most frequently reported relevant PTs (≥2%): Off label use (29,562) and Product use issue (2531). Of note, of the 29,805 cases, 696 did not report additional events. The majority of cases described off-label use as:
    - intentionally used in unapproved populations such as those mentioned below:
        - It is unknown whether the BNT162b2 vaccine is excreted in human milk.
        - Administration of the vaccine in pregnancy should be considered when potential benefits outweigh any potential risks for the mother and foetus.
        - Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.
        - The administration of the BNT162b2 vaccine should be postponed in individuals suffering from acute severe febrile illness.
        - The safety and efficacy have not yet been established in individuals under 5 years of age. The safety and effectiveness of a booster dose of in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.
    - alternative dosing or scheduling regimens (i.e., Full primary series not received, longer/shorter number of days between doses than recommended)

        - The primary series of the BNT162b2 vaccine is administered as 2 doses at greater than or equal to 21 days (preferably 3 weeks) apart. Off label is currently considered when the 2nd dose of the vaccine is administered outside the 19-42 day range from the 1st dose.
    - co-administration with other vaccines (i.e., influenza)
        - No interaction studies have been performed
    - administration of COVID-19 vaccines from different manufacturers and third/booster/extra doses.
    - administration of COVID-19 vaccine formulations indicated for a different age group.
    - usage of poor quality COVID-19 vaccines due to either preparation (i.e., dilution technique) and/or storage issues (i.e., used after the expiry or beyond use date).

Analysis by dose interval

- Among these cases, 9 (all non-serious) reported administration of 3 doses of BNT162b2 with different time intervals than the recommended posology and included the relevant PTs Off label use (9) and Product use issue (1).
- Upon review, there were no significant differences were identified in the occurrence of the most frequently relevant PTs and clinical co-reported AEs reported in those who received the 3 doses of vaccine at a different time interval than the recommended posology when compared to the population receiving BNT162b2 in unapproved conditions Clinical events reported more than once in this population included Headache (4), Pain, Pyrexia, and Vaccination site pain (2 each).

Literature

- Review of the literature did not identify any significant new information with regards to the off-label use of BNT162b2.

MAH's conclusion

Review of these cases did not identify new safety information related to off-label use.

Rapporteur assessment comment:

No new important safety concern could be identified for off-label use. For future PSURs in the section 'Evaluation of special situations', the off-label use 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**

Unexpected therapeutic effect

Search criteria: *PTs Device effect increased; Drug effect faster than expected; Drug effective for unapproved indication; Therapeutic product effective for unapproved indication; Therapeutic response changed; Therapeutic response increased; Therapeutic response prolonged; Therapeutic response unexpected; Therapeutic product effect increased; Therapeutic product effect prolonged*.

Clinical trial data

- No serious clinical trial cases with the above PTs reported during the reporting period; no serious cases were retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 664 (0.1 % of 507,683 cases in the total PM dataset), compared to 844 cases (0.1%) retrieved in the PSUR #2.
- In most of the cases (when specified), the unexpected therapeutic effect included improvement in the following: pain, breathing, allergies, skin conditions (including warts and psoriasis), autoimmune/inflammatory diseases (e.g., arthritis, multiple sclerosis, ulcerative colitis), migraine/headache, infections (e.g., herpes and other viral infections, fungal infections), neoplasia (remission/regression of various cancers), movement/mobility, energy, hair growth/loss, menstruation, and general health/well-being (e.g., "felt better").

Analysis by age group

- Post-marketing: Paediatric (3 [1 Child, 2 Adolescent]), Adults (285), Elderly (109), Unknown (267). There was no meaningful difference between different age groups.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and unexpected therapeutic effect.

MAH's conclusion

In most of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, menstrual disorders, breathing, skin conditions (including warts and psoriasis), arthritis, migraine, headache, herpes infections, taste, smell, eyesight and cognitive skills. In the majority of the cases, the subject's experienced the unexpected therapeutic effect following the first dose. No significant new information was identified with regards the use of BNT162b2 and unexpected therapeutic effects.

Rapporteur assessment comment:

No new important safety concern could be identified for unexpected therapeutic effect. For future PSURs in the section 'Evaluation of special situations', the 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. **Request for next PSUR**

Update on special populations

Use in elderly

Clinical trial data

- Number of cases: Number of cases: 211 (BNT162b2 [180], blinded therapy [26], placebo [4], BNT162b2S01 [1]; (31.6 % of 668 cases in the total CT dataset), compared to 233 cases (32.3%) retrieved in the PSUR #2.
- Number of events: 274.
- Most frequently (≥5 occurrences) reported PTs: Atrial fibrillation (11), Cerebrovascular accident, Osteoarthritis, Prostate cancer (9 each), Condition aggravated (8), Acute kidney injury, Acute respiratory failure, Dyspnoea (5 each).
- Of the 274 events, the only related event was for BNT162b2 and coded to the PT Dehydration (1).

Post-authorisation data

- Number of cases: 56,584 (11.1% of 507,683 cases in the total PM dataset), compared to 87,982 cases (13.4%) retrieved in the PSUR #2.
- MC cases (28,690), NMC cases (27,894).
- Country of incidence (>500 occurrences): Germany (10,884), Austria (9277), France (7504), US (3203), UK (3119), Japan (2225), Netherlands (2140), Sweden (2091), Australia (1747), Italy (1596), Spain (1187), Malaysia (1025), Denmark (992), Belgium (984), Poland (804), Philippines (689), Slovenia (614), Norway (602), Finland (592), Canada (556); the remaining 4753 cases were distributed among 62 countries.
- Subjects' gender: female (33,348), male (22,179), unknown (1057).
- Subjects' age in years (n = 54,943), range: 65 – 120, mean: 73.9, median: 72.
- Medical history (n = 18,647): the most frequently (≥1000 occurrences) reported medical conditions included the following HLGTs: Vascular hypertensive disorders (6169), Glucose metabolism disorders (incl diabetes mellitus) (2721), Allergic conditions (2365), Bronchial disorders (excl neoplasms) (1789), Cardiac arrhythmias (1712), Lipid metabolism disorders (1683), Joint disorders (1580), Thyroid gland disorders (1409), Therapeutic procedures and supportive care NEC (1392), Lifestyle issues (1342), Coronary artery disorders (1226), Central nervous system vascular disorders (1081).
- COVID-19 Medical history (n = 1489): COVID-19 (1150), Suspected COVID-19 (282), COVID-19 pneumonia (39), Exposure to SARS-CoV-2 (16), SARS-CoV-2 test positive (13), Asymptomatic COVID-19, Post-acute COVID-19 syndrome (8 each), Coronavirus infection (7), Occupational exposure to SARS CoV 2 (1).
- Co-suspects (n = 1956 cases) the most frequently (≥10 occurrences) reported co-suspect medications included: COVID-19 vaccine (422), COVID-19 vaccine mRNA (mRNA 1273) (274), COVID-19 vaccine NRVV AD (258), influenza vaccine (154), adalimumab (151), influenza vaccine INACT SAG 4V (100), influenza vaccine INACT SPLIT 4V (58), pneumococcal polysaccharide vaccine 23-valent (32), apixaban (29), upadacitinib (24), influenza vaccine INACT SAG 3V (23), JNJ 78436735 (18), prednisone (17), mepolizumab (16), rivaroxaban (13), rituximab (12), casirivimab, imdevimab, influenza vaccine INACT SPLIT 3V (11 each), atorvastatin, ibrutinib, levothyroxine, risankizumab (10 each).
- Number of events: 167,970; the most frequently (>1000 occurrences) reported events were coded to the PTs were: COVID-19 (8394), Inappropriate schedule of product administration (5063), Fatigue (4864), Headache (4712), Drug ineffective (4627), Vaccination failure (4515), Pyrexia (4261), Off label use (3847), Myalgia (3431), Immunisation (3355), Arthralgia (3137), Interchange of vaccine products (2920), Dizziness (2815), Vaccination site pain (2798), Pain in extremity (2796), Malaise (2468), Dyspnoea (2455), Nausea (2155), Chills (2012), Asthenia (1966), Herpes zoster (1771), Pain (1706), Rash (1677), Pruritus (1194), Vomiting (1178), Diarrhoea (1175), Paraesthesia (1096), Chest pain (1089).
- Event seriousness: serious (73,170), non-serious (94,882).
- Time to event onset (n = 119,721), range: from <24 hours to 492 days, median: 2 days.
- Event outcome: fatal (5367), resolved/resolving (52,311), resolved with sequelae (4003), not resolved (39,949), unknown (66,774).

Analysis by presence of comorbidities

- Number of elderly subjects with reported comorbidities: 10,304 (18.2% of the 56,584 cases in the total elderly dataset).
- Of the cases that reported medical histories, the percentage of cases reporting an AE with a fatal outcome is higher in subjects with comorbid conditions (72.1%) when compared to the percentage of cases involving an AE with a fatal outcome in subjects without comorbidities (27.9%).
- Upon review of the most frequently (≥200 occurrences) reported AEs in cases that recorded medical histories, the PT COVID-19 Pneumonia was the only event that had a significant proportional reporting ratio of >3:1 in the elderly population with comorbidities compared to the elderly population without comorbidities.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 in elderly patients.

MAH's conclusion

No significant differences in the reporting proportion of the most frequently reported AEs were noted between the elderly dataset and the non-elderly dataset, apart from the PTs indicative of lack of therapeutic effect, for which the reporting proportion is higher in the elderly population: COVID-19 (14.8% versus 8.8%) and Vaccination failure (7.9% versus 4.4%). This is expected due to age-related decline in immunity that results not only in increased susceptibility to infection, but also reduces the prophylactic efficacy of vaccinations. The interval data reviewed did not identify any new safety information regarding the use of BNT162b2 in elderly patients.

Rapporteur assessment comment:

No important new information could be identified regarding the use of Comirnaty in the elderly.

Use in paediatric population

Paediatric subjects <5 years of age

Clinical trial data

- Number of cases: 62 (blinded therapy [43], BNT162b2 [18] and pre-randomisation [1]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (9.3% of 668 cases, the total CT dataset), compared to 25 cases (3.5%) retrieved in the PSUR #2.

Post-authorisation data

- Number of cases: 275 (0.5% of 507,683 cases, the total PM dataset), compared to 83 cases (0.01%) retrieved in the PSUR #2.

Rapporteur assessment comment:

During the reporting period, the use of Comirnaty in children <5 years old was not within the current approved indication in the EU and therefore considered off-label use.

Paediatric subjects ≥5 years and ≤ 11 years of age

Clinical trial data

- Number of cases: 25 (blinded therapy [6] and BNT162b2 [19]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (3.7% of 668 cases, the total CT dataset), compared to 18 cases (2.5%) retrieved in the PSUR #2.
- PTs (34): Gastroenteritis (3), Dermatomyositis, Intestinal obstruction, Pyrexia (2 each), Appendicitis, Asthma, Colitis, Condition aggravated, Constipation, Depression, Depression suicidal, Device related infection, Diarrhoea, Drug therapy, Febrile convulsion, Hypertension, Hyponatraemia, Influenza, Kidney transplant rejection, Large intestine benign neoplasm, Mental status changes, Myalgia, Myositis, Rhinovirus infection, Seizure, Small intestinal obstruction, Syncope, Tibia fracture, and Vomiting (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 9605 (1.9% of 507,683 cases, the total PM dataset), compared to 1227 cases (0.2%) retrieved in the PSUR #2.
- MC cases (6573), NMC cases (3032).
- Country of incidence (≥2%): US (2503), Australia (1428), Philippines (1264), Germany (1177), Japan (859), Italy (409), and Spain (386).
- Subjects' gender: female (3925), male (4133) and unknown (1547).
- Subjects' age in years (n = 8372), range: 5 – 11,25, mean: 8.4, median: 9.0.
- Medical history (n = 846): the most frequently (≥10) reported medical conditions included Asthma (158), Food allergy (62), Seasonal allergy (59), Attention deficit hyperactivity disorder (41), Hypersensitivity (34), Autism spectrum disorder, Epilepsy (30 each), Drug hypersensitivity (28), Rhinitis allergic (27), Eczema (26), Dermatitis atopic (23), Mite allergy (21), Allergy to animal (19), Constipation, Type 1 diabetes mellitus, Urticaria (15 each), Bronchospasm, Headache, Seizure (12 each), Obesity (11), Migraine (10).
- COVID-19 Medical history (n = 136): COVID-19 (121), Suspected COVID-19 (10), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (2 each), and Post-acute COVID-19 syndrome (1).
- Co-suspects (n = 44): the most frequently (>1) reported co-suspect vaccines/medications included influenza vaccine (8), adalimumab, COVID-19 vaccine (7 each), measles vaccine live (Enders-Edmonston)/ mumps vaccine live (Jeryl Lynn)/ rubella vaccine live (Wistar RA 27/3), varicella zoster vaccine live (Oka/Merck) (3 each), diphtheria vaccine toxoid/ pertussis vaccine acellular/tetanus vaccine toxoid, influenza vaccine inact split 3V, meningococcal vaccine B RFHBP, NADA, NHBA OMV, and sodium chloride (2 each).
- Number of events: 22,457.
- Event seriousness: (3735), non-serious (18,725).
- Most frequently reported PTs (>3% of cases): Product administered to patient of inappropriate age (1338), Pyrexia (1289), Vaccination site pain (1213), Poor quality product administered (1063), Headache (976), Product administration error (753), Vomiting (733), Rash (556), Overdose (516), Product preparation error (429), Fatigue (425), Nausea (410), Abdominal pain (371), Dizziness (366), Chest pain (331), COVID-19 (309), Pain in extremity (293), and Underdose (290).

- Time to event onset (n = 16,236) , range: from <1 day to 385 days, median: <1 day.
- Duration of relevant events (n = 3787 out of 7329 occurrences with outcome of resolved/resolved with sequelae), range: from <1 day to 109 days, median 1 day.
- Relevant event outcome: resolved/resolving (9811), resolved with sequelae (73), not resolved (3274), fatal (58), unknown (9257).
- Fatal cases: 20
    - Age: 5 years (1), 6 years (3), 7 years (4), 8 years (2), 9 years (1), 10 years (2), 11 years (5), unknown (2).
    - MC cases (17), NMC cases (3).
    - Gender: females (9), males (9), unknown (2).
    - Country: Philippines (6), Australia (4), Germany, Spain (3 each), Albania, Japan, Portugal, UK (1 each).
    - Fatal PTs (58): the most frequently (≥ 2) reported AEs included Dyspnoea (4), Cardiac arrest, Cardio-respiratory arrest, Pyrexia (3 each), Abdominal pain, Cough, COVID-19, Death, Headache, Myocarditis, Seizure, and Vomiting (2 each).
    - Medical history (n = 7): Autoimmune thyroiditis, Asphyxiating thoracic dystrophy, Brain malformation, Bronchitis, Bronchospasm, Cerebral palsy, Cognitive disorder, COVID-19, Dependence on respirator, Developmental delay, Dysphagia, Epilepsy, Gastrostomy, Hypoxic-ischaemic encephalopathy, Immunodeficiency, Intellectual disability, Joint dislocation, Kidney transplant rejection, Motor dysfunction, Myoclonic epilepsy, Neonatal asphyxia, Obstructive sleep apnoea syndrome, Pneumonia, Renal impairment, Renal transplant, Rhinitis allergic, Scoliosis, Seizure, Severe myoclonic epilepsy of infancy, Type 1 diabetes mellitus, and Varicella zoster virus infection (1 each).
    - The 20 fatal cases are summarised below:
        - In 2 cases (1 MC and 1 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The limited information provided prevented any meaningful assessment.
        - In 2 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:
            - MC case; age: 11 years; gender: male; fatal PT: Acute respiratory failure, occurred 2 days after the 1st dose of BNT162b2; medical history: brain malformation, bronchitis, cognitive disorder, dysphagia, gastrostomy, joint dislocation, myoclonic epilepsy, obstructive sleep apnoea syndrome, pneumonia, scoliosis; autopsy: not performed.
            - MC case; age: 6 years; gender: female; fatal PTs: Renal impairment, Epilepsy, Apnoea, Varicella zoster virus infection, Seizure, Sudden death, Product administered to patient of inappropriate age, death occurred 7 days after the 1st dose of BNT162b2; medical history: developmental delay, epilepsy, immunodeficiency, renal impairment, seizure, severe myoclonic epilepsy of infancy, varicella zoster virus infection; autopsy: unknown if performed.

- In one case, the reporter concluded that the death "had nothing to do" with the administration of BNT162b2 and was due to natural causes:
    - MC case; age: 6 years; gender: male; fatal PTs: Myocarditis, Cardio-respiratory arrest, COVID-19, occurred 7 days after the 1st dose of BNT162b2; medical history: rhinitis allergic, autoimmune thyroiditis), type I diabetes mellitus); autopsy: performed, results are pending.
- In the remaining 15 cases (13 MC and 2 NMC) reporting the following fatal PTs Dyspnoea (4), Cardiac arrest, Pyrexia (3 each), Abdominal pain, Cardio-respiratory arrest, Cough, Headache, Vomiting (2 each), Abdominal pain upper, Acute respiratory distress syndrome, Adverse event following immunisation, Arteriovenous malformation, Blood pressure decreased, Blood pressure immeasurable, Bradycardia, Cardiac failure acute, Cerebral haemorrhage, COVID-19, Cyanosis, Diarrhoea, Drug ineffective, haematemesis, Heart rate decreased, Immunisation, Influenza like illness, Multisystem inflammatory syndrome, Myocarditis, Nasopharyngitis, Nausea, Off label use, Pulmonary embolism, Respiratory failure, and Seizure (1 each), no confounding factors have been identified. In most cases (9) the limited information available does not allow a medically meaningful assessment; in the remaining cases (6) a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results provided evidence of a causal relationship.

Rapporteur assessment comment:

Although the Comirnaty exposure in persons aged 5-11 years is considered increased based on the EU/EEA exposure (current reporting period an estimated 3,569,821 administered doses in 5-9 years versus 391,327 administered doses in 5-9 years in the previous reporting period), worldwide interval exposure in persons aged 5-11 years (or any other age category) is not presented in the PSUR and therefore the relative post-marketing reporting rate of fatal cases in persons aged 5-11 years is not known.

There were 17 medically confirmed fatal cases in persons aged 5-11 years compared to 1 medically confirmed fatal cases in the previous reporting period. The MAH only briefly described the 17 medically confirmed fatal cases and did not provide a WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases in persons aged 5-11 years, perform per case a WHO causality assessment, and an assessment according to Brighton Collaboration case definition and Level of certainty classification, if applicable. **Request for supplementary information**

Paediatric subjects ≥12 years of age

Clinical trial data

- Number of cases: 15 (BNT162b2 [14] and blinded therapy [1]) originated from Protocol C4591001 (2), C4591001-OPEN LABEL (10), C4591007-OPEN LABEL (1), C4591024 (1), and C4591031-OPEN LABEL (1) (2.2% of 668 cases, the total CT dataset), compared to 24 cases (3.3%) retrieved in the PSUR #2.
- PTs (17): Suicidal ideation, Suicide attempt, Toxic shock syndrome (2 each), Addison's disease, Appendicitis, Constipation, Depression, Fractured skull depressed, Herpes zoster,

Major depression, Mucocutaneous rash, Pectus excavatum, Subdural haematoma, and Syncope (1 each).

- All events were assessed as unrelated to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 21,945 (4.3% of 507,683 cases, the total PM dataset), compared to 18,451 cases (2.8%) retrieved in the PSUR #2.
- MC cases (13,478), NMC cases (8467).
- Country of incidence (>2%): Germany (3333), Philippines (3026), Australia (2220), UK (1656), Austria (1645), Malaysia (1189), Taiwan, Province of China (1186), France (1061), US (1025), Italy (628), Netherlands (582), Japan (484), and Mexico (454).
- Subjects' gender: female (11,656), male (9813) and unknown (476).
- Subjects' age in years (n = 21,661), range: 12 - 17, mean: 14.7, median: 15.0.
- Medical history (n = 2837): the most frequently (>1%) reported medical conditions included Asthma (286), Hypersensitivity (210), Seasonal allergy (194), Food allergy (108), Attention deficit hyperactivity disorder (90), Drug hypersensitivity (74), Mite allergy (73), Epilepsy (62), Depression (51), Autism spectrum disorder (48), Allergy to animal (45), Anxiety, Migraine (40 each), Immunodeficiency, Obesity (39 each), Rhinitis allergic (37), Eczema (35), Non-tobacco user (34), Acne (33), Headache (31), and Dermatitis atopic (29).
- COVID-19 Medical history (n = 675): COVID-19 (457), Suspected COVID-19 (226), Asymptomatic COVID-19 (6), SARS-CoV-2 test positive (5), Post-acute COVID-19 syndrome (4), Coronavirus infection (3), and Exposure to SARS-CoV-2 (2).
- Co-suspects (n = 148): the most frequently (>2%) reported co-suspect vaccines/medications included COVID-19 vaccine (33), adalimumab (18), influenza vaccine (15), COVID-19 vaccine MRNA (MRNA 1273) (13), influenza vaccine inact split 4V, mestranol/norethisterone (8 each), HPV vaccine VLP RL1 9V (yeast) (7), HPV vaccine VLP RL1 2V (baculovirus) (5), HPV vaccine, infliximab (4 each), ibuprofen, and semaglutide (3 each).
- Number of events: 61,071.
- Relevant event seriousness: serious (19,558), non-serious (41,530).
- Most frequently reported PTs (>2%): Headache (3495), Pyrexia (3395), Dizziness (2376), Chest pain (1956), Fatigue (1919), Vaccination site pain (1804), Nausea (1669), COVID-19 (1600), and Dyspnoea (1267).
- Time to event onset: (n = 45,162) , range: from <1 day to 476 days, median: 1 day.
- Duration of relevant events (n = 9201 out of 19,141 occurrences with outcome of resolved/resolved with sequelae), range: <1 day to 329 days, median 1 day.
- Relevant event outcome: fatal (169), resolved/resolving (28,719), not resolved (12,336), resolved with sequelae (332), unknown (19,645).
- Fatal cases (62)
- Age: 12 years (12), 13 years (13), 14 years (5), 15 years (6), 16 years (11), 17 years (9), unknown (6).
- MC cases (45), NMC cases (17).

- Gender: females (28), males (32), unknown (2).
- Country (≥ 2): Philippines (19), US (8), Malaysia, Poland (6 each), Germany (4), Austria, Brazil, Japan, Taiwan (Province of China), UK (2 each).
- Fatal PTs (169): the most frequently (≥ 3) reported AEs included Death (16), Dyspnoea (8), Pyrexia (7), Cardiac arrest (6), Myocarditis (5), Cardiac failure, Headache (4 each), Asthenia, Seizure, Shock, and Vomiting (3 each).
- Medical history (n = 13): Attention deficit hyperactivity disorder, Obesity (2 each), Abdominal pain, Agitation, Amenorrhoea, Asthma, Bedridden, Chest pain, Colloid brain cyst, Cough, Cystic fibrosis, Cyst removal, Decreased appetite, Depression, Diabetes insipidus, Dizziness, Drug hypersensitivity, Dyspnoea, Dyssomnia, Exercise adequate, Fatigue, Feeling abnormal, Fracture, Headache, Hereditary cerebral degeneration, Hypertension, Kawasaki's disease, Lipoedema, Liver disorder, Lymphoedema, Lymphostasis, Oral contraception, Osteogenesis imperfecta, Ovarian enlargement, Palpitations, Physical deconditioning, Pulmonary embolism, Pulmonary veno-occlusive disease, Seasonal allergy, Somatic symptom disorder, Substance abuser, Substance use, and Weight decreased (1 each).
- The 62 fatal cases are summarised below:
- In 15 cases (9 MC and 6 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The time to fatal event onset is available in 4 cases: 5 days, 7 days, 49 days, and 144 days (1 each). The limited information provided prevented any meaningful assessment.
- In 2 cases, the subjects did not die due to illness, but due to unfortunate accidents:
- MC case; age: 17 years; gender: male; fatal PT: Fall, occurred 24 days after the vaccination; autopsy: unknown if performed.
- MC case; age: 16 years; gender: male; fatal PT: Road traffic accident, occurred approximately 110 days after the 2nd dose of BNT162b2; autopsy: unknown if performed.
- In 6 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:
- MC case; age: 16 years; gender: female; fatal PT: Dyspnoea, occurred 3 days after the 1st dose of BNT162b2; medical history: bronchial asthma; autopsy: unknown if performed.
- NMC case; age: 16 years; gender: female; fatal PTs: Dyspnoea (developed 6 days after the 1st dose of BNT162b2), Brain injury, Cardiac failure acute, Hypoxia, Cardiac failure (all developed 38 days after the 1st dose of BNT162b2), Sudden death, Pulmonary veno-occlusive disease, Pulmonary arterial hypertension (all developed 41 days after the 1st dose of BNT162b2), Brain oedema, Sudden cardiac death, Brain injury, Acute kidney injury, Pneumonitis, Epistaxis, Acute respiratory failure, Cardiac failure congestive (all unknown onset date); medical history: pulmonary veno-occlusive disease, amenorrhoea, cough, dyspnoea, fatigue, fracture, hypertension, lipoedema, lymphoedema, lymphostasis, osteogenesis imperfecta, ovarian enlargement; autopsy: not performed.
- NMC case; age: 16 years; gender: female; fatal PTs: Pulmonary embolism, Cardiac arrest (all developed 2 days after the 3rd dose of BNT162b2); medical history: obesity, oral contraception, pulmonary embolism; autopsy: performed, results not provided.
- MC case; age: 17 years; gender: male; fatal PTs Pneumococcal sepsis, Cardiac failure, Pneumonia pneumococcal (all occurred 92 days after the 2nd dose of BNT162b2); medical history: [redacted]

[redacted] agitation, attention deficit hyperactivity disorder, depression, dyssomnia, regular exercise. Autopsy results: the subject died after consumption of [redacted] from the beginning pneumonia and the influx of germs into the bloodstream as a result of cardiovascular failure. The [redacted] concentration determined in the blood and brain does not justify in itself a fatal intoxication in view of a long-term intake with a tolerance effect but may have favoured the onset of death due to a substance-typical respiratory and circulatory depressive effect, also increased in combination with the effect of [redacted] The findings obtained during the autopsy and the results of the chemical-toxicological examination can be reconciled with a protracted occurrence of death.

- MC case; age: 13 years; gender: female subject; fatal PTs: Malaise (developed 1 day after the 1st dose of BNT162b2, Lot number FJ1763), Palpitations, Chest pain (all occurred 5 days after the 1st dose of BNT162b2, Lot number FJ1763), Loss of consciousness, Pulseless electrical activity, Cardiac arrest (all occurred 64 days after the 1st dose of BNT162b2, Lot number FJ1763); medical history: Kawasaki's disease, palpitations, weight decreased, decreased appetite, feeling abnormal. Autopsy results showed that there was no possibility of myocarditis and angina pectoris, and there was no thrombus. Since symptoms such as episodes of palpitations had appeared before the vaccination, it was assessed that the vaccination was possibly related to the death, but the possibility of being the exacerbation factor could not be ruled out.
- MC case; age: 13 years; gender: male; fatal PTs Brain death, Condition aggravated (all occurred within 1 month of unknown dose number of BNT162b2, Lot number FG9428); medical history: colloid brain cyst; autopsy: unknown if performed.
- In the remaining 39 cases (30 MC and 9 NMC) reporting the following fatal PTs Pyrexia (7), Dyspnoea (6), Myocarditis (5), Cardiac arrest, Headache (4 each), Asthenia, Seizure, Shock, Vomiting (3 each), Cardiac failure, Cardiac infection, Cardiomegaly, Depressed level of consciousness, Diarrhoea, Dizziness, Hypoaesthesia, Multiple organ dysfunction syndrome, Myocardial infarction, Myocardial injury, Pneumonia, Toxic cardiomyopathy (2 each), Abdominal pain upper, Adverse event following immunisation, Agranulocytosis, Aneurysm ruptured, Anisocoria, Anuria, Atrioventricular block, B-cell type acute leukaemia, Brain injury, Cardiogenic shock, Cerebral haemorrhage, Chest discomfort, Chills,, Coma, Compartment syndrome, Completed suicide, Contusion, Cough, COVID-19, Death, Dehydration, Diabetic ketoacidosis, Enterovirus infection, Extensive swelling of vaccinated limb, Fallot's tetralogy, Gait inability, Haematemesis, Haemorrhage intracranial, Head banging, Hypertension, Immunisation, Loss of consciousness, Malaise, Meningitis meningococcal, Metabolic acidosis, Multi-organ disorder, Musculoskeletal stiffness, Nausea, Nervous system disorder, Off label use, Pain in extremity, Peripheral swelling, Pleural effusion, Pruritus, Pulse absent, Pulseless electrical activity, Rash, Rash pruritic, Renal failure, Respiratory arrest, Rhinovirus infection, Sepsis, Septic shock, Slow response to stimuli, Stress cardiomyopathy, Sudden death, Thrombosis, Unresponsive to stimuli, Vaccination failure, Vaccination site pain, and Ventricular tachycardia (1 each), no confounding factors have been identified. In 19 cases the limited information available does not allow a medically meaningful assessment, in the remaining 20 cases a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results provided evidence of a causal relationship.

<u>Analysis by presence of comorbidities</u>

- Number of subjects with comorbidities: 960 (3.0% of 31,927 cases, the total paediatric dataset). Upon review, there was no significant differences in the occurrence of the most frequently reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

Analysis of confounders and risk factors

- Among the 31,927 cases involving paediatric subjects, 4423 included one or more confounders that prevented a clear causality assessment: co-suspect and/or multiple concomitant drugs (1286 cases), underlying medical history and/or comorbidities (4037 cases) or predisposing factors (e.g., asthma, cardiac disorders, depression, diabetes, menstrual disorders, renal disease, respiratory disorders, seizures/epilepsy) (503 cases).

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

MAH's conclusion

No relevant differences in the occurrence of the most frequently reported events, case seriousness and case outcomes were identified among the 3 paediatric age groups presented above. Additionally, no significant differences in the reporting proportion of the most frequently reported AEs were noted between the paediatric dataset and the non-paediatric dataset, apart from the PTs Vomiting (6.1% versus 2.0%) and Product administered to patient of inappropriate age (5.8% versus 1.3%).

No new significant safety information was identified based on the review of the cases reported in the overall paediatric population. The most frequently reported AEs were consistent with the known reactogenicity of the vaccine and listed in Section 4.4 Special warnings and precautions for use and/or in Section 4.8 Undesirable effects of the CDS.

Rapporteur assessment comment:

There were 45 medically confirmed fatal cases in persons aged 12-17 years compared to 40 medically confirmed fatal cases in the previous reporting period. The MAH only briefly described the 40 medically confirmed fatal cases and did not provide a WHO causality assessment per case regarding Comirnaty exposure. This is not accepted. The MAH is requested to provide detailed information concerning the fatal cases in persons aged 12-17 years, perform per case a WHO causality assessment, and an assessment according to Brighton Collaboration case definition and Level of certainty classification, if applicable. **Request for supplementary information**

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

Cumulative review (Pregnancy Cases)

- Number of pregnancy cases:697 (28.7% of the total 2426 cases from the CT dataset). These 697 cases represent 669 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 28 pregnancies). Cases originated from clinical studies C4591001 (155), C4591015 (120), C4591001-OPENLABEL (91), C4591031-OPENLABEL (7), C4591031 (6), C4591020 (2), C4591017 (1), BNT162-01-OPENLABEL (1), BNT162-17 (2), and C4591006 (328) and study treatment was reported as BNT162B2 (466), blinded therapy (188), placebo (42) and BNT162C2 (1).
- Country of incidence: Japan (322), US (200), Brazil (49), Argentina (46), South Africa (44), Spain (19), UK (12), Germany (3) and Turkey (2).
- Of the 597 mother cases, 431 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The frequently reported pregnancy related events (>1 occurrence) were coded to the PTs Maternal exposure before pregnancy (272), Maternal exposure during pregnancy (139), Maternal exposure timing unspecified (12), Exposure during pregnancy (6), Drug exposure before pregnancy (2).
- One hundred sixty-six (166) mother cases, 139 serious and 27 non-serious, reported additional clinical events, which occurred in the vaccinated mothers:
    - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (57), Abortion spontaneous (46), Maternal exposure before pregnancy (30), Pre-eclampsia (7), Cephalo pelvic disproportion (6), Abortion missed, Foetal death, Postpartum haemorrhage, Premature separation of placenta (4 each), Abortion threatened, Delivery, Ectopic pregnancy, Gestational hypertension, Premature delivery, Premature labour (3 each), Abortion incomplete, Hyperemesis gravidarum, Maternal exposure via partner during pregnancy, Miscarriage of partner, Uterine disorder (2 each).
    - Other reported clinical events were coded to the PTs COVID-19 (9), Anaemia (2), Abdominal wall haematoma, Cholelithiasis, Dehydration, Drug eruption, Endometritis, Lower respiratory tract infection, Osteoarthritis, Pneumonia, Pruritis, Pyelonephritis, Urinary tract infection, Urinary tract procedural complication, Vascular pseudoaneurysm, Venous thrombosis limb (1 each).
    - Of the 58 cases reporting spontaneous abortion or abortion related events, in 25 cases the mother had a medical history of spontaneous abortion, alcohol/tobacco use during pregnancy, ectopic pregnancy, obesity, diabetes mellitus, uterine disorder, depression or anembryonic gestation, which might have contributed to the event and in 33 cases there was limited information regarding the mother's obstetric history, which precluded meaningful assessment.
    - Of the 19 cases reporting elective termination, in 10 cases, the mother had a medical history of spontaneous abortion, induced abortion, alcohol/tobacco use and in the remaining 9 cases there was limited information regarding mother's obstetric history which precluded meaningful assessment.
    - In 3 cases reporting foetal death/stillbirth the mother had a medical history of amniotic cavity infection, HIV infection and/or spontaneous abortion, which might have contributed to the event.

- In 3 cases reporting ectopic pregnancy, in 1 case, the mother had a medical history of tobacco use which might have contributed to the event, and in the remaining 2 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful assessment.

- Hundred (100) baby/foetal cases, 98 serious and 2 non serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: Thirty-one (31) of these cases reported 39 congenital anomalies that were coded to the PTs Atrial septal defect (4), Ankyloglossia congenital, Hypoxic-ischaemic encephalopathy, Neonatal hypotension, Trisomy 21 (2 each), Cleft lip, Coma neonatal, Congenital rubella syndrome, Congenital skin dimples, Congenital skin disorder, Craniosynostosis, DiGeorge's syndrome, Gnathoschisis, Microcephaly, Neonatal pneumothorax, Neonatal intestinal perforation, Neonatal seizure, Nervous system disorder, Newborn persistent pulmonary hypertension, Osteochondrodysplasia, Patent ductus arteriosus, Polydactyly, Pyelonephritis acute, Renal failure neonatal, Renal tubular necrosis, Sepsis neonatal, Sex chromosome abnormality, Syndactyly, Thanatophoric dwarfism, Thrombocytopenia neonatal, Ventricular septal defect, Vesicoureteric reflux (1 each). Of these 31 cases, information regarding trimester of exposure was available in 17 cases. Of these 17 cases, in 12 cases foetus was exposed during the 3rd trimester, in 4 cases foetus was exposed during the 2nd trimester, and in 1 case exposure occurred during the 1st trimester. Of these 31 cases, in 5 cases the mother of the baby was on multiple concomitant medications, alcohol use, advanced age of the mother (i.e., 43 years) and/or had a medical history of in vitro fertilization which increases the chance of gene mutation. In the remaining 26 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.
    - Pregnancy outcome: Still birth without foetal defect: During the reporting period there was 1 case reporting stillbirth without foetal defect. The event reported in this case was coded to the PT Neonatal respiratory distress syndrome. The information regarding trimester of exposure was unknown. In this case the mother of the baby had underlying medical history of amniotic cavity infection, which might have led to the development of the reported event.
    - Pregnancy outcome: Live birth without congenital anomaly: Sixty-eight (68) cases reported live birth babies without congenital anomaly. Of these 68 cases, information regarding trimester of exposure was available in 40 cases. Of these 40 cases, in 23 cases, foetus was exposed during the 3rd trimester, in 14 cases foetus was exposed during the 2nd trimester, and in 3 cases exposure occurred during the 1st trimester. The frequently reported events (>1 occurrence) in these 68 cases were coded to PTs Jaundice neonatal (11), Foetal distress syndrome (8), Premature baby (6), Neonatal pneumonia, Neonatal respiratory distress, Bronchiolitis, Neonatal respiratory distress syndrome, Hyperbilirubinaemia neonatal (3 each), Foetal hypokinesia, Neonatal tachypnoea, Dehydration, Gastroenteritis, Patent ductus arteriosus, Anaemia neonatal, Sepsis neonatal, Hypoglycaemia neonatal, Meconium aspiration syndrome (2 each). In all these 68 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

- Of the 697 cases, 658 cases provided pregnancy outcomes, which are provided in Table 67 (not reproduced here).

Cumulative review (Lactation cases)

- Number of lactation cases: 141 (5.8% of the total 2426 cases from the CT dataset). All these 141 cases were non serious. Of these 141 cases, 140 cases reported only exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events. In the remaining case the clinical event was coded to the PT Respiratory syncytial virus infection. In this case there was limited information regarding mother's obstetric history, which precluded meaningful causality assessment.

Incremental review (CT cases)

- Number of pregnancy cases: 41 (6.1% of the total 668 cases from the CT dataset). These 41 cases represent 37 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 4 pregnancies). Cases originated from clinical studies C4591015 (24), C4591001-OPENLABEL (10), C4591001, C4591031-OPENLABEL (3 each), C4591031 (1) and study treatment was reported as blinded therapy (27), and BNT162b2 (14).
- Country of incidence: South Africa (15), Brazil (11), US (6), Argentina (5), Spain (3), UK (1).
- Twenty-three (23) serious maternal cases reported additional clinical events, which occurred in the vaccinated pregnant females:
    - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (8), Abortion spontaneous (7), Cephalo pelvic disproportion (3), Abortion missed, Maternal exposure before pregnancy (2 each).
    - Other reported clinical events were coded to the PTs Abdominal wall haematoma, COVID-19, Pneumonia, Urinary tract infection (1 each).
    - Of the 11 cases reporting spontaneous abortion or abortion related events, in 4 cases, the mother had a medical history of spontaneous abortion or had underlying condition of obesity, which might have contributed to the event and in 7 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.
- Eighteen (18) serious baby/foetal cases are classified according to pregnancy outcome:
    - Pregnancy outcome: Live birth with congenital anomaly: Five (5) of these cases reported 5 congenital anomalies that coded to the PTs Congenital rubella syndrome, DiGeorge's syndrome, Pyelonephritis, Syndactyly, Trisomy 21 (1 each). Of these 5 cases, information regarding trimester of exposure was available in 2 cases and in these 2 cases foetus was exposed during the 2nd trimester in 1 case and the 3rd trimester in the remaining case. Of these 5 cases, in 1 case reporting Trisomy 21, the age of the mother was 43 years and advanced maternal age is a risk factor for Trisomy 21. In the remaining 4 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.
    - Pregnancy outcome: Live birth without congenital anomaly: Thirteen (13) cases reported live birth babies without congenital anomaly. Of these 13 cases, information regarding trimester of exposure was available in 7 cases. Of these 7 cases, in 5 cases, foetus was exposed during the 2nd trimester and in 2 cases foetus was exposed during the 1st and the 3rd trimester each. The frequently reported clinical events (>1 occurrence) in these 13 cases were coded to the PTs Foetal distress syndrome (3), Meconium aspiration syndrome, Gastroenteritis, Jaundice neonatal (2 each). In all

these 13 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

- Of the 41 cases, 38 cases provided pregnancy outcomes, which are provided in Table 68 (not reproduced here).

Post-authorisation data

Incremental review (Pregnancy)

- Number of pregnancy cases: 3642 (0.7% of 507,683 cases, the total PM dataset), compared to 5239 cases (0.8%) retrieved in the PSUR #2. These 3642 cases represent 3419 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 223 pregnancies).
- Country of incidence (>100 occurrences): Germany (837), UK (475), Netherlands (461), Philippines (309), France (302), Sweden (162), Australia (110).
- Of the 3320 mother cases, 535 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 (355), Maternal exposure timing unspecified (116), Maternal exposure before pregnancy (52), Exposure during pregnancy (7), Drug exposure before pregnancy (4), Foetal exposure during pregnancy (1).
- There were 2785 mother cases of which 1479 were serious and 1306 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. Additional pregnancy related events reported in these cases (≥50 occurrences) were coded to the PTs Abortion spontaneous (566), Labour pain (151), Vaginal haemorrhage (78), Heavy menstrual bleeding (50). Other frequently reported (>100 occurrences) clinical events were coded to the PTs Headache (410), Vaccination site pain (407), Fatigue (363), Pyrexia (206), Malaise (194), Myalgia (192), Nausea (178), Chills (156), Pain in extremity (135). The distribution of clinical events that were not pregnancy related (>100 occurrences) was similar in the pregnant mothers when compared with non-pregnant women of childbearing age.
- Three hundred twenty-two (322) baby/foetal cases, 283 serious and 39 non-serious. Cases are classified according to pregnancy outcome:
    - Pregnancy outcome: Live birth with congenital anomaly: Thirty-nine (39) of these cases reported 72 congenital anomalies that were coded to the PTs Foetal malformation (4), Atrial septal defect, Congenital anomaly, Ventricular septal defect (3 each), Congenital cystic lung, Congenital hydronephrosis, Congenital skin dimples, Exomphalos, Foetal cardiac disorder, Foetal chromosome abnormality, Foetal growth restriction, Kidney malformation, Pulmonary valve stenosis congenital (2 each), Anal atresia, Ankyloglossia congenital, Arnold-Chiari malformation, Cleft lip, Cleft palate, Cloacal exstrophy, Congenital amputation, Congenital foot malformation, Congenital haematological disorder, Congenital hand malformation, Congenital heart valve disorder, Congenital musculoskeletal disorder, Congenital musculoskeletal disorder of limbs, Congenital musculoskeletal disorder of spine, Congenital oral malformation, Cryptorchism, Double outlet right ventricle, Dysmorphism, Enlarged foetal cisterna magna, Fallot's tetralogy, Foetal arrhythmia, Foetal growth abnormality, Growth retardation, Heart disease congenital, Heart valve incompetence, Hepatic cytolysis, Hypospadias, Meningomyelocele, Neonatal deafness, Neonatal infection, Polydactyly, Pulmonary artery stenosis congenital, Pulmonary sequestration, Renal aplasia, Renal disorder, Renal dysplasia, Renal failure, Renal fusion anomaly, Renal hypertrophy,

Spina bifida, VACTERL syndrome (1 each). Of these 39 cases, information regarding trimester of exposure was available in 19 cases. Of these 19 cases, in 13 cases foetus was exposed during the 1st trimester, in 4 cases foetus was exposed during the 2nd trimester, and in 2 case exposure occurred during the 3rd trimester. Of these 39 cases, in 2 cases the mother of the baby was an asymptomatic gene carrier or had familial risk factors. In the remaining 37 cases, there was limited information regarding mother's obstetric history, which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: Thirty-seven (37) cases reported spontaneous abortion. Of these 37 cases, information regarding trimester of exposure was provided in 17 cases. Of these 17 cases, in 15 cases, foetus was exposed during the 1st trimester, in 2 cases foetus was exposed during the 2nd and the 3rd trimester each. The most frequently reported events (>1 occurrence) in these 37 cases other than exposure related events were coded to PTs Foetal growth restriction (18), Congenital anomaly (8), Foetal heart rate abnormal (3), Cytogenetic abnormality, Foetal vascular malperfusion (2 each). Of these 37 cases, in 4 cases mother had underlying medical history (i.e., spontaneous abortion, induced abortion and/or tobacco abuse), which might have contributed to the reported events. In the remaining 33 cases, there was limited information regarding obstetric history or co suspect medications of the mother, which precluded meaningful causality assessment.

- Pregnancy outcome: Elective termination: Twenty-three (23) cases reported elective termination of pregnancy. Of these 23 cases, 22 cases reported elective termination due to foetal defects and 1 case reported elective termination without foetal defects or unknown. Of these 23 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 7 cases foetus was exposed during the 1st trimester, in 1 case, foetus was exposed during the 2nd trimester. The most frequently reported events (>1 occurrence) in these 23 cases other than exposure related events were coded to the PTs Heart disease congenital (4), Foetal malformation (3), Congenital central nervous system anomaly, Abortion induced (2 each). Of these 23 cases, in 5 cases mother had underlying medical history (i.e., spontaneous abortion, and/or gestational diabetes), which might have contributed to the reasons for elective termination of foetus. In the remaining 18 cases, there was limited information regarding obstetric history or co suspect medications of mother, which precluded meaningful assessment.

- Pregnancy outcome: Stillbirth: Twenty one (21) cases reported foetal death/neonatal death. Of these 21 cases, 15 cases reported stillbirth with foetal defects and remaining 6 cases reported stillbirth without foetal defect. Of these 21 cases, information regarding trimester of exposure was provided in 6 cases. Of these 6 cases, in 3 cases foetus was exposed during the 1st trimester, in the remaining 3 cases, foetus was exposed during the 2nd trimester. The most frequently reported events (>1 occurrence) in these 21 cases other than exposure related events were coded to the PTs Premature baby (7), Foetal hypokinesia (5), Foetal death, Foetal heart rate abnormal (4 each), Foetal growth restriction (3). Of these 21 cases, in 5 cases the mother had underlying medical history (i.e., spontaneous abortion, and/or obesity), which might have contributed to the reported event. In the remaining 16 cases, there was limited information regarding obstetric history or co suspect medications of mother, which precluded meaningful causality assessment.

- Pregnancy outcome: Live birth without congenital anomaly: Two hundred two (202) cases reported live birth babies without congenital anomaly. Of these 202 cases, information regarding trimester of exposure was available in 58 cases. Of these 58 cases, in 26 cases, foetus was exposed during the 3rd trimester, in 20 cases foetus was exposed during the 2nd trimester, and in 12 cases exposure occurred during the 1st trimester. The frequently reported events (≥5 occurrence) in these 202 cases other than exposure related events were coded to PTs Premature baby (74), Foetal growth restriction (22), Foetal hypokinesia (12), Jaundice neonatal (9), Foetal heart rate abnormal, Congenital anomaly, Foetal distress syndrome (7 each), Immunisation (6), Neonatal respiratory distress syndrome, Breech presentation (5 each). Of these 202 cases, in 1 case reporting cerebral thrombosis and cerebral haemorrhage foetal the baby was delivered using vacuum extractor, which might have led to development of reported event. In the remaining 201 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

- Of the 3642 cases, 1898 cases provided pregnancy outcomes, which are provided in Table 69 (not reproduced here).

Literature

During the reporting period an article including new significant information regarding the use of BNT162b2 in pregnant/lactating women was identified: Citu IM, Citu C, Gorun F, et al. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. J Clin Med. 2022; 11(6):1698. This article contributes to the growing evidence that risk of spontaneous abortion after COVID-19 vaccine immunisation during the first trimester of pregnancy is commensurate with the predicted risk in nonvaccinated pregnant 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

Cumulatively, 58 cases (35%) out of 166 mother cases reported spontaneous abortion or abortion related events. In 25 cases the mother had a confounding medical history (spontaneous abortion, alcohol/tobacco use during pregnancy, ectopic pregnancy, obesity, diabetes mellitus, uterine disorder, depression or anembryonic gestation) and in 33 cases there was limited information which precluded meaningful assessment.

Post-marketing data

During the interval period, 566 cases (20%) out of 2,785 mother cases reported abortion spontaneous compared to 1040 cases (27%) out of 3,740 mother cases retrieved in the previous interval period.

Regarding pregnancy outcome, 37 cases (11%) out of 322 baby/foetal cases reported spontaneous abortion compared to 101 cases (23%) out of 443 baby/foetal cases retrieved in the previous interval period.

Literature

An article was published which showed that the risk of spontaneous abortion does not increase following first trimester mRNA COVID-19 vaccination (Citu et al.).

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

Use in immunocompromised patients

Search criteria: *Patients with Medical history of PTs included in Malignancy related conditions (SMQ Narrow); Malignancy related therapeutic and diagnostic procedures (SMQ Narrow); Malignant or unspecified tumours (SMQ Narrow); HLGT: Immunodeficiency syndromes (Primary Path); HLT: Retroviral infections (Primary Path); PTs: Allogenic bone marrow transplantation therapy; Allogenic stem cell transplantation; Autologous bone marrow transplantation therapy; Autologous haematopoietic stem cell transplant; Bone marrow transplant; Cord blood transplant therapy; Heart transplant; Liver transplant; Lung transplant; Pancreas islet cell transplant; Renal transplant; Small intestine transplant; Stem cell transplant.*

Clinical trial data

- Number of cases:110 (BNT162b2 [90], blinded therapy [18], and BNT162B2S01, placebo [1 each]) (16.5% of 668 cases, the total CT dataset), compared to 110 cases (15.3%) retrieved in the PSUR #2.
- Most frequently reported clinical PTs (>2%): Condition aggravated (8), Atrial fibrillation (4), Cerebrovascular accident (4), Gastroenteritis (4), Osteoarthritis (4), Pneumonia (4), Acute kidney injury (3), Peritonitis (3), Pyrexia (3).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.

Post-authorisation data

- Number of cases:8,815 (1.7% of 507,683 cases, the total PM dataset), compared to 14,657 cases (2.2%) retrieved in the PSUR #2.
- MC cases (3474), NMC cases (5341).
- Country of incidence: France (2200), UK (2070), Germany (1085), US (726), Italy (314), Sweden (312), Japan (212), Austria (192), Spain (158), Netherlands (156), Denmark (131), Belgium (119), Canada (116), Norway (112); the remaining 912 cases were distributed among 53 countries.
- Subjects' gender: female (5967), male (2628) and unknown (220).
- Subjects' age in years (n = 8073), range: 5 – 100, mean: 58.2, median: 60.0.
- Medical history (n = 8815). The most frequently (≥200 occurrences) reported relevant medical conditions included Immunodeficiency (1647), Breast cancer (1121), Thyroidectomy (566), Neoplasm malignant (466), Hysterectomy (407), Chemotherapy (377), Prostate cancer (330), Radiotherapy (272), Chronic lymphocytic leukaemia (243), Neoplasm (239).
- COVID-19 Medical history (n = 689): COVID-19 (418), Suspected COVID-19 (249), COVID-19 pneumonia (22), Post-acute COVID-19 syndrome (15), SARS-CoV-2 test positive (4), Asymptomatic COVID-19, Exposure to SARS CoV 2 (3 each), Coronavirus infection, Coronavirus test positive (2 each).

- Co-suspects (n = 608): The most frequently (≥10 cases) reported co-suspect vaccines/medications included COVID-19 vaccine NRVV AD (113), COVID-19 vaccine (101), COVID-19 vaccine MRNA (95), Influenza vaccine (23), prednisone (20), mycophenolate mofetil (18), adalimumab (16), casirivimab/ imdevimab, tacrolimus (13 each), Influenza vaccine inact split 4V, JNJ 78436735, nivolumab, ocrelizumab (10 each).
- Number of events: 38,399.
- Event seriousness: serious (21,926), non-serious (16,507).
- Most frequently reported clinical PTs (≥3%): Immunisation (1248), Interchange of vaccine products (1223), Headache (1096), Fatigue (1030), Pyrexia (827), COVID-19 (740), Pain in extremity (686), Dyspnoea (605), Arthralgia (589), Myalgia (535), Dizziness (516), Pain (510), Nausea (488), Asthenia (478), Lymphadenopathy (456), Malaise (420), Chills (401), Chest pain (389), Vaccination site pain (374), Palpitations (326), Paraesthesia (313), Vomiting (292), Condition aggravated (254), Tachycardia (246).
- Time to event onset (n = 23,969 events), range: from <24 hours to ≤540 days, median: 1 day.
- Duration of event (n = 3184 of 6987 events with outcome of resolved/resolved with sequelae) , range: <24 hours to 200 days, median: 3 days.
- Event outcome: fatal (1006), resolved/resolving (10,930), resolved with sequelae (821), not resolved (8997), unknown (16,862).

Analysis by age group

- Clinical trial data: Paediatric (16), Adults (39), and Elderly (55). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing data: Paediatric (96), Adults (4828), Elderly (3198) and Unknown (693).
    - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to the PTs Headache, Lymphadenopathy, Palpitations and Tachycardia.
    - A higher reporting proportion of events coded to the PT Headache was observed in the adult population (16.6% [752 cases] in adults vs 8.2% [251 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Lymphadenopathy was observed in the adult population (7.4% [334 cases] in adults vs 2.6% [78 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Palpitations was observed in the adult population (5.2% [234 cases] in adults vs 2.1% [64 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Tachycardia was observed in the adult population (4.1% [185 cases] in adults vs 1.5% [46 cases] in elderly) compared to the elderly population.
    - No comparison was made to the paediatric population considering the limited number of cases.

MAH's conclusion

No new significant safety information was identified based on a review of these cases.

Rapporteur assessment comment:

No new important safety information could be identified in immunocompromised patients exposed to Comirnaty.

Use in patients with autoimmune or inflammatory disorders

Search criteria: *Patients with Medical history PTs included in SMQ Immune-mediated/autoimmune disorders (Narrow and Broad scope); HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction*.

Clinical trial data

- Number of cases:102 (BNT162b2 [86], blinded therapy [14], and placebo [2]) (15.3% of 668 cases, the total CT dataset), compared to 101 cases (14.0%) retrieved in the PSUR #2.
- Of the 102 cases, the most frequently reported PTs (≥3%) included: Condition aggravated (6, 5.9%) and Atrial fibrillation (4, 3.9%).
- Event outcome: fatal (10), resolved/resolving (93), resolved with sequelae (3), and not resolved (24).
- In 6 cases (reporting 10 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Acute myeloid leukaemia, Adenocarcinoma pancreas, Cardiac failure congestive, Cardio-respiratory arrest, Completed suicide, Condition aggravated, COVID-19, Death, Pneumonia, and Sudden cardiac death (1 each). Of note, limited information regarding the cause of death was provided in 1 case (PT Death). Half (3 of 6 cases) of the fatal cases involved elderly subjects. The medical history reported included hypothyroidism, (3), colitis ulcerative, diabetes mellitus, narcolepsy, neuropathy peripheral (1 each).
- BNT162b2 related events coded to the PT Dehydration (1). Time to onset of event is 1 day and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-authorisation data

- Number of cases:21,000 (4.1% of 507,683, the total PM dataset), compared to 35,514 cases (5.4%) retrieved in the PSUR #2.
- MC cases (6424), NMC cases (14,576).
- Of the 21,000 cases, the most frequently reported clinical PTs (>3%) included: Fatigue (3103, 14.8%), Headache (3082, 14.7%), Pyrexia (2207, 10.5%), Immunization (1750, 8.3%), Pain in extremity (1680, 8.0%), Arthralgia (1675, 8.0%), Interchange of vaccine products (1568, 7.5%), Myalgia (1535, 7.3%), Dizziness (1478, 7.0%), Dyspnoea (1385, 6.6%), Vaccination site pain (1360, 6.5%), COVID-19 (1344, 6.4%), Nausea (1308, 6.2%), Pain (1226, 5.8%), Malaise (1180, 5.6%), Chills (1174, 5.6%), Asthenia (1083, 5.2%), Chest pain (932, 4.4%), Paraesthesia (929, 4.4%), Lymphadenopathy (896, 4.3%), Condition aggravated (813, 3.9%), Palpitations (794, 3.8%), Tachycardia (646, 3.1%), and Hypoaesthesia (640, 3.1%).
- Event seriousness: serious (39,651), non-serious (43,889).
- Event outcome: fatal (1295), resolved/resolving (27,683), resolved with sequelae (2277), not resolved (25,409), unknown (27,206).
- In 409 cases (reporting 1295 relevant events with a fatal outcome), the reported causes of death (≥ 20 occurrences) were coded to the PTs Death (63), Immunisation (44), Cardiac arrest, COVID-19 (36 each), COVID-19 pneumonia (33), Dyspnoea (23), Cardio-respiratory

arrest (22), Interchange of vaccine products, Sudden death (21 each), and Cardiac failure (20). Of note, in 84 cases, limited information regarding the cause of death was provided (PTs Death and Sudden death). Immunisation and Interchange of vaccine products are discussed in the Section Off Label Use. Most (326 of 409 cases) of the fatal cases involved elderly subjects. The most frequently (≥10 occurrences) reported medical history included diabetes mellitus (169), hypothyroidism (53), rheumatoid arthritis (36), type 1 diabetes mellitus (20), pulmonary fibrosis (15), rheumatic disorder (13), colitis ulcerative, psoriasis, and thyroid disorder (10 each).

- The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

Exacerbation or flare-up

- A focused analysis on exacerbation or flare of autoimmune or inflammatory disorders was conducted using PTs of interest (i.e., condition aggravated, disease progression), rather than all events.
- Of the 1117 cases that reported PTs indicative of exacerbation or flare, 345 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
    - The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (e.g., pain, arrhythmia, elevated blood pressure/hypertension, deep vein thrombosis, renal disease, migraine, fatigue/tiredness).
- Therefore, 772 cases are included in the analysis below.
- Clinical trial data
    - 1 case (BNT162b2) (0.1% of 668 cases, the total CT dataset), compared to 1 (0.1%) retrieved in the PSUR #2. The events were considered unrelated to BNT162b2.
- Post-authorisation data
    - Number of cases:771 (0.2% of 507,683 cases, the total PM dataset), compared to 750 (0.1%) retrieved in the PSUR #2.
    - MC cases (274), NMC cases (497).
    - Country of incidence: France (185), Germany (126), UK (118), Netherlands (54), Italy (51), US (35), Austria (23); the remaining 179 cases were distributed among 34 countries.
    - Subjects' gender: female (584), male (180) and unknown (7).
    - Subjects' age in years (n = 736), range: 9 – 90 years, mean: 50.7 years, median: 51 years.
    - Relevant medical history: the most frequently (>20 occurrences) reported medical conditions included: Autoimmune thyroiditis (79), Hypothyroidism (53), Rheumatoid arthritis (49), Psoriasis (34), Pericarditis (29), Colitis ulcerative, Diabetes mellitus, Multiple sclerosis (28 each), Autoimmune disorder, Basedow's disease (27 each), Ankylosing spondylitis, Systemic lupus erythematosus (26 each), Immune thrombocytopenia (25), Sjogren's syndrome (22), Crohn's disease (21), Arthritis, and Psoriatic arthropathy (20 each).

- COVID-19 Medical history (n = 61): COVID-19 (43), Suspected COVID-19 (20), Post-acute COVID-19 syndrome (5), and SARS-CoV-2 test positive (1).
- Co suspect vaccines/medications: Influenza vaccine (5), COVID-19 Vaccine MRNA (MRNA) 1273) (3), Adalimumab, COVID-19 Vaccine NRVV AD (CHADOX1 NCOV-19) (2 each), acyclovir, colchicine, Hepatitis B vaccine, hydroxychloroquine, ocrelizumab, and pneumococcal vaccine polysacch 23V (1 each).
- Number of events: 4633 (of which 782 were events of interest ie, exacerbation/flare AEs).
- Relevant event seriousness: serious (521), non-serious (266).
- Most frequently reported relevant PTs (≥2%): Condition aggravated (548), Disease recurrence (200), and Concomitant disease aggravated (22).
- Time to event onset (n = 424), range: from 1 day to 164 days, median: 4 days.
- Duration of relevant events (n = 41 out of 112 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 160 days, median 17 days.
- Relevant event outcome: fatal (4), resolved/resolving (224), resolved with sequelae (18), not resolved (332), unknown (208).
- In 4 cases (reporting 4 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Disease recurrence (3), and Condition aggravated (1). Three of the 4 cases involved elderly subjects. The medical history reported included arthritis, autoimmune hepatitis, Miller Fisher syndrome, and thrombotic thrombocytopenic purpura.

- Analysis by age group
  - Clinical trial: Paediatric (1).
  - Post-marketing: Paediatric (19), Adults (572), Elderly (155) and Unknown (25).
    - Exacerbation and/or flare of underlying autoimmune or inflammatory disorders occurred more frequently in the adult population, which is likely due to autoimmune disorders being more common in adults and the fact that adults are the largest group of vaccinated individuals reporting adverse events

MAH's conclusion

Overall, there were 772 cases (1 CT case and 771 PM cases [0.2% of the overall dataset]) that reported exacerbation/flares in subjects with autoimmune or inflammatory disorders following administration of BNT162b2. Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders occurred more frequently in the adult population which is likely due to the fact that the largest group of vaccinated individuals reporting AEs are in this age group. Also, the autoimmune or inflammatory disorders often occur during adulthood. The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

Rapporteur assessment comment:

No new important safety information could be identified in patients with autoimmune or inflammatory disorders.

Use in frail patients with comorbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis)

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.*

Clinical trial data

- Number of cases: 153 (BNT162b2 [125], blinded therapy [25], and placebo [3]) (22.9% of 668 cases, the total CT dataset), compared to 176 cases (24.4%) retrieved in the PSUR #2.
- Country of incidence: US (123), Argentina (11), Germany (9), Brazil (3), China, Spain (2 each); the remaining 3 cases were distributed among 3 countries.
- Subjects' gender: female (56), male (97).
- Subjects' age in years (n = 153), range: 0.83 – 87 years, mean: 59.6 years, median: 64 years.
- Medical history (n = 153): the most frequently (≥5 occurrences) reported relevant medical conditions included Type 2 diabetes mellitus (71), Asthma (33), Chronic obstructive pulmonary disease (23), Diabetes mellitus (14), Cardiac failure congestive, Chronic kidney disease (10 each), Pulmonary embolism (7), and Bronchitis chronic (5).
- COVID-19 Medical history: COVID-19 (2).
- Co-suspects (n = 33 cases): The reported co-suspect agents included metformin (2), amiodarone, amlodipine, aripiprazole, atenolol, diltiazem, duloxetine, furosemide, hydrochlorothiazide/triamterene, hydroxyzine, losartan, semaglutide, tamsulosin, warfarin (1 each).
- Number of events: 187.
- Most frequently reported clinical PTs (>2%): Condition aggravated, Pneumonia (6 each), Cerebrovascular accident, Dyspnoea (5 each), and Coronary artery disease (4).
- BNT162b2 related events were coded to the PT: Dehydration (1). Time to onset of event is 1 day and the event outcome is reported as resolved. None of the events were related to blinded therapy.
- Time to event onset: (n = 131), range: from 1 day to 178 days, median: 106 days.
- Duration of relevant events (n = 78 out of 103 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 78 days, median 5 days..
- Reported event outcome: fatal (13), resolved/resolving (128), resolved with sequelae (10), not resolved (36), and unknown (0).
- In 9 cases (reporting 13 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Death (2), Adenocarcinoma pancreas, Cardiac failure congestive, Cardio-respiratory arrest, Completed suicide, Condition aggravated, COVID-19, Drowning, Pneumonia, Pulmonary embolism, Respiratory failure, and Sudden cardiac death (1 each). Of

note, in 2 cases, limited information regarding the cause of death was provided (PT Death). Most (5 of 9 cases) of the fatal cases involved elderly subjects. The most frequently (>1 occurrence) reported medical histories included type 2 diabetes mellitus (6) and Asthma (2).

Post-authorisation data

- Number of cases:18,276 (3.6% of 507,683, the total PM dataset), compared to 33,889 cases (5.2%) retrieved in the PSUR #2.
- MC cases (6964), NMC cases (11,312).
- Country of incidence: France (3532), Germany (3124), UK (2189), US (1520), Sweden (1062), Japan (765), Italy (616), Austria (471), Norway (448), Spain (442), Denmark (408), Netherlands (396), Finland (305), Canada (260), Belgium (240), Czech Republic (234), Estonia (222), Iraq (220), Ireland (196), Greece (164), Taiwan, province of China (144), Portugal (143), Switzerland (136), Poland (102); the remaining 937 cases were distributed among 54 countries.
- Subject's gender: female (11,576), male (6436), and unknown (264).
- Subject's age in years (n = 17,342), range: 3 - 107 years, mean: 54.1 years, median: 55 years.
- Medical history (n = 18,276): the most frequently (≥75 occurrences) reported relevant medical conditions included Asthma (7896), Diabetes mellitus (3121), Type 2 diabetes mellitus (2001), Chronic obstructive pulmonary disease (1201), Type 1 diabetes mellitus (649), Cardiac failure (616), Chronic kidney disease (608), Pulmonary embolism (564), Renal failure (343), Parkinson's disease (247), Dementia (242), Hypokinesia (168), Cognitive disorder (166), Dementia Alzheimer's type (146), Bronchitis chronic (133), Renal disorder (117), Bronchiectasis (107), Asthma exercise induced (100), Cardiac failure chronic (81), Cardiac failure congestive (77), Bronchospasm, IgA nephropathy (76 each), and Hepatic cirrhosis (75).
- COVID-19 Medical history (n = 1226): COVID-19 (912), Suspected COVID-19 (268), COVID-19 pneumonia (38), Post-acute COVID-19 syndrome (36), SARS-CoV-2 test positive (13), Coronavirus infection (8), Asymptomatic COVID-19 (5), and Exposure to SARS-CoV-2 (1).
- Co-suspects (n = 929 cases): The most frequently (>5 occurrences) reported co-suspect vaccines/medications included COVID-19 vaccine (250), COVID-19 vaccine MRNA (MRNA 1273) (141), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (129), influenza vaccine (58), influenza vaccine inact split 4V (24), ocrelizumab, prednisone (19 each), JNJ 78436735, mycophenolate mofetil (15 each), apixaban (14), influenza vaccine inact SAG 4V (13), tacrolimus (12), adalimumab (11), rituximab (9), prednisolone (8), atorvastatin, levothyroxine, methotrexate (7 each), allopurinol, clopidogrel, influenza vaccine inact SAG 3V, and pregabalin (6 each).
- Number of events: 70,918
- Relevant event seriousness: serious (34,905), non-serious (36,098).
- Most frequently reported (≥3%) clinical PTs: Headache (2624, 15.0%), Fatigue (2570, 14.6%), Pyrexia (2012, 11.5%), Dyspnoea (1797, 10.2%), Immunisation (1533, 8.7%), COVID-19 (1446, 8.2%), Interchange of vaccine products (1383, 7.9%), Pain in extremity (1366, 7.8%), Dizziness (1255, 7.2%), Myalgia (1212, 6.9%), Arthralgia (1179, 6.7%), Vaccination site pain (1173, 6.7%), Nausea (1146, 6.5%), Malaise (1073, 6.1%), Asthenia (970, 5.5%), Chills (925, 5.3%), Pain (907, 5.2%), Chest pain (826, 4.7%), Palpitations (668, 3.8%),

Lymphadenopathy (614, 3.5%), Paraesthesia (602, 3.4%), Cough (585, 3.3%), and Vomiting (561, 3.2%).

- Time to event onset (n = 46,814), range: from 1 day to 180 days, median: 2 days.
- Duration of relevant events (n = 8391 out of 16,690 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 181 days, median 3 days.
- Relevant event outcome: fatal (2258), resolved/resolving (24,735), resolved with sequelae (1867), not resolved (19,410), unknown (23,001).
- In 801 cases (reporting 2258 relevant events with a fatal outcome), the reported cause of death (≥26 occurrences) was coded to the PTs Death (144), Immunisation (92), COVID-19 (91), COVID-19 pneumonia (80), Cardiac arrest (62), Cardiac failure, Dyspnoea (50 each), Interchange of vaccine products (49), Sudden death (42), Cardio-respiratory arrest (40), Pulmonary embolism (38), Pneumonia (34), Respiratory failure (29), Pyrexia (28), and Myocardial infarction (26). Of note, in 186 cases, limited information regarding the cause of death was provided (PTs Death and Sudden death). Most (689 of 801 cases) of the fatal cases involved elderly subjects. The most frequently (≥20 occurrences) reported medical history included diabetes mellitus (169), type 2 diabetes mellitus (117), cardiac failure (113), chronic obstructive pulmonary disease (95), dementia (83), chronic kidney disease (72), asthma (55), cognitive disorder, pulmonary embolism (39 each), renal failure (38), Parkinson's disease (35), dementia Alzheimer's type (31), Cardiac failure chronic (27), and type 1 diabetes mellitus (20).

Analysis by age group

- Clinical trial: Paediatric (12), Adults (67), Elderly (74). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (625), Adults (11,157), Elderly (5906) and Unknown (588).
    - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the event coded to PT Lymphadenopathy.
    - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (4.7% [520 cases] in adults vs 1.0% [59 cases] in elderly) compared to the elderly population.
    - No comparison was made to the paediatric population considering the limited number of cases.

MAH's conclusion

The reporting proportion of not resolved cases (36.1%) and cases resolved with sequelae (3.1%) in frail subjects is similar to the reporting proportion observed in the overall population (31.7% for outcome of not resolved, 1.9% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (4.4%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (0.6%). This is expected, considering that most of the cases reporting a fatal outcome (64.4%) among the frail subjects involved subjects over 75 years of age who, due to their advanced age and underlying comorbidities, are more likely to die than younger individuals. Underlying comorbidities are likely to be contributory to their deaths.

The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity). It has not been systematically studied in frail individuals with severe comorbidities but there is much

post-authorisation data in this population as they have generally been targeted as high priority for vaccination. No safety signals have emerged that would be considered specific to this population.

Rapporteur assessment comment:

No important new safety information could be identified regarding use in frail patients with co-morbidities. For future PSURs in the section 'Update on special patient populations', the use in frail patients with co-morbidities 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**

Interactions with other vaccines

Search criteria: *HLT Interactions.*

Clinical trial data

- No relevant serious clinical trial cases reported during the reporting period, as in the PSUR #2.

Post-authorisation data

- Number of cases:3 (0.0006% of 507,683 cases, the total PM dataset), compared to 18 (0.003%) retrieved in the PSUR #2.

MAH's conclusion

Among the overall 146 cases, 143 were considered not relevant, as a drug interaction did not occur in 1 case, the interacting agents was not specified in 32 cases, BNT162b2 was not involved in 1 case and in the remaining 110 cases, the interaction occurred with alcohol, herbal or medications rather than another vaccine.

There were 3 cases in the overall post-marketing dataset that involved a vaccine interaction. The most frequently co-reported event (>2 occurrences) other than off label use and interchange of vaccines PTs was Pyrexia, which is consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS. There is no indication of a safety signal noted based on the review of these cases.

Rapporteur assessment comment:

No important new safety information could be identified regarding interactions with other vaccines. For future PSURs in the section 'Update on special patient populations', the 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. **Request for next PSUR**

2.4. Characterisation of risks

As reported in Section 16.1 Summary of Safety Concerns of the PSUR, on 08 July 2022 (after the DLP of this PSUR), the MAH submitted the EU RMP version 5.1 to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received on 10 March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087) and based on the accumulation of post-authorisation safety information.

In line with this update to the EU-RMP, the MAH proposes to remove the important identified risk of anaphylaxis from the list of safety concerns for the next PSUR reporting period, because anaphylaxis is

a known risk of vaccines that is understood by HCPs who administer vaccines and patients and does not considerably impact the benefit/risk profile of the vaccine. Product labelling and standards of medical care during the vaccination procedure provide adequate risk mitigation.

Rapporteur assessment comment:

Please refer regarding the important identified risk Anaphylaxis to 2.3. 'Evaluation of risks and new information', section 'Evaluation of important identified risks' of this AR.

2.4.1. Characterisation of important identified and potential risks

- Important Identified Risk: Anaphylaxis
- Important Identified Risk: Myocarditis and Pericarditis
- Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Rapporteur assessment comment:

Please refer regarding the important identified risks - Anaphylaxis – and - Myocarditis and Pericarditis - to 2.3. 'Evaluation of risks and new information', section 'Evaluation of important identified risks' of this AR.

Please refer regarding the important potential risk - Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) – to 2.3. 'Evaluation of risks and new information', section 'Evaluation of important potential risks' of this AR.

2.4.2. Description of missing information

Missing information:

- Use in pregnancy and while breast feeding

Rapporteur assessment comment:

Please refer regarding pregnancy and lactation to 2.3. 'Evaluation of risks and new information', section Use in pregnant/lactating women' of this AR. No important new safety information could be identified.

- Use in immunocompromised patients

Rapporteur assessment comment:

Please refer regarding immunocompromised patients to 2.3. 'Evaluation of risks and new information', section 'Use in immunocompromised patients' of this AR. No important new safety information could be identified.

- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Rapporteur assessment comment:

Please refer regarding frail patients with co-morbidities to 2.3. 'Evaluation of risks and new information', section 'Use in frail patients with co-morbidities' of this AR. No important new safety information could be identified.

- Use in patients with autoimmune or inflammatory disorders

Rapporteur assessment comment:
Please refer regarding patients with autoimmune or inflammatory disorders to 2.3. 'Evaluation of risks and new information', section 'Use in patients with autoimmune or inflammatory disorders' of this AR. No important new safety information could be identified.

- Interaction with other vaccines

Rapporteur assessment comment:
Please refer regarding interaction with other vaccines to 2.3. 'Evaluation of risks and new information', section 'Interaction with other vaccines' of this AR. No important new safety information could be identified.

- Long term safety data

  At the time of the initial submission, 2-month post dose 2 safety data were available for approximately half of the patients who have received BNT162b2 mRNA vaccine in Study C4591001. The pivotal clinical study is ongoing and ongoing non-interventional safety studies will collect longer term post-marketing safety data.

Rapporteur assessment comment:
The information regarding long-term safety data is noted.

3. Benefit evaluation

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS CoV-2 virus in individuals 5 years of age and older.

Rapporteur assessment comment:
There are no new data on efficacy that alters previous assessments, and which are described in the approved product information of Comirnaty. Of note, after the DLP of this PSUR: Comirnaty is currently also available as two adapted vaccines (only to be used in people aged 12 years and older who have received at least a primary vaccination course against COVID-19): - Comirnaty Original/Omicron BA.1 contains tozinameran and riltozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2. (procedure EMEA/H/C/005735/II/0140) - Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2. (procedure EMEA/H/C/005735/II/0143) The Comirnaty indication was extended to children 6 months - 4 years old (Tris/Sucrose presentation 3 micrograms/dose). (procedure EMEA/H/C/005735/X/0138) An EU procedure is ongoing concerning the extension application to add a new strength of 5/5 µg (tozinameran, famtozinameran) for children between 5 to 11 years of age. (procedure

4. Benefit-risk balance

During the reporting period of the PSUR, the posology recommendations for the booster use was amended from "individuals 18 years of age and older" to "individuals 12 years of age and older", provided further details on heterologous boosting and the boosting interval was shortened to at least 3 months after completion of the primary series (EMEA/H/C/005735/II/0093, EMEA/H/C/005735/II/0104 and EMEA/H/C/005735/II/0111).

There are safety issues identified, which include that dizziness should be added as an ADR to section 4.8 with frequency unknown in the Comirnaty product information. However, as the MAH already submitted a variation to amend the Comirnaty product information accordingly (procedure EMEA/H/C/005735/II/0152), this PSUSA procedure can be concluded with maintenance of the marketing authorisation(s).

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 (tozinameran) 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.

There is no need for changes to the frequency of PSUR submission for Comirnaty.

5. Rapporteur request for supplementary information

1. Regarding **multiple repeated booster doses**, during the reporting period the number of persons receiving multiple booster doses (i.e., homologous, heterologous, different strains) is increasing whereas the impact on safety and efficacy remains uncertain. In addition the impact (including long-term) of repeatedly (e.g., yearly) receiving booster doses (with or without strain updates) also remains unknown. The MAH is requested to discuss whether 'safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)' should be considered as *Missing information* in the RMP, and proposals should be provided how to address this knowledge gap in ongoing or newly proposed PASSs, as applicable.
2. Regarding ***multisystem inflammatory syndrome in children and in adults*** (MIS-C/ -A):
    a. During the reporting period, the MAH identified a total of 130 potential new MIS-A cases. Of these, 1 was classified as BC level 1 and considered probably related with Comirnaty. However, given the extensive exposure of Comirnaty in adults this is not considered unexpected and does not present a new safety concern. Another BC level 1 MIS-A (AER number [redacted]) reported by the MAH in the 14th SSR (interval period 16 Feb 2022-15 Apr 2022) was considered confounded by previous COVID-19 infection and therefore unlikely to be associated with Comirnaty. However, this case seems not to be retrieved in current safety database search. The MAH is requested to

explain why the BC level 1 MIS-A case (AER number [redacted]) from the 14th SSR was not included in current MIS-A overview (interval period 19 Dec 2021 to 18 Jun 2021).

b. During the interval period, the MAH reported post-marketing 207 relevant MIS-C/ -A cases. However, in Appendix 6A.4 of the PSUR the MAH reported 199 MIS-C/ -A cases during the interval period. The MAH is requested to explain this discrepancy in the numbers of retrieved MIS-C/ -A cases.

3. Regarding ***myocarditis***,

   a. The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 5-11 years, aged 12-15, aged 18-24, aged 25-29, aged 30-39, and aged ≥40 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, a WHO causality assessment, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.

   b. Upon analysis of the requested details of the fatal myocarditis cases the MAH is expected to discuss whether the current risk minimisation measures is still adequate.

4. Regarding ***pericarditis***:

   a. The MAH is requested to provide detailed information concerning the fatal cases with pericarditis in persons aged 18-24 years, 25-29 years, and ≥40 years and perform per case an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, a WHO causality assessment, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.

   b. Upon analysis of the requested details of the fatal pericarditis cases the MAH is expected to discuss whether the current risk minimisation measures is still adequate.

5. Regarding ***glomerulonephritis***, the MAH is requested to provide detailed information concerning the 46 cases with glomerulonephritis in the interval period and perform an WHO-UMC causality assessment per case, and to provide an updated review with DLP 14 Nov 2022 of cases reporting glomerulonephritis from their safety database including a WHO-UMC causality assessment per case regarding Comirnaty exposure.

6. Regarding ***fatal cases reported in paediatric persons***, the MAH is requested to provide detailed information concerning the fatal cases in persons aged 5-11 years and 12-17 years, perform per case a WHO causality assessment, and an assessment according to Brighton Collaboration case definition and Level of certainty classification, if applicable.

6. MAH responses to request for supplementary information

1. *Regarding **multiple repeated booster doses**, during the reporting period the number of persons receiving multiple booster doses (i.e., homologous, heterologous, different strains) is increasing whereas the impact on safety and efficacy remains uncertain. In addition the impact (including long-term) of repeatedly (e.g., yearly) receiving booster doses (with or without strain updates) also remains unknown. The MAH is requested to discuss whether 'safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)' should be considered as Missing information in the RMP, and proposals should be provided how to address this knowledge gap in ongoing or newly proposed PASSs, as applicable.*

MAH response

For the monovalent and bivalent booster doses, the safety of the vaccine in persons receiving multiple booster shots (including homologous, heterologous, and different strains) is being monitored across the MAH's portfolio of ongoing and planned PASS studies (Table 1).

Table 1. List of Relevant Planned and Ongoing PASS Studies

PASS Study	End of Data Collection	Final Report Date
C4591009	30 Sep 2025	31 Mar 2026
C4591010	31 Oct 2023	30 Sep 2024
C4591011	31 Jul 2024	31 Jan 2025
C4591012	30 Jun 2023	31 Dec 2023
C4591021	31 Mar 2024	30 Sep 2024
C4591022	30 Jun 2024	31 Dec 2024
C4591036	19 Nov 2028	27 Apr 2029
C4591038	31 Mar 2024	30 Sep 2024
C4591051	TBD	TBD
C4591052	TBD	TBD

All studies include a subset of patients with the MAH's primary series (2 or 3 doses, as applicable per age population). Some studies also include subsets of heterologous primary series. An overview of the booster combination doses collected in each study is summarised in Table 2.

Table 2. Overview of the Monovalent and/or Bivalent Booster Combinations Assessed in Ongoing PASS Studies

	Monovalent Booster				Bivalent Booster			
	Pfizer monovalent		Non-Pfizer monovalent		Pfizer bivalent	Non-Pfizer bivalent		
PASS Study [a]	1 Pfizer monovalent booster	Multiple Pfizer monovalent boosters	1 non-Pfizer monovalent booster	Multiple non-Pfizer monovalent boosters	Pfizer monovalent booster + 1 Pfizer bivalent booster	Non-Pfizer monovalent booster + 1 Pfizer bivalent booster	Pfizer monovalent booster + 1 non-Pfizer bivalent booster	Non-Pfizer monovalent booster + 1 non-Pfizer bivalent booster
C4591009	X							
C4591010	X	X						
C4591011	X	X	X					
C4591012	X	X	X		X	X	X	X
C4591021	X	X						
C4591022	X							
C4591036	X	X			X	X		
C4591038	X	X						
C4591051					X	X		
C4591052					X	X		

[a] All studies include a subset of patients with a Pfizer primary series (2 or 3 doses, as applicable). Some studies also include subsets of heterologous primary series

For future booster doses, the safety surveillance approach will depend on the outcome of current and future discussions with the EMA and the FDA surrounding the future of the COVID-19 vaccine. The MAH will assess the feasibility and the suitability of implementing an enhanced active safety surveillance when a new booster dose becomes available. For example, once a new booster dose becomes available, and depending on the level of completeness of ongoing studies, vaccinees from at

least 1 country could be enrolled and followed for potential safety events. Initial findings from this new active safety surveillance could be available shortly after launch of the new booster dose. This framework could be established then repeated for each subsequent booster dose. Therefore, studies of subsequent booster doses could enrol new patients but apply the same enhanced active surveillance framework for consistent safety surveillance.

The MAH does not consider that "safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)" should be considered missing information in the EU-RMP. For the purpose of the RMP, missing information refers to gaps in knowledge about the safety of the product within the approved indication. Regulatory authorities in various countries, including in the EU and US, have included in COMIRNATY product labelling, implicit and explicit information regarding the use of COMIRNATY in homologous and heterologous dosing scenarios. As such, there has been widespread use of COMIRNATY in primary and boosting mixed use scenarios without new significant safety information emerging from the experience, particularly as followed in the medical literature. In addition, routine pharmacovigilance has not uncovered new safety concerns relating to the use of different COVID-19 strain vaccines, namely bivalent vaccines against original and OMICRON BA.1 and BA.4/BA.5 strains of SARS-CoV-2. Routine pharmacovigilance will continue, and any new significant safety information will be reported appropriately.

Rapporteur assessment comment:

At the moment we agree that there is no gap in knowledge about the safety concerning the primary and boosting mixed use scenarios of Comirnaty since there is no new significant information that Comirnaty would be associated with a different safety profile when administered in such situations. Therefore, MAH's conclusion is endorsed that 'safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)' should not be considered missing information in the Comirnaty RMP.

However, after the DLP of the 3rd PSUR, Comirnaty has been variant updated (bivalent vaccines), approved and is currently being used in the EU. In light of this, in the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent Comirnaty or, indeed, when comparing the two different variant updated bivalent Comirnaty vaccines, should be discussed. **Request for next PSUR**

Issue solved

2. *Regarding **multisystem inflammatory syndrome in children and in adults** (MIS-C/ -A):*

    a. *During the reporting period, the MAH identified a total of 130 potential new MIS-A cases. Of these, 1 was classified as BC level 1 and considered probably related with Comirnaty. However, given the extensive exposure of Comirnaty in adults this is not considered unexpected and does not present a new safety concern. Another BC level 1 MIS-A (AER number [redacted]) reported by the MAH in the 14th SSR (interval period 16 Feb 2022-15 Apr 2022) was considered confounded by previous COVID-19 infection and therefore unlikely to be associated with Comirnaty. However, this case seems not to be retrieved in current safety database search. The MAH is requested to explain why the BC level 1 MIS-A case (AER number [redacted] from the 14th SSR was not included in current MIS-A overview (interval period 19 Dec 2021 to 18 Jun 2021).*

MAH response

AER numbers [redacted] and [redacted] are individual case reports which were identified from a single literature article[1] and entered into the MAH safety database. One case (AER# [redacted]) described a 48-year-old female patient who developed multisystem inflammation following receipt of the Moderna COVID-19 vaccine. This case was made invalid during the PSUR reporting period because the suspect product was not BNT162b2. The second case (AER #[redacted]) describes a 51-year-old male patient which was reported by the MAH in the 14th SSR; in error this case was presented with the other AER number from the 2 literature cases ([redacted]). This error has been corrected in the dataset and the BC level 1 case of the 51-year-old male who received BNT162b2 (AER #[redacted]) is presented below. This case is significantly confounded by a recent COVID-19 infection. As COVID-19 infection within the last 12 weeks is the current known aetiology of MIS-A, this is the most likely cause in this case and the case does not change the MAH's overall assessment of the potential association between BNT162b2 and MIS-A/C.

AER #[redacted] 51-year-old male, reported to be previously healthy.

Self-limiting COVID-19 symptoms in April 2021 concurrent with positive SARS-CoV-2 PCR tests in household contacts. Dose 1: 11 May 2021. 2 weeks later, onset of fever, watery diarrhoea and escalating abdominal discomfort. The patient sought care on 31 May 2021, 20 days after dose 1 for fever [redacted] and diarrhoea.

On admission he was tachycardic (130 bpm), hypotensive (90/60 mmHg), leucocytosis 19.4 x 103/µL (92% neutrophils). Anaemia (Hb 11 g/dL), thrombocytopenic (72000/µL) and had elevated CRP (334 mg/L), brain natriuretic protein (17768 pg/ml) and troponin (0.248 µg/l). Antibody testing confirmed previous COVID-19 infection. PCR testing for SARS-CoV-2 and enteric pathogens was negative. Imaging of the chest and abdomen was initially normal.

Despite fluids he required vasopressors and overt pulmonary oedema developed. Echocardiography confirmed biventricular dilatation with EF 20%.

After empiric MIS-A treatment with steroids and 1 dose of intravenous immunoglobulins (IV Ig) the symptoms, haemodynamics and inflammatory markers rapidly improved. EF was normal (60%) on 14 and 28 June 2021 whilst patient was on prednisolone. On steroids he experienced superficial desquamation of palms of hands and soles of feet and 2 episodes of mild conjunctivitis. He remained fully recovered as of February 2022 and received no further vaccination.

References

1. Jenny-Avital ER, Howe RA. Severe Multisystem Inflammatory Symptoms in 2 Adults after Short Interval between COVID-19 and Subsequent Vaccination. Emerg Infect Dis. 2022;28(5):1017-20.

Rapporteur assessment comment:

The BC level 1 MIS-A case (AER number [redacted] from the 14th SSR was not included in current MIS-A overview (interval period 19 Dec 2021 to 18 Jun 2021) because in error this case was presented with the wrong AER number [redacted]. This error has been corrected in the dataset and the BC level 1 case of the 51-year-old male who received Comirnaty (AER number [redacted]) is now also included. Because this case [redacted] is confounded by a recent COVID-19 infection which could be the cause of the MIS-A. Therefore, the case is considered unlikely related to Comirnaty exposure.

In conclusion, there were 2 BC level 1 MIS-A cases with AER numbers [redacted] and [redacted] a 50-year-old female (case reported in the literature from [redacted]; not considered unexpected and does not present a new safety concern) and a 51-year-old male (case reported in the

literature from [redacted]; considered not likely related to Comirnaty exposure), respectively.

No new important safety concern could be identified for MIS-A.

Issue solved

b. *During the interval period, the MAH reported post-marketing 207 relevant MIS-C/ -A cases. However, in Appendix 6A.4 of the PSUR the MAH reported 199 MIS-C/ -A cases during the interval period. The MAH is requested to explain this discrepancy in the numbers of retrieved MIS-C/ -A cases.*

MAH response

Eight cases were included in PSUR #3 section 16.3.3.1.9 which were erroneously not presented in Appendix 6.4, as the cases had previously been presented by the MAH in SBSR #2 (reporting period 16 December 2021 through 15 February 2022) (AER #s: [redacted] and SBSR #3 (reporting period 16 February through 15 April 2022) (AER #[redacted]).

Three cases were classified as BC level 4, and 4 cases as BC level 5 (all adult patients). One case was classified as a BC level 2 (probable) case of MIS-C. The clinical details are presented below and were reported in SBSR #2.

[redacted] 15-year-old male from the [redacted].

Reported preferred terms: drug ineffective, covid-19, myocarditis, pericarditis, renal impairment, shock, multisystem inflammatory syndrome in children, blood creatinine increased, oropharyngeal pain, abdominal pain, left ventricular dysfunction, pleural effusion, fatigue, pyrexia, sinus tachycardia.

The patient was reported to have no significant medical history and described as "previously fit and well". The patient's concomitant medications were not reported.

Dose 1; 20 October 2021. The patient had a history of COVID-19 infection (positive PCR) with mild symptoms 3 weeks prior to hospitalisation (given the reported information the positive PCR would have been approximately 2-3 weeks after dose 1). The patient presented to Accident and Emergency with a sore throat, generalised abdominal pain and in shock. Echocardiogram showed severe LV dysfunction and the patient required inotropes, intubation and ventilation. He was treated with IV antibiotics and high-dose steroids. Suspected paediatric inflammatory multisystem syndrome "associated with COVID-19 or vaccine (or combination of both)".

Significant renal impairment, high CRP (547), high ferritin (6000 µg/L), high D-dimers, creatinine kinase, creatinine and lactate dehydrogenase (values not reported). Echocardiogram (09 Dec 2021) showed severe LV dysfunction (EF 45%). Chest x-ray (06 Dec 2021) showed pleural effusions and possible fluid on the right side. Electrocardiogram (06 Dec 2021): sinus tachycardia, no ST changes. SARS-CoV-2 test (unspecified date) positive; troponin (normal high range 34): 08 Dec 2021 437 ng/L. Patient remained an inpatient at the time of the report and was "for IV Ig".

The patient was less than 12 weeks from COVID-19 infection and there is report of a positive SARS-CoV-2 test at the time of hospitalisation. Given COVID-19 is the current known aetiology of MIS-C this is the most likely cause in this case.

The additional 8 cases do not change the overall assessment of MIS-C/A.

Rapporteur assessment comment:

The MAH explained the discrepancy in the number of retrieved MIS-C/ -A cases (199 versus 207 cases). The missing 8 cases were previously reported in the 13th and 14th SSRs, and should have been included in Appendix 6A.4 of the PSUR. No new important safety concern could be identified for MIS-C/ -A.

Issue solved

3. *Regarding **myocarditis**,*

    a. *The MAH is requested to provide detailed information concerning the fatal cases with myocarditis in persons aged 5-11 years, aged 12-15, aged 18-24, aged 25-29, aged 30-39, and aged ≥40 years and perform per case an assessment according to Brighton Collaboration Myocarditis case definition and Level of certainty classification, a WHO causality assessment, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.*

    b. *Upon analysis of the requested details of the fatal myocarditis cases the MAH is expected to discuss whether the current risk minimisation measures is still adequate.*

MAH response

The PBRER described a total of 87 interval myocarditis events reporting a fatal outcome (86 unique cases). After the DLP of the PBRER, 2 of those cases were updated according to follow up data and no longer include a myocarditis event. The remaining 84 cases are analysed in Appendix 3 (see below in comment box) and a case narrative listing is provided in Appendix 5 (not reproduced here). Where cases reporting fatal myocarditis also co-reported a pericarditis event, the pericarditis event is also included in the analysis.

Overall, no new safety information was identified from the analysis of these cases and thus, no changes to the risk management measures are warranted.

Rapporteur assessment comment:

Please refer regarding the assessment of the 84 fatal cases to the PRAC Rapporteur's comments in:

Appendix 3.pdf

In persons aged 5-11 years, there were 2 fatal cases with myocarditis of which one case is considered BC level 1 and unlikely related to Comirnaty exposure and the other case considered BC level 3 and unassessable.

In persons aged 12-15 years, there were 3 fatal cases with myocarditis of which 1 case is considered BC level 3 and unlikely related to Comirnaty exposure and the other 2 cases considered BC level 4-5.

In persons aged 18-24 years, there were 4 fatal cases with myocarditis of which 2 cases are considered BC level 1 of which one case is considered possible related to Comirnaty exposure and the other case considered unclassified. The remaining 2 cases are considered BC level 4-5.

In persons aged 25-29 years, there were 5 fatal cases with myocarditis of which 3 cases are considered BC level 1 of which one case is considered possible related to Comirnaty exposure, one case unclassified, and one case unassessable. The remaining 2 cases are considered BC level 4.

In persons aged 30-39 years, there were 5 fatal cases with myocarditis of which 3 cases are

considered BC level 1 and all considered unlikely related to Comirnaty exposure. The remaining 2 cases are considered BC level 4-5.

In persons aged ≥40 years, there were 59 fatal cases with myocarditis of which:

- 15 cases are considered BC level 1 of which three cases are considered possible related to Comirnaty exposure, nine cases unlikely, and three cases unassessable;

- 3 cases are considered BC level 2 of which one case is considered unlikely related to Comirnaty, and two cases unassessable;

- 2 cases are considered BC level 3 and considered both unlikely related to Comirnaty;

- the remaining 39 cases are considered BC level 4-5.

The 6 cases with unknown age are considered all BC level 4.

Based on the information provided concerning the fatal cases reporting myocarditis and despite the 5 BC level 1 cases considered possible related, no new important safety information could be identified.

Issue solved

4. Regarding ***pericarditis***:

    a. *The MAH is requested to provide detailed information concerning the fatal cases with pericarditis in persons aged 18-24 years, 25-29 years, and ≥40 years and perform per case an assessment according to Brighton Collaboration Pericarditis case definition and Level of certainty classification, a WHO causality assessment, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.*

    b. *Upon analysis of the requested details of the fatal pericarditis cases the MAH is expected to discuss whether the current risk minimisation measures is still adequate.*

MAH response

The PBRER described a total of 19 interval pericarditis events reporting a fatal outcome. Of them, 8 cases co-reported a myocarditis event and were thus analysed in the myocarditis dataset. The remaining 11 cases are analysed in Appendix 4 (see below in comment box) and a case narrative listing is provided in Appendix 6 (not reproduced here).

Overall, no new safety information was identified from the analysis of these cases and thus, no changes to the risk management measures are warranted.

Rapporteur assessment comment:

Please refer regarding the assessment of the 11 fatal cases to the PRAC Rapporteur's comments in:

Appendix 4.pdf

In persons aged 25-29 years, there were 2 fatal cases with pericarditis of which both cases are considered BC level 1 and unlikely related to Comirnaty exposure.

In persons aged ≥40 years, there were 9 fatal cases with pericarditis of which two cases are considered BC level 1 and both unlikely related to Comirnaty exposure. The remaining 7 cases are considered BC level 4-5.

Based on the information provided concerning the fatal cases reporting pericarditis, no new important safety information could be identified.

Issue solved

5. *Regarding **glomerulonephritis**, the MAH is requested to provide detailed information concerning the 46 cases with glomerulonephritis in the interval period and perform an WHO-UMC causality assessment per case, and to provide an updated review with DLP 14 Nov 2022 of cases reporting glomerulonephritis from their safety database including a WHO-UMC causality assessment per case regarding Comirnaty exposure.*

MAH response

Details of 46 cases

As of the most current latest information reported in 46 cases as of 18 November 2022:

There were 2 sets of cases which appeared to be duplicates:

- two cases (AER # [redacted]; only AER # [redacted] will be discussed below in the Table 3).
- two other cases (AER # [redacted] and [redacted]; only AER # [redacted] will be discussed below in the Table 4).

Nine cases (AERs [redacted] reported a pre-existing medical condition and/or use of co-suspect/concomitant medication representing a reasonable alternative cause of the relevant event Glomerulonephritis: a pre-existing glomerulonephritis, COVID-19, autoimmine conditions of Autoimmune hepatitis, Psoriatic arthropathy, Autoimmune hypothyroidism and/or use of loop diuretics and immunosuppressants. The WHO causality of the relevant event in these 9 cases is considered as Unlikely. For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Twenty-three cases co-reported other renal serious PTs (eg. nephrotic syndrome, renal failure) and/or other PTs suggesting a possible alternative aetiology for development of the relevant event (eg, Systemic inflammatory response syndrome, Vasculitis). Table 3 ((see below in comment box) presents some details of these 23 cases and WHO causality assessment derived based on details reported (eg age of the patient, latency, medical history, co-reported PTs). For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Rapporteur assessment comment:

Please refer regarding the assessment of the 23 cases reporting glomerulonephritis and/or other PTs suggesting a possible alternative aetiology for development of the relevant event, to the PRAC Rapporteur's comments in:

Table 3.pdf

Of the 23 cases there were 2 cases considered possible related to Comirnaty exposure, 14 cases unlikely and 7 cases unassessable.

Table 4 (see below in comment box) presents details of the last 12 cases and WHO causality assessment derived based on details reported (eg, age of the patient, latency, medical history, co-reported PTs). For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Rapporteur assessment comment:

Please refer regarding the assessment of the 12 remaining cases reporting glomerulonephritis to the PRAC Rapporteur's comments in:

Table 4.pdf

Of the 12 cases there were 2 cases considered possible related to Comirnaty exposure, 2 cases unlikely and 8 cases unassessable.

Additional two (2) cases from the last PSUR

Two cases (AER # [redacted] and [redacted] were identified as reported in the PSUR#3 and were updated with a newly added PT glomerulonephritis post DLP of 18 June 2022. Based on the information reported in these cases:

1. The WHO causality assessment in case [redacted] is Unlikely; the complex medical history and the use of concomitant medication candesartan confound an assessment in a 62 YO male who developed relevant event about 4 months post Dose 2 with many renal co-reported PTs including vasculitis.

2. The WHO causality assessment in case [redacted] is Unlikely; the medical history of autoimmune thyroiditis confounds an assessment in a 15 YO female who developed relevant event 2 days post Dose 3 (the case reported exacerbation of haematuria that patient experienced after dose 2 as well).

These 2 cases will not be reported in the upcoming PSUR#4. For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Rapporteur assessment comment:

MAH's conclusion is endorsed, these 2 cases are considered unlikely related to Comirnaty exposure.

Cumulative Review Through 14 November 2022

As per the updated search, through 14 Nov 2022, 15 new cases reporting PT glomerulonephritis were identified.

Five cases (AER# [redacted] reported a pre-existing medical condition representing a reasonable alternative cause of the relevant event: a pre-existing glomerulonephritis, IgA nephropathy, Nephropathy, Pyelonephritis, COVID-19, and/or Systemic lupus erythematosus. The WHO causality of the relevant event in these 5 cases is considered as Unlikely. For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Table 5 (see below in comment box) presents details of the last 10 cases and WHO causality assessment derived based on details reported (eg, age of the patient, latency, medical history, co-

reported PTs). For complete narratives of these cases, refer to Appendix 1 Narrative Line Listing (not reproduced here).

Rapporteur assessment comment:

Please refer regarding the assessment of the 10 last cases reporting glomerulonephritis to the PRAC Rapporteur's comments in:

Table 5.pdf

Of the 10 cases there were 4 cases considered unlikely related to Comirnaty exposure and 6 cases unassessable.

MAH's conclusion

At this time, considering the available information, there are not sufficient data to conclude a causal relationship between COMIRNATY™ and the new onset or exacerbation of Glomerulonephritis.

Rapporteur assessment comment:

The MAH provided detailed information concerning the 46 cases with glomerulonephritis in the interval period and performed an WHO-UMC causality assessment per case, and provided an updated review with DLP 14 Nov 2022 of cases reporting glomerulonephritis.

Interval period of the PSUR

Of the 46 cases retrieved there were two duplicate cases, resulting in 44 cases. Two additional cases were added to the interval period, resulting finally in 46 cases:

- 4 cases are considered possible related to Comirnaty exposure;

- 27 cases unlikely related;

- 15 cases unassessable.

Review through 14 Nov 2022

Retrieved were 15 new cases reporting glomerulonephritis:

- 9 cases are considered unlikely related to Comirnaty exposure;

- 6 cases unassessable.

In conclusion, despite the 4 cases considered possible related, MAH's conclusion is endorsed that based on the provided data no causal association of Comirnaty with glomerulonephritis can be concluded. No new important information could be identified concerning glomerulonephritis. The MAH should closely monitor any new cases, patterns, or trends of reporting glomerulonephritis through routine pharmacovigilance.

Issue solved

6. *Regarding **fatal cases reported in paediatric persons**, the MAH is requested to provide detailed information concerning the fatal cases in persons aged 5-11 years and 12-17 years, perform per case a WHO causality assessment, and an assessment according to Brighton Collaboration case definition and Level of certainty classification, if applicable.*

MAH response

There were 81 fatal cases in persons aged 5-11 years and 12-17 years, one case ([redacted] was a 19-year-old subject. A listing of the 82 cases, including narratives, is provided in Appendix 2 (not reproduced here).

Of note, there were 3 reports [redacted] originating from EMA EudraVigilance-WEB that described non-fatal cases of pyrexia and pyrexia with somnolence; these cases were downgraded to non-serious cases.

Of the remaining 79 cases, 56 cases [redacted] were classified as unassessable because the information provided is either insufficient to assess or contradictory and could not be verified.

Rapporteur assessment comment:
The MAH considered all 56 cases unassessable. However, the PRAC Rapporteur considered cases [redacted] and [redacted] unclassified.

Of the remaining 23 cases, 6 described myocarditis ([redacted]) contributing to death and are therefore included in the response to Question 3.

Rapporteur assessment comment:
The cases [redacted] and [redacted] were not presented in detail in MAH's response on question 3 concerning myocarditis cases. These 2 cases are considered the 2 cases that 'were updated according to follow up data and no longer include a myocarditis event' in MAH's response on question 3, and considered unclassified. Of the remaining 4 cases, 3 cases are considered unlikely related to Comirnaty exposure and 1 case unassessable.

The remaining 17 fatal cases are described in Table 6 (see below in comment box).

Rapporteur assessment comment:
Please refer regarding the assessment of the 17 remaining fatal cases to the PRAC Rapporteur's

comments in:

Table 6.pdf

Of the 17 cases there were 15 cases considered unlikely related to Comirnaty exposure and 2 cases unassessable.

MAH's conclusion

There is no information in the review of these 82 paediatric fatal cases that identifies BNT162b2 as a contributor to the reported deaths. Fatal cases will continue to be monitored via routine pharmacovigilance.

Rapporteur assessment comment:

Of the 82 cases retrieved 3 cases were non-fatal cases, resulting in 79 cases:

- 18 cases are considered unlikely related to Comirnaty exposure;

- 4 cases unclassified;

- 57 cases unassessable.

Overall, MAH's conclusion is endorsed that based on the provided data no causal association of Comirnaty with the reported deaths can be concluded. No new important information could be identified concerning the reported deaths. The MAH should closely monitor any new cases, patterns, or trends of reporting fatal outcome through routine pharmacovigilance.

Issue solved

7. Comments from member states

MS1

We endorse the PRAC Rapporteur's assessment of the above-mentioned procedure, and have no further comments.

Rapporteur assessment comment:

The endorsement of the PSUR assessment is appreciated.

MS2

We agree with the Rapporteur and the MAH that dizziness should be added as an ADR in the Comirnaty SPC. Further, we would like to point out that there are also other events that are currently considered listed by the MAH as anxiety-related reactions, but which we consider not covered by the current SPC.

The table 18 in the PSUR presents the most commonly reported ADRs in the post-marketing data, and in this table dyspnoea and palpitations are marked as "listed or consistent with the listed AEs in the

current RSI". We assume that the MAH considers these events to be covered by the text in the section 4.4 describing anxiety-related reactions, as they are not listed in SPC section 4.8. However, based on the medical assessment of the reports received by MS2, in majority of the reports describing dyspnoea or palpitations these symptoms have lasted several days or even weeks, and thus are not considered to be anxiety-related reactions as described by the text in the section 4.4.

Correspondingly, in the section "Vaccination stress/anxiety related ADRs" tachycardia is presented as one of the stress/anxiety-related reactions covered by the current text in the SPC. However, in the reports received by MS2 describing tachycardia/increase in heart rate, these events have lasted several days or even weeks in majority of the reports, and thus are not covered by the text concerning anxiety-related reactions in the section 4.4.

We propose that in the next PSUR the MAH should present cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase, with special focus on the duration of the events. The MAH should evaluate whether these events should be added in the section 4.8 of the SPC.

Rapporteur assessment comment: Here we can agree with the comments. The proposed request for the next PSUR that the MAH should present cumulative analyses of dyspnoea, palpitations and tachycardia/heart rate increase, with special focus on the duration of the events not considered stress/anxiety-related reactions and to evaluate whether these events should be added in the section 4.8 of the SPC, is added.

MS3

The MS3 PRAC Rapporteur notes the request no 1 for supplementary information regarding multiple repeated booster doses.

At the time of approval of the bivalent mRNA vaccines, the MAHs committed to include additional pharmacovigilance activities (the new strains) in relevant PASS protocols at the first regulatory opportunity. These updates are currently ongoing. With this in mind and also given that the vast majority of future post-marketing data are expected to originate from vaccines used as part of multiple repeated booster dose schemes, the PRAC Rapporteur is unsure regarding to which extent a missing information category in the RMP summary of safety concerns will contribute additionally to the PSUR.

If potential safety issues specifically related to the new strains are of interest, a request *{confidential information deleted}* might be considered:

"Bivalent variant updated Comirnaty vaccines: After the DLP of the PSUR no 3, Comirnaty has been variant updated (bivalent vaccines), approved and is currently being used in the EU. In light of this, in the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent Comirnaty or, indeed, when comparing the two different variant updated bivalent Comirnaty vaccines, should be discussed."

Rapporteur assessment comment: Please refer to our assessment of MAH's response on the 1st request for supplementary information in section 6. Proposed request by the MS3 PRAC Rapporteur is added to the requests for next PSUR.

MS4

MS4 endorses the Rapporteur assessment report. However, MS4 has two additional comments regarding cases of "hearing loss" and "acquired haemophilia".

Hearing loss

In MS4, hearing loss following vaccination against COVID-19 with mRNA vaccines are closely monitored and analysed.

A national cross-sectional audiogram-based study was conducted, using the MS4 pharmacovigilance active surveillance system for COVID-19 vaccines. All suspected Sudden Sensorineural Hearing Loss (SSNHL) cases following mRNA COVID-19 vaccination between January 2021 and February 2022 were included. They were retrospectively reviewed based on a comprehensive audiological and medical evaluation by ENT. *{confidential information removed}*

Over the study period, 97,840,529 doses of Tozinameran (Pfizer-BioNTech BNT162b2) were administered in MS4. The Reporting Rates (RR) of mRNA vaccine-induced SSNHL cases were calculated per 1,000,000 injections. Clinical classification was made according to patient history, unilaterality or bilaterality of the hearing loss, its degree, and recovery after a minimum 3-month follow-up.

For these Tozinameran-induced SSNHL cases, the delay onset was ⩽21 days for 108 (76%) cases whose median (range) delay onset was 4 (2.0-9.0) days. Women were concerned in 84 (59%) cases. The median (range) age was 51 (13-83) years, and 98 (69%) patients were in the 30-64 years age class. A total of 50 (35%) patients had a medical history, it was otoneurologic in 17 (12%) cases. The vaccination rank was known for 125 cases, the first injection was involved in 60 (42%) cases. Steroids were administered orally in 67 (47%) cases. SSNHL was unilateral in 142 (79%) cases. Detailed audiometric thresholds were available in 98 (69%) cases, with SSNHL being measured as mild to moderately severe in 61/98 (62%) cases, and as profound in 17 (17%) cases. Tinnitus was associated with SSNHL in 75 (53%) cases and vertigo in 41 (29%) cases. Total recovery was observed in 37 (25%) cases while hearing aid fitting was required in 10 (7%) cases (Table 1). Deafness was more often unilateral than bilateral (p<0.001). Neither sex effect nor vaccination rank effect was found. Case follow-up identified 5 (4%) cases of positive rechallenge (Table 2).

The total RR was estimated at 1.45/1,000,000 doses for Tozinameran.

Table 1: Characteristics of the included SSNHL cases

	Tozinameran			
				p-value
	≤21 d	**>21 d**	**Total**	
Number of patients	**108 (76)**	**34 (24)**	**142 (100)**	
Sex				
Male	43 (40)	15 (44)	58 (41)	
Female	65 (60)	19 (56)	84 (59)	
Age, years, median (range)	**50 (13-83)**	**52 (16-72)**	**51 (13-83)**	
0-18	3 (3)	1 (3)	4 (3)	
19-29	7 (6)	0	7 (5)	
30-49	43 (40)	12 (35)	55 (39)	

50-64	26 (24)	17 (50)	43 (30)	
65-74	19 (18)	4 (12)	23 (16)	
≥75	10 (9)	0	10 (7)	
Medical History	**38 (35)**	**12 (35)**	**50 (35)**	
Cardiovascular (CV)	9 (8)	5 (15)	14 (10)	
Otoneurologic (ON)	12 (11)	5 (15)	17 (12)	
Auto immune disease (AIM)	7 (6)	2 (5)	9 (6)	
CV and ON	4 (4)	0	4 (3)	
ON and AIM	3 (3)	0	3 (2)	
Other etiology	3 (3)		3 (2)	
Delay onset*, days, median (range)	**4 (2.0-9.0)**	**41 (25-67)**		
Vaccination Rank				
First injection	47 (44)	13 (38)	60 (42)	
Second injection	39 (36)	14 (41)	53 (37)	
Booster	12 (11)	0	12 (9)	
Unknown	10 (9)	7 (21)	17 (12)	
Oral steroid administration	**48 (44)**	**19 (56)**	**67 (47)**	
Laterality				
Unilateral	87 (80)	25 (73)	112 (79)	p<0.001
Bilateral	16 (15)	4 (12)	20 (14)	
Unknown	5 (5)	5 (15)	10 (7)	
Degree of Hearing Loss [Pure Tone Average]	**76 (70)**	**22 (65)**	**98 (69)**	
Slight [16–25 dB HL]	4 (5)	1 (5)	5 (5)	
Mild [26–40 dB HL]	27 (35)	4 (18)	31 (32)	
Moderate [41–55 dB HL]	14 (18)	5 (22)	19 (20)	
Moderately severe [56–70 dB HL]	8 (11)	3 (14)	11 (11)	
Severe [71–90 dB HL]	11 (15)	4 (18)	15 (15)	
Profound [> 90 dB HL]	12 (16)	5 (23)	17 (17)	

Associated cochleovestibular disorders				
Tinnitus	59 (55)	16 (47)	75 (53)	
Vertigo and balance disorders	33 (30)	8 (24)	41 (29)	
Time to recovery, days, median (range)	**15 (5-67.5)**	**11 (8-22.5)**		
Outcome				
Total recovery	26 (24)	11 (32)	37 (25)	
No recovery at follow-up	66 (62)	18 (53)	84 (60)	
Hearing aid fitting requirement	8 (7)	2 (6)	10 (7)	
Unknown	8 (7)	3 (9)	11 (8)	
Positive Rechallenge	**5 (5)**	**0**	**5 (4)**	

Table 2: Characteristics of patients who experienced a positive rechallenge

Cases	Sex	Age	Medical History	Vertigo	Tinnitus	Vaccination rank	Delay onset	Unilateral/ bilateral	Deafness degree	Progression
N[redacted]	F	61	0	yes	yes	D1 D2	4 days 7 days	Unilateral	Moderate	Lasting
N[redacted]	M	47	0	no	yes	D1 D2	9 days 9 days	Unilateral	Moderate	Lasting
N[redacted]	F	74	**Fluctuating deafness and vertigo** treated by cortisone punctually	no	yes	D1 D2	8 days 9 days	Bilateral	Moderate	Resolved
N[redacted]	F	32	Protein S deficiency	no	no	D1 D2	8 days 2 days	Unilateral	Mild	Resolved
N[redacted]	F	79	**Diabetes stabilized** since 1977, **Left Meniere's disease** since 1977, Hypothyroidism stabilized, **High blood pressure** stabilized since 1985, **Hypercholesterolemia** stabilized since 1985	yes	yes	D1 D2 R1	8 days 8 days 1 day	Bilateral	Moderate	Resolved

D1: first vaccine injection, D2: second vaccine injection, R1: first booster, R-: no recurrence of deafness

{confidential information removed}

Conclusions

MS4 endorses that a causal association between Comirnaty and hearing loss or tinnitus cannot be concluded at this time.

However, taking into account that there is 5 well documented cases of positive rechallenge with a compatible TTO (⩽21 days) of which 2 are bilateral hearing loss and 13 cases of bilateral hearing loss with a compatible TTO (⩽21 days), MS4 considers that a causal association between hearing loss and the vaccination cannot be completely ruled out.

Therefore, MS4 considers that the MAH should continue to closely monitor hearing loss and all new cases should be reported and discussed in the future PSURs.

Rapporteur assessment comment:

An interesting submitted manuscript from the MS4 PV experts is shared prior to publication which is appreciated. However, the manuscript is not (yet) peer-reviewed and published. Therefore it is currently unknown whether a peer-review process would introduce changes to the manuscript that would impact on the results of the performed MS4 study. We assume that the described MS4 cases (between Jan 2021 – Feb 2022) had been submitted to EudraVigilance and therefore were also included in the current assessed cumulative review (through 18 Jun 2022). Also, there is endorsement that a causal association between Comirnaty and hearing loss or tinnitus cannot be concluded at this time after a thorough assessment of the current available information through 18 Jun 2022. When the manuscript is published in the near future, the MAH should discuss the study in the PSUR and the new cases reporting hearing loss as appropriate.

Acquired haemophilia

MS4 endorses the Rapporteurs conclusions that a causal association between Comirnaty and acquired haemophilia cannot be concluded at this time.

Moreover, taking into account the recent literature data, for example the review of Franchini et al.[1], and the potential mechanism of action[2,3,4], MS4 endorses the request that the MAH should continue to closely monitor acquired haemophilia and all new cases should be reported and discuss in the future PSURs.

[1] *Franchini M, et al. Investigating a Signal of Acquired Hemophilia Associated with COVID-19 Vaccination: A Systematic Case Review. Semin Thromb Hemost 2022 Sep 2. doi: 10.1055/s-0042-1754389.*

[2] *Franchini M, et al. The first case of acquired hemophilia A associated with SARS-CoV-2 infection. Am J Hematol. 2020;95(8):E197-e198*

[3] *Olsen GM, et al. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. Transfusion. 2020;61(3):989-991.*

[4] *Hirsiger JR, et al. Investigating potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. J Thromb Haemost. 2022 Feb 2. doi: 10.1111/jth.15665.*

Rapporteur assessment comment:

The endorsement regarding acquired haemophilia is appreciated.

MS5

We overall agree with Rapporteur's assessment, but would like to highlight some issues:

Autoimmune hepatitis

Overall, we endorse the PRAC Rapporteur assessment report. At this stage, only 99 cases with biopsy results (60 cases) or laboratory data (39 cases) were identified. From the cases with biopsy results, only 7 meet IAIHIG-revised scores and 9 meet IAIHIG-simplified scores. However, from the cases that meet criteria some of them have a time to onset not compatible with AIH (2 and 4 cases respectively). Regarding the cases with laboratory data available, none had sufficient information to score ≥6 and they cannot be classified as definite or probable cases. As the MAH stated there are several limitations regarding the interpretation of reports submitted voluntarily such as the underreporting and the lack of some important data for a thorough case evaluation, with impact in the O/E analysis.

We want to highlight a pre-proof article (Codoni et al, 2022) performed with cases collected from members of the International AIH Group (IAIHG) and the European Reference Network on Hepatological Diseases (ERN RARE-LIVER). The main advantages of this article are that only cases without known pre-existing liver diseases and transaminase Levels ≥5xULN within 3 months after any anti-SARS-CoV-2 vaccine were considered and that all cases have available liver biopsy. Fifty-nine patients, from 26 centers in 11 countries and exposed to seven different SARS-COV-2 vaccines were recruited. Most of the patients (35) were female patients. Hepatitis was diagnosed after the second vaccine dose in the majority of patients. Although the study included cases with 7 different COVID-19 vaccines, patients with liver injury after mRNA vaccines had higher transaminase levels and higher impairment of coagulation. A comparison between the two mRNA vaccines was limited by the small patient numbers. In three quarters of the cases, liver histology showed a picture of predominant lobular hepatitis while predominant portal hepatitis was present in less than 1/5 of patients. The absence of advanced liver fibrosis in the work-up of an acute liver injury suggests drug-induced liver injury (DILI) or AIH-like DILI as more probable than AIH. In addition, AIH-like is characterized by a low relapse rate after withdrawal of a short-term steroid course. 91% of patients were treated with steroids, ± azathioprine. Serum transaminase levels improved in all cases and normalised 24/58 (41%) after three months, and in 30/46 (65%) after six months. One patient required liver transplantation. Re-exposure to SARS-CoV-2 vaccines of 15 patients resulted in four relapses (three after the same vaccine and one in a heterologous vaccination).

The systematic review mentioned by the MAH (Roy et al) including 23 patients with histopathological data in 13 studies showed similar results to the data observed for Comirnaty and the previous article. The authors of this systematic review stated that biochemically and histologically, most of the cases with ILI resembled AIH.

In summary, AIH should continue to be closely monitored in next PSURs. It would be important to follow-up the cases to differentiate real cases of AIH or AIH-like DILI, and consider the addition of some information in the SmPC.

Ref: Codoni G, Kirchner T, Engel B. et al. "Histological and serological features of acute liver injury after SARS-CoV-2 vaccination, JHEP Reports (2022), doi: https://doi.org/10.1016/j.jhepr.2022.100605.

Rapporteur assessment comment:

The endorsement of our autoimmune hepatitis assessment is appreciated and we agree that

autoimmune hepatitis should be closely monitored in the PSURs (as is stated in the AR). To differentiate at this stage between cases of AIH or AIH-like DILI without any new important information/signal concerning the occurrence of autoimmune hepatitis after Comirnaty exposure, seems however premature.

Thromboembolic events

We endorse the Rapporteur evaluation of thromboembolic events performed in previous monthly reports and summarized in this PSUR. To note that pulmonary embolism is one the most frequently reported events. Recently, 7 cases included under the HLT pulmonary thrombotic and embolic conditions have been reported in MS5 after the administration of Comirnaty Original/Omicron BA.4-5 within 2 weeks after vaccination. In four of these seven cases, flu vaccine was administered the same day of COVID-19 vaccine and in 1 case two days after. No disproportionality was found in the O/E analyses, but in view of these cases, we consider that pulmonary embolism should be closely monitored in the next PSUR. Particularly, a detailed analysis of the cases occurring with the Comirnaty original/omicrom BA 4-5 should be performed.

Rapporteur assessment comment:

The endorsement of the evaluation of thromboembolic events is appreciated. As stated no disproportionality was found in the O/E analyses. Therefore, there is no new important information/signal concerning the occurrence of pulmonary embolism after Comirnaty exposure and no need at the moment to request a review of pulmonary embolism in the next PSUR. AESIs including thromboembolic events will be closely monitored in PSURs.

Please refer to the MS3 comments regarding a detailed analysis of the cases occurring with the Comirnaty original/omicrom BA 4-5, above.

Hearing loss

18 896 spontaneous cases have been identified, 755 medically confirmed. We want to highlight the following considerations regarding these cases:

-Those cases that did not report diagnostic procedures or test have been considered "unassessable" according to the WHO-UMC criteria. In our view, this restrictive approach would not be appropriate, considering that these are cases already medically confirmed and it can be assumed that clinical judgement applies. This would affect around 386 out of 755 medically confirmed cases. It is worrying that serious cases, clinically confirmed may not be taken into account based on these criteria, but the number of serious cases clinically confirmed as well as the seriousness criteria has not been presented by the MAH. Therefore, the MAH should rather conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss.

-It seems that the majority occur after the first and second dose and they do not recover (392 of the 755), they recover or are recovering (292 of the 755). In addition, there are 33 patients that recover but with sequels. The MAH should provide further information on these patients that recover with sequela to better understand their particular situations and evaluate possible patterns.

Moreover, there are still 9023 cases that although not medically confirmed have not been taken into account despite some of them may have plausible TTO and/or not confounding factors.

Regarding O/E analysis, the assessors noted that the MAH imputed missing values of age, sex, dose and time to onset based on observed cases with known data. Although this may be a correct approach,

this should have been conducted as a sensitivity analysis, to be able to assess differences in O/E rates according to missing values. Nevertheless, it is known that these analysis although support the evaluation, would not confirm a causal association with the vaccine.

Moreover, in our view's, not all PTs should have the same weight in this analysis, being the sensorineural hearing loss is of utmost importance since the damage can be irreversible, depending on form (unilateral or bilateral) and symptoms onset. A distinction between sudden or progressive sensorineural hearing loss should be considered. In fact, the PRAC already requested to perform the cumulative review of cases of sudden sensorineural hearing loss, but further PTs have been included in this cumulative review. This may have diluted the evaluation of the cases.

In summary, we consider that based on the data presented, a causal association cannot be stablished nor discarded and changes in the product information are not warranted at this stage, but it should be monitored in the next PSUR. In particular, the MAH should reconsider PTs for the evaluation focussing on sudden sensorineural hearing loss and medically confirmed cases, and provide an updated cumulative review applying the Brighton Collaboration criteria for the evaluation of these cases, indicating serious cases and the seriousness criteria applied, as well as cases with outcome recovered with sequela, and rechallenge cases if new ones arise. Particular attention should be taken with regard to event outcome to determine whether patients recover from the event, and when, or not.

Rapporteur assessment comment:

Here we agree that serious clinically confirmed cases may not be taken into account due to that the MAH considered cases that did not report diagnostic procedures or test, as 'unassessable'. However, the number of serious clinically confirmed cases as well as the seriousness criteria has not been presented by the MAH. Therefore, we endorse that the MAH should conduct the analysis using the Brighton Collaboration Criteria for sensorineural hearing loss in future reviews of cases reporting hearing loss which is added as a request for next PSUR.

Please also refer to the MS4 comments above regarding hearing loss. Requesting the MAH to reconsider PTs for the evaluation focussing on sudden sensorineural hearing loss and medically confirmed cases in the next PSUR is not considered of added value because the O/E analysis showed that all O/E ratios were well below 1 and there is at the moment no new important information/signal concerning the occurrence of hearing loss after Comirnaty exposure.

IgA nephropathy and other glomerulonephritis

We consider that this safety topic should be kept as an important potential risk in the PSURs. Although at this stage there is no enough data to establish a causal relationship between Comirnaty and the development of IgA nephropathy, there are several cases with close temporal association. Additionally, a possible mechanism of action is described in the article by Farooq et al. The Rapporteur asked for clarifications regarding the increase in the number of cases of glomerulonephritis cases during this current interval. In MS5, 22 cases with glomerulonephritis were cumulatively reported and only 2 cases were IgA nephropathy. To note that there have been two cases with positive rechallenge. One of them in 53-year-old male patient who suffered macroscopic hematuria and nephritic syndrome after the two doses of Comirnaty and the other one in a 32-year-old male patient that suffered flares of its nephrotic syndrome after the two doses of Comirnaty. Therefore, if no additional conclusions are obtained from the responses required in the comments period, we consider that glomerulonephritis other than IgA nephropathy should be also closely monitored in the next PSUR.

Rapporteur assessment comment:

Please refer to the assessment of MAH's response on the 5th request for supplementary information in section 6. Here the PRAC Rapporteur concludes that based on the provided data no new important information could be identified concerning glomerulonephritis. The MAH should closely monitor any new cases, patterns, or trends of reporting glomerulonephritis through routine pharmacovigilance.

8. Late-breaking information PRAC rapporteur

Rapporteur assessment comment:

Regarding **post orthostatic tachycardia syndrome** (POTS), a recent publication has been noticed:

Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8

The authors found, for new diagnoses made after vaccination, that the five conditions with the highest post-vaccination odds of (new) diagnoses were myocarditis, dysautonomia, POTS, mast cell activation syndrome and urinary tract infection (UTI). Overall, the post-vaccination odds of new POTS-associated diagnoses (n = 4,526, odds = 1.33 (1.25–1.41), P < 0.001) was higher than for common primary care (CPC) diagnoses (n = 33,590, odds = 1.21 (1.18–1.23), P < 0.001) but lower than for myocarditis (n = 25, odds = 2.57 (1.02–6.77), P = 0.046). In repeated analyses around receipt of second (rather than the first) vaccination dose, overall similar findings were observed. In summary, POTS-related diagnoses appear to occur with increased frequency in the time period after COVID-19 vaccination as compared to the time period before, particularly when compared to more commonly diagnosed conditions, but at a rate that is approximately five times lower than after SARS-CoV-2 infection.

Therefore, the MAH is requested to discuss the publication of Kwan et al. concerning post orthostatic tachycardia syndrome and Comirnaty exposure and, if applicable, to perform a cumulative review on the association between Comirnaty and post orthostatic tachycardia syndrome. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.
Request for next PSUR