EMA/PRAC/617719/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202112

Active substance(s): covid-19 mRNA vaccine (nucleoside-modified) (COMIRNATY)

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

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:	10 March 2022	10 March 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	10 May 2022	09 May 2022
☐	MS/PRAC members and MAH comments	08 June 2022	08 June 2022
☐	PRAC Rapporteur's updated assessment report following comments	23 June 2022	21 Jun 2022
☒	PRAC recommendation	07 July 2022	07 July 2022

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for covid-19 mRNA vaccine (nucleoside-modified) (COMIRNATY).

2. Assessment conclusions and actions

The MAH submitted the 2nd EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 18 Feb 2022) covering the period 19/06/2021 through 18/12/2021.

During the current reporting interval, the indication was extended from "individuals 12 years of age and older" to "individuals 5 years of age and older" (EMEA/H/C/005735/X/0077). A booster dose of Comirnaty (at least 6 months after the second dose) for individuals 18 years of age and older was approved (EMEA/H/C/005735/II/0067). Also, a third dose of Comirnaty (at least 28 days after the second dose) for individuals 12 years of age and older who are severely immunocompromised was approved (EMEA/H/C/005735/II/0062). After the covering period of the PSUR, the posology recommendations for the booster use were further amended from "individuals 18 years of age and older" to "individuals 12 years of age and older", to provide 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).

Comirnaty (tozinameran) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals aged 5 years and older.

During the current reporting interval, an estimated 1,430,363,611 doses of Comirnaty were administered. Cumulatively, an estimated 2,100,134,815 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:

- Liver injury/Autoimmune hepatitis, Multisystem inflammatory syndrome in adults and children, Uveitis, Rhabdomyolysis, Hypoaesthesia/Paraesthesia, Erythema multiforme, Thrombocytopenia thrombosis syndrome, Myasthenia gravis, Immune thrombocytopenia, Herpes zoster including ophthalmic herpes zoster, and Appendicitis.

The evaluation of the following signals lead to the update of the product information within the current reporting interval for which no new important safety information was identified based on the data provided in the PSUR:

- Myocarditis and pericarditis - the EMA (following the PRAC meetings in July and December 2021) and other Health Authorities have requested updates to the label to address findings on myocarditis and pericarditis cases following vaccination with Comirnaty (EMEA/H/C/005735/II/0059 and EMEA/H/C/005735/SDA/032). The sections 4.4 and 4.8 of the SmPC were updated: the warning in section 4.4 was refined; the frequency category in section 4.8 was amended from 'not known' to 'very rare' and additional information was included in subsection 'Description of selected adverse reactions'; the package leaflet was updated accordingly. EMA has also requested the distribution of a direct healthcare professional communication (DHPC) on 19 July 2021.

The following are ongoing signals:

- Glomerulonephritis and Nephrotic Syndrome, in the previous signal procedure (EPITT ref. 19722) with DLP 25 July 2021, a total of 7 (of which 5 from literature) probable cases and 3 possible cases were identified. As part of the RSI responses, the MAH provided a cumulative review with a more recent DLP, both from the literature and its own safety database. For the period between 19 December 2021 to 9 May 2022, the MAH identified 12 relevant articles discussing 14 case reports from literature databases; additionally, 10 articles were presented that included 14 other cases from MAH's safety database. Not all case classification are agreed with (for more details, please see Annex section 6). As of 9 May 2022, the MAH identified a total of 201 additional cases of which 110 reported TTO between 1 to 42 days post vaccination (for more details, please see Annex section 6). In conclusion, probable/possible related (literature) cases of both new onset (n=7) and cases in patients with pre-existing renal disease (n=7) were identified. However, given that O/E ratios were well below one, that the currently available data are in line with the previous PRAC conclusion, and taking into account Comirnaty exposure, it is agreed with the MAH that no new safety concern could be identified and no product information update is warranted at this stage.
- Vasculitis, in the 13th SSR of Comirnaty a cumulative review with cases reporting vasculitis retrieved through 15 Nov 2021 (N=504 cases) was assessed. The signal was not closed because a detailed causality assessment of the remaining 207 cases considered without a known confounding factor was lacking, which resulted in a request for the next upcoming 14th SSR of Comirnaty, to perform a updated cumulative review through the end date of the safety summary report interval period, with detailed information of the cases which are considered the most informative cases and a causality assessment per case using the WHO-UMC system for standardised case causality assessment (procedure EMEA/H/C/005735/MEA/002.12). The assessment of the (updated) review of vasculitis in the 14th SSR (data through 15 Apr 2022) concluded that no new safety concern could be identified. Another update review of vasculitis cases through 18 Jun 2022, with only 2 months extra data, is not expected to change this conclusion and therefore the request concerning the (update) cumulative review of vasculitis cases for the 3rd PSUR is removed. At the moment it seems sufficient that the MAH continues to monitor the occurrence of vasculitis after Comirnaty exposure.
- Cerebral venous sinus thrombosis (CVST), in the 13th SSR of Comirnaty cases reporting cerebral venous sinus thrombosis through 24 Nov 2021 were assessed which resulted in a request for the next upcoming 14th SSR, to provide a cumulative review of cases reporting cerebral venous sinus thrombosis through the end date of the next SSR interval period (with matching exposure data), with detailed information of the CVST cases (which are considered the most informative cases) and a causality assessment per case using the WHO-UMC system for standardised case causality assessment (procedure EMEA/H/C/005735/MEA/002.12). However, the EMA provided a cumulative review of CVST cases (below 30 years of age) that were reported to EudraVigilance and O/E analyses up to 16 March 2022 and it was concluded that the data does not represent a signal for Comirnaty at this stage (Section Stroke in the AESIs evaluation of this AR).

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:

- Exacerbation (flare-up) of pre-existing AI/Inflammatory disorders
- Use in Pregnancy and lactation
- Chronic urticaria/Worsening of pre-existing chronic urticaria
- Polymyalgia rheumatica and exacerbation or flare-up
- Subacute thyroiditis

According to the European Risk Management Plan (EU-RMP) version 2.0 in effect at the beginning of the reporting interval, the important identified risk is Anaphylaxis, and the important potential risk is Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD); missing information are 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 and Long term safety data. During the reporting interval, the EU-RMP was updated (version 2.3) to include myocarditis/pericarditis as an important identified risk (EMEA/H/C/005735/II/0059 and EMEA/H/C/005735/SDA/032).

Based on the evaluation of the interval data provided, no new important safety information or change in benefits with potential impact on the overall evaluation of the benefit-risk profile of Comirnaty has emerged during the reporting period.

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 covid-19 mRNA vaccine (nucleoside-modified) (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. The MAH is requested to continue to report on the number of processed cases downloaded from EudraVigilance in the PSUR.
2. 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.
3. 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.
4. 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.
5. 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.

5. PSUR frequency

☒ No changes to the PSUR frequency

The current 6-months 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 2nd PSUR for BNT162b2 (Comirnaty) covering the period 19 June 2021 to 18 Dec 2021, 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.

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

1.2. Worldwide marketing authorisation status

BNT162b2 was first authorised (conditional approval) in Switzerland on 19 December 2020 and in the EU on 21 December 2020. First temporary authorisation for emergency supply was received on 1 December 2020 in the UK.

BNT162b2 is authorised for the following formulations:

- PBS/Sucrose – Purple cap 30 µg formulation:
  - in individuals aged 16 years and older in 99 countries including full (3), conditional (48), EUA and other type of approvals (48).
  - in individuals aged between 12 and 15 years in 81 countries including full (3), conditional (46), EUA and other type of approvals (32).
- Tris/Sucrose formulation:
  - Grey cap: at the dosage of 30 µg formulation in individuals aged 12 years and older in 52 countries including full (1), conditional (36), EUA and other type of approvals (15).
  - Orange cap: at the dosage of 10 µg formulation in individuals aged between 5 and 11 years in 59 countries including full (2), conditional (36), EUA and other type of approvals (21).

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

Table 2. Regulatory Actions Taken During the Reporting Period for Safety Reasons

Issue	Country	Action Taken	Date
Final recommendation from PRAC on the myocarditis, pericarditis signal for the BNT162b2 (EMEA/H/C/5735/SDA/032)	EU	A joint DHPC[a] for both Comirnaty and Spikevax, distributed in all Member States, Amendment to the Product Information (Variation 50, already effective, introducing myocarditis and pericarditis in sections 4.4 and 4.8 of the SmPC.	08 July 2021
Risk of myocarditis and pericarditis (Joint DHPC Pfizer and Moderna).[b]	Switzerland	With Decision dated 30 July 2021 Swissmedic requested a joint DHPC (Pfizer, Moderna) on myocarditis/pericarditis. Distribution of DHPC 12 August 2021. The label was updated in parallel, approval from Swissmedic on 03 August 2021.	Distribution of DHPC on 12 August 2021.
Risk of myocarditis and pericarditis Brazilian Health Authority (ANVISA) [b]	Brazil	A DHPC was issued to ensure that HCPs are aware of the risk for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use.	08 December 2021

a. The DHPC was distributed by the MAH on 19 July 2021 to all EU member states where the respective vaccines are authorised.
b. Content of DHPC based on the EU DHPC for the same topic.

Rapporteur assessment comment:

The provided information is noted. No further action is required.

1.3.2. Changes to reference safety information

The reference safety information for this PSUR is the Core Data Sheet version 9.0 dated 02 Dec 2021, which is located in Appendix 1 of the PSUR. The 5 previous CDS versions (19 May 2021 version 4.0, 14 Jul 2021 version 5.0, 11 Aug 2021 version 6.0, 08 Sep 2021 version 7.0, 19 Oct 2021 version 8.0) 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 is in line with the CDS. Following the PRAC meetings in July and December 2021, myocarditis and pericarditis were added to sections 4.4. and 4.8 of the SmPC, and the package leaflet accordingly (EU procedures EMEA/H/C/005735/II/0059 and EMEA/H/C/005735/SDA/032).

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively, 61,098 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates:

- BNT162b2: 54,755 participants of which 27,814 had received BNT162b2; 25,110 had received BNT162b2 post-unblinding and had received placebo before; 959 had received BNT162b2/placebo; 872 had received BNT162b2 and blinded booster.
- Variant vaccines based on BNT162b2: 1085 participants of which 374 had received BNT162b2 (B.1.351); 392 had received BNT162b2 (B.1.617.2);299 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: 6469 participants.
- Placebo: 3430 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

During the reporting period, there were 2 regulatory commitments about the exposure and number of third doses administered:

- 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 7 through Table 11 of the PSUR (only table 7 and 11 are reproduced here). Details for the cumulative number of third doses administered by age group cumulatively and during the interval period in the EU/EEA countries are shown in Table 7 and in Table 11:

Table 7. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Dose Number

Age Group	1st Dose	2nd Dose	3rd Dose	Dose Unknown
< 18 years[a]	9236293	7519624	49641	2
0 – 4 years[b]	1780	799	43	2
5 – 9 years[c]	373907	18002	23	0
10 – 14 years[d]	3288510	2461423	6283	97
15 – 17 years[e]	3379369	3044134	27313	77
18 – 24 years[f]	10981358	9936737	833035	195
25 – 49 years[f]	50393078	47162531	7501918	1438
50 – 59 years[f]	23376071	22487980	6437386	619
60 – 69 years[f]	16033179	15644801	9487000	696
70 – 79 years[f]	15472212	15189651	11972000	780
≥ 80 years[f]	11987222	11672595	8961371	683
Age Unknown[e]	61876	53234	3943	0
EEA – All[g]	218788147	212080186	79556521	4411

a. Data from 19 countries.
b. Data from 12 countries.
c. Data from 15 countries.
d. Data from 16 countries.
e. Data from 17 countries.
f. Data from 26 countries.
g. Data from 30 countries.

Cumulative period up to week 50, 20 December 2021- as of 17 December 2021
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea

Table 11. EU/EEA – Interval Number of BNT162b2 Administered Doses by Age Group and Dose Number

Age Group	1st Dose	2nd Dose	3rd Dose	Dose Unknown
< 18 years[a]	8814155	7452687	49633	0
0 – 4 years[b]	1599	702	43	0
5 – 9 years[c]	373543	17761	23	0
10 – 14 years[d]	3193064	2460793	6283	97
15 – 17 years[e]	3072613	3024855	27305	77
18 – 24 years[f]	8284201	8906310	832976	169
25 – 49 years[f]	29461689	38211867	7501640	1143
50 – 59 years[f]	5130288	14583459	6437242	425
60 – 69 years[f]	2547918	6217733	9486869	520
70 – 79 years[f]	1190821	2426802	11971709	557
≥ 80 years[f]	565635	779052	8961064	263
Age Unknown[d]	45157	47230	3943	0
EEA – All[g]	81696424	128938838	79555014	3077

a. Data from 19 countries.
b. Data from 12 countries.
c. Data from 15 countries.
d. Data from 16 countries.
e. Data from 17 countries.
f. Data from 26 countries.
g. Data from 30 countries.

Interval reporting period including week 24 through to week 50, 20 December 2021- as of 17 December 2021
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 doses of Comirnaty, cumulatively and during the interval period, for EU-EEA, US and Japan. Cumulatively, in the EU-EEA an estimated total of 79,556,521 third doses of Comirnaty were administered and during the interval period 79,555,014 third doses of Comirnaty.

Issue solved

Worldwide exposure:

- approximately 2,443,245,455 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on **01 Dec 2020 through 18 Dec 2021**, corresponding to **2,100,134,815 estimated administered doses**.
- approximately 1,661,566,580 doses of BNT162b2 were shipped worldwide during the current reporting interval from **19 Jun 2021 through 18 Dec 2021**, corresponding to **1,430,363,611 estimated administered doses**.
- overall, through 18 Dec 2021, a total of 47,038,200 paediatric Tris/Sucrose doses were shipped worldwide.

Rapporteur assessment comment:

Cumulatively, worldwide a total of 2,100,134,815 doses of Comirnaty were administered.

During the reporting period, in the EU-EEA a total of 290,193,353 doses of Comirnaty were administered and cumulatively 510,429,265 doses.

1.3.4. Data in summary tabulations

Response to the PRAC request 1 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *The MAH is requested to continue to report on the number of processed cases downloaded from EudraVigilance in the PSUR and on the actions done and foreseen in the near future in order manage all the AE reports received.*

MAH's response: Please refer to Appendix 6A of the PSUR: As of 21 December 2021, 307,601 cases were downloaded from EudraVigilance and 297,489 cases (96.7% of the total downloaded cases, 84,238 serious and 213,251 non serious) were included in the data tabulations presented in the PSUR.

The remaining 10,112 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 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 10,112 case reports from EudraVigilance not included in this PSUR, 2443 were serious and 7669 were non-serious.

The table below (not reproduced here) provides updates on the corrective actions that have been or are being initiated with progress update as of 19 December 2021 to manage the volume of adverse event cases received.

Since 21 August 2021, the MAH has implemented an increased AESI prioritization and monitoring strategy both on serious and non-serious cases.

The MAH prioritizes all serious cases. Fatal and life threatening are the highest priority, followed by other serious cases with AESIs over all other case types. For non-serious cases, those non-serious cases with an AESI term are prioritized over non-serious cases without AESI terms. The following Figure 1 and Figure 2 show the progress on the completion of Fatal/Life threatening cases, serious cases and cases with AESI terms.

Figure 1. Serious COVID Vaccine Cases beyond Day 15 Open in Workflow

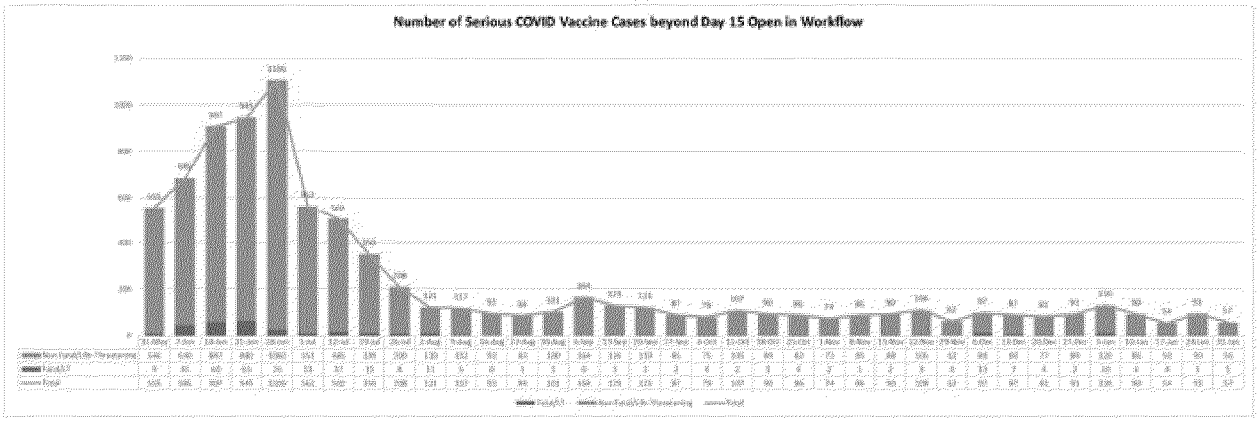
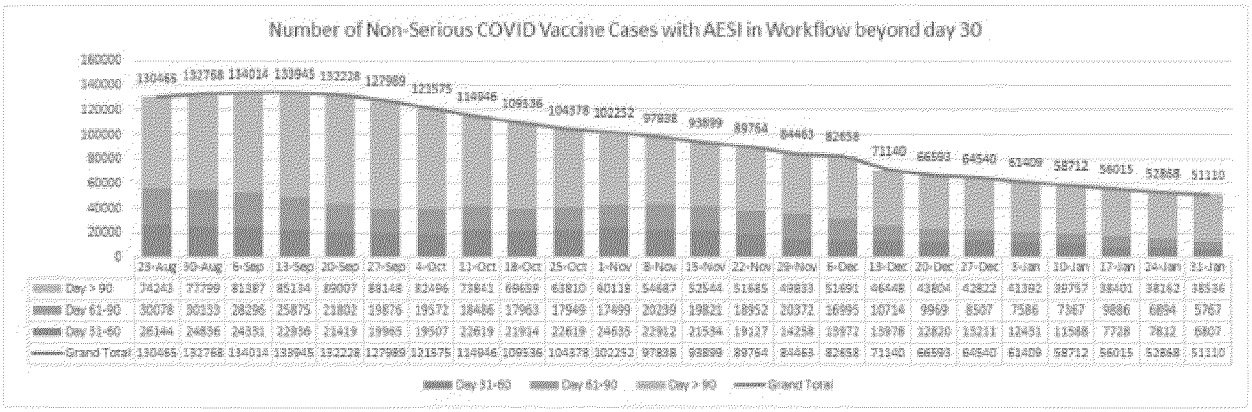


Figure 2. Non-Serious COVID Vaccine Cases with AESI in Workflow beyond Day 30



Rapporteur assessment comment:

The number of processed cases downloaded from Eudravigilance in the current 2nd PSUR is 297,489 cases (96.7% of the total downloaded cases, 84,238 serious and 213,251 non serious). Although the percentage of the processed cases downloaded from Eudravigilance is considered a significant improvement compared to previous updates provided in the (M)SSR, the aim remains a 100% processing of downloaded cases, the MAH is requested to continue to report on the number of processed cases downloaded from EudraVigilance in the PSUR. **Request for next PSUR**

Issue partly solved

During the reporting period, a total of 658,249 case reports (721 from clinical trials and 657,528 from post-marketing) containing 2,174,419 adverse events were retrieved, compared to 327,827 case reports in the previous first PSUR.

Clinical trial data

During the reporting period, in the CT dataset the number of female and male participants was balanced (49.9% vs 48.5%); the number of SAEs experienced by female participants is slightly higher than male (500 vs 476). A total of 1002 SAEs were reported in 721 cases.

The overall safety evaluation includes a review of the most frequently reported events by SOC and PT for events reported in ≥2% of all clinical trial cases during the reporting interval as compared to the cumulative period through 18 December 2021 (Table 14).

Table 14. Clinical Trial Data: Serious Events Reported in ≥2% Cases

	Reporting Period 19 Jun 2021 - 18 Dec 2021		Cumulatively through 18 Dec 2021	
	All Cases[a]	BNT162b2 / b2s01 / b3 / BT Cases	All Cases[b]	BNT162b1 / b2 / b2s01 / b3 / c2/ BT Cases
MedDRA SOC MedDRA PT	(N=721) AEs (n=1002)	(N=690) AEs (n=953)	(N=1766) AEs (n=2320)	(N=1643) AEs (n=2156)
	n (AERP,[c] %)	n (AERP,[c] %)	n (AERP,[c] %)	n (AERP,[c] %)
General disorders and administration site conditions				
Condition aggravated	18 (2.5)	15 (2.2)	54 (3.1)	47 (2.9)
Infections and infestations				
Appendicitis	14 (1.9)	14 (2.0)	46 (2.6)	42 (2.6)
Pneumonia	16 (2.2)	16 (2.3)	40 (2.3)	39 (2.4)
Injury, poisoning and procedural complications				
Maternal exposure during pregnancy[d]	88 (12.2)	80 (11.6)	98 (5.5)	90 (5.5)

a. Includes BNT162b2 (b2), BNT162b2s01 (b2s01), BNT162b3 (b3), Blinded Therapy (BT) and Placebo.
b. Includes BNT162b1, b2, b2s01, b3, BNT162c2 (c2), BT and Placebo.
c. Reporting proportion calculated as n/N (% of cases) in the current reporting period or cumulatively.
d. 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*.
N: Number of cases; n: Number of events.

There were 11 SAEs assessed as related to BNT162b2; of these,

- Myocarditis (2), Pain in extremity and Pyrexia (1 each) were assessed as related by both the Investigator and the Sponsor.
- Hepatic enzyme increased and Transient ischaemic attack (2 each), Angioedema, Appendicitis and Tachycardia (1 each) were 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 2.6 times the number of male subjects (68.4% vs 26.7%).

Of the reports 2,173,417 AEs, 542,562 were serious and 1,631,402 non-serious.

The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (738,521), Nervous system disorders (308,965), Musculoskeletal and connective tissue disorders (242,863), Gastrointestinal disorders (140,894), Skin and subcutaneous tissue disorders (96,458), Injury, poisoning and procedural complications (82,952), Reproductive system

and breast disorders (93,828), Respiratory, thoracic and mediastinal disorders (80,334), Infections and infestations (59,737), and Cardiac disorders (52,788).

The overall safety evaluation includes a review of the most frequently reported events by SOC and by the PT for events reported in ≥2% of all post-marketing cases during the interval period as compared to the cumulative period through 18 December 2021 (Table 16).

Table 16. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Jun 2021 – 18 Dec 2021		Cumulatively through 18 Dec 2021
	All Cases (N=657,528) AEs (n=2,173,417)	Serious Cases (N=173,179) Serious AEs[a] (n=542,562)	All Cases (N=982,006) AEs (n=3,365,224)
	n (AERP,[h] %)	n (AERP, %)	n (AERP, %)
Blood and lymphatic system disorders			
Lymphadenopathy [b]	29,431 (4.5)	4187 (2.4)	48,081 (4.9)
Gastrointestinal disorders			
Nausea [b]	55,741 (8.5)	9083 (5.2)	93,727 (9.5)
Diarrhoea [b]	20,881 (3.2)	3562 (2.1)	34,169 (3.5)
Vomiting [b]	15,923 (2.4)	4432 (2.6)	27,477 (2.8)
General disorders and administration site conditions			
Fatigue [b]	109,479 (16.7)	14,173 (8.2)	166,902 (17.0)
Pyrexia [b]	106,127 (16.1)	12,153 (7.0)	170,558 (17.4)
Vaccination site pain [b]	95,981 (14.6)	3422 (2.0)	139,567 (14.2)
Malaise [b]	81,598 (12.4)	6391 (3.7)	109,616 (11.2)
Chills[b]	53,523 (8.1)	5452 (3.1)	94,925 (9.7)
Pain[c]	37,943 (5.8)	6245 (3.6)	63,924 (6.5)
Vaccination site swelling[b]	22,115 (3.4)	670 (0.4)	29,275 (3.0)
Asthenia[b]	21,198 (3.2)	4773 (2.8)	45,807 (4.7)
Chest pain[c]	17,528 (2.7)	7437 (4.3)	22,706 (2.3)
Influenza like illness[c]	12,656 (1.9)	1831 (1.1)	21,409 (2.2)
Vaccination site erythema[b]	13,101 (2.0)	569 (0.3)	19,852 (2.0)
Infections and infestations			
COVID-19[d]	19,691 (3.0)	18,857 (10.9)	27,943 (2.8)
Injury, poisoning and procedural complications			
Off label use[e]	22,049 (3.4)	5764 (3.3)	25,873 (2.6)
Inappropriate schedule of product administration[e]	18,827 (2.9)	467 (0.3)	23.218 (2.4)
Musculoskeletal and connective tissue disorders			
Myalgia[b]	84,891 (12.9)	7203 (4.2)	134,432 (13.7)
Arthralgia[b]	56,611 (8.6)	7251 (4.2)	92,100 (9.4)
Pain in extremity[b]	39,010 (5.9)	8030 (4.6)	67,970 (6.9)
Nervous system disorders			
Headache[b]	135,039 (20.5)	16,738 (9.7)	219,030 (22.3)
Dizziness[c]	37,982 (5.8)	8760 (5.1)	62,240 (6.3)
Paraesthesia[f]	19,809 (3.0)	4766 (2.8)	29,497 (3.0)
Hypoaesthesia[f]	13,597 (2.1)	3980 (2.3)	19,995 (2.0)
Reproductive system and breast disorders			
Heavy menstrual bleeding[c]	16,613 (2.5)	4150 (2.4)	17,535 (1.8)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea[b]	23,757 (3.6)	9714 (5.6)	35,024 (3.6)
Skin and subcutaneous tissue disorders			
Rash[b]	17,591 (2.7)	3095 (1.8)	28,255 (2.9)
Pruritus[b]	16,653 (2.5)	2980 (1.7)	27,923 (2.8)
Surgical and medical procedures			
Immunisation[g]	21,712 (3.3)	8339 (4.8)	21,737 (2.21)

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

MAH's conclusion: Overall, during the reporting period, the serious cases represented 26.3% of the total PM; fatal outcomes occurred in less than 1% of the cases. More than 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 post-marketing cases, no new safety issues were identified.

Rapporteur assessment comment:

After DLP, the safety signal procedures concerning Heavy menstrual bleeding and Amenorrhea are ongoing (EPITT 19783/19784).

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

Analysis by doses

Response to the PRAC request 4a from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *In the PSUR under off-label use and in other relevant sections, the MAH should assess if the safety profile of Comirnaty when administered with different time intervals between dose 1, 2 and 3 than the recommended posology is consistent with the known safety profile.*

MAH's response:

Cases were evaluated based on the time intervals specified in the RSI. Search criteria: subjects who received dose 1, 2, and 3 of BNT162b2 with reported time interval between dose 1 and dose 2 different from 21 to 42 days and with reported time interval between dose 2 and dose 3 different from 181 to 183 days. Please refer to Appendix 6A of the PSUR for details:

Of the 4599 cases involving subjects, who received 3 doses of BNT162b2 with different time intervals than the recommended intervals, 4 cases were determined to be non-contributory and are not included in the discussion, since the subjects were exposed to the vaccine during mother's pregnancy or breastfeeding.

- Number of cases: 4595 (0.7% of 657,528 cases, the total post-marketing dataset) of which 1543 medically confirmed cases.
- Country of incidence (≥ 2%): US (2044), UK (936), Netherlands (444), France (221), Italy (205), Spain (144) and Germany (108).
- Subjects' gender: female (3386), male (1118) and unknown (91).
- Subjects' age in years (n = 4384), range: 12-100, mean: 55.5, median: 55.0.
- Medical history (n = 2813): the most frequently (≥50 occurrences) reported medical conditions included Hypertension (459), Disease risk factor (317), Drug hypersensitivity (296), Asthma (263), Hypothyroidism (158), Hypersensitivity (149), Food allergy (129), Diabetes mellitus (125), Depression (115), Atrial fibrillation (91), Immunodeficiency (81), Gastrooesophageal reflux disease (79), Type 2 diabetes mellitus (76), Anxiety (75), Migraine (72), Obesity (69), Arthritis, Rheumatoid arthritis (68 each), Seasonal allergy (63), Chronic obstructive pulmonary disease (58), Blood cholesterol increased (57) and Pain (50).
- COVID-19 Medical history: the most frequently (≥4 occurrences) reported COVID-19 (171), Suspected COVID-19 (120), Asymptomatic COVID-19, COVID-19 pneumonia, Post-acute COVID-19 syndrome and SARS-CoV-2 test positive (4 each).

- Co-suspects (n=272): the most frequently (≥2 occurrences) reported co-suspect vaccines/medications included influenza vaccine (137), influenza vaccine inact sag 4V (23), hepatitis A vaccine (18), influenza vaccine inact split 4V (16), influenza vaccine inact sag 3V (12), adalimumab, influenza vaccine inact split 3V (8 each), diphtheria vaccine toxoid/ HIB vaccine/ pertussis vaccine/ polio vaccine inact/ tetanus vaccine toxoid, paracetamol (4 each), carbidopa/levodopa, imatinib mesilate, levothyroxine sodium, ocrelizumab, pneumococcal vaccine polysacch 23V and prednisone (2 each).
- Number of events: 24,610.
- Event seriousness: serious (6846), non-serious (17,771).
- Most frequently reported PTs (≥2%): Immunisation (3473), Headache (1081), Off label use (1069), Fatigue (991), Pyrexia (970), Chills (773), Myalgia (619), Pain (595), Pain in extremity (581), Lymphadenopathy (579), Vaccination site pain (568), Nausea (526), Arthralgia (512) and Malaise (497).
- Event outcome: fatal (360), resolved/resolving (9403), resolved with sequelae (322), not resolved (5484), unknown (9158).

Event seriousness and clinical outcome and the most frequently (≥ 2%) reported AEs were compared between the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the remaining post-marketing dataset in Table 2 and Table 3 (not reproduced here), respectively:

- No significances differences were observed in the proportions of event seriousness and clinical outcome between the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the overall post-marketing dataset.
- There was a slightly higher proportion of fatal outcomes in the group with different time intervals compared to the remaining group. The comparatively low number of subjects in the group and selection bias for subjects most likely to receive a third dose are likely contributing factors.
- The 101 cases reporting fatalities (360 fatal AEs) involved 97 elderly and 4 adult subjects. The most frequently (≥ 2%) reported AEs leading to death the subjects, who received 3 doses of BNT162b2 administered with time intervals different from recommended posology[Immunisation (65), Death (21), Sudden death (15), Off label use (11), Cardiac failure (10), Pyrexia (9) and Cardiac arrest (8)], are consistent with the most commonly reported fatal events in the remaining PM dataset, except for the PT Immunisation that is selected per case processing conventions to collect cases reporting third/booster doses5 and the PT Off label use that is reported in this dataset due to the administration of dosages in unapproved time intervals.
- In general, the most frequently reported events observed in these cases were consistent with those observed in the remaining population, apart from the PTs Immunisation and Off label use that are selected per case processing conventions to collect cases reporting third/booster doses and the PTs Chills, Pain, Vaccination site swelling, Pain in extremity and Lymphadenopathy that are consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS. In general, the proportion of events reported by the group with different intervals than recommended, is higher than the proportions in the remaining PM dataset. This may be due to the comparatively lower number of subjects in the different intervals group.

Among the 4595 cases, 1114 (468 serious and 646 non-serious) included PTs indicative of use of BNT162b2 in unapproved conditions: Off label use (1069), Product use issue (120) and Product administered to patient of inappropriate age (3). As shown in Table 4 (not reproduced here), there were no significant differences between the AEs co-reported along with the terms indicative of the off-label use

in the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the remaining cases reporting off-label use, apart from the PT Immunisation, which is selected per case processing conventions to collect cases reporting third/booster doses.

MAH's conclusion: No new safety information was identified by the review of data regarding the administration of 3 doses of BNT162b2 with different time intervals than the recommended posology.

Rapporteur assessment comment:

As requested the MAH evaluated 4595 subjects (0.7% of the total post-marketing dataset) who received dose 1, 2, and 3 of Comirnaty with reported time interval between dose 1 and dose 2 different from 21 to 42 days and with reported time interval between dose 2 and dose 3 different from 181 to 183 days. MAH's conclusion is endorsed that the data do not indicate that the safety profile is amended when Comirnaty doses are administered with different time intervals than the recommended posology.

Issue solved

Tris/Sucrose Formulation

On 14 October 2021 a positive EMA's CHMP opinion was issued to add a new pharmaceutical form (dispersion for injection) with a new strength (0.1 mg/ml – Tris/Sucrose adult – grey cap) (Procedure No. EMEA/H/C/005735/X/0044/G).

On 25 November 2021, a positive EMA's CHMP opinion was received with regard to the line extension "5-11 years old" for a Tris/Sucrose paediatric formulation (0.1 mg/ml Concentrate for dispersion for injection – orange cap) (Procedure No. EMEA/H/C/005735/X/0077).

On 29 October 2021, FDA revised the EUA to authorise the use of BNT162b2 for children 5 through 11 years of age and a manufacturing change to include an additional formulation of BNT162b2 that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorised BNT162b2 vaccine. The formulation of the BNT162b2 vaccine that uses Tris buffer is authorised in two presentations:

- Multiple dose vials, with grey caps and labels with a grey border, formulated to provide, without need for dilution, doses (each 0.3 mL dose containing 30 µg nucleoside-modified messenger RNA (modRNA) for individuals 12 years of age and older; and,
- Multiple dose vials, with orange caps and labels with an orange border, formulated to provide, after dilution, doses (each 0.2 mL dose containing 10 µg modRNA) for individuals 5 through 11 years of age.

A total of 963 post-marketing case reports with Tris/Sucrose formulation containing 2426 events (0.15% of the total post-marketing dataset) fulfilled criteria for inclusion in this PSUR reporting period. Since the grey cap presentation was not administered during the reporting period.

More than 80% of these cases (805) were reported in paediatric subjects (aged ≤ 17 years). There were no large differences in the demographic data between paediatric subjects receiving Tris/Sucrose formulation and those receiving PBS.

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 (cross-referenced with Section Medication Errors for errors related to Tris/Sucrose 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 4.0 of the EU-RMP. The BLA US-PVP v 1.3 includes as routine pharmacovigilance activities label information on vial differentiation.

With regard to the reported events, the majority were reported in lower proportion in the Tris/Sucrose group compared to the PBS/Sucrose group although there were 2 events (Vomiting and Rash) with a higher AERP (5.8% and 3.5%, respectively) in the Tris/Sucrose paediatric group. On review, few occurrences were serious (as important medical events – 3 for Rash and 1 for Vomiting). The clinical outcome of the serious occurrences was resolved/resolving (3) and not resolved (1) at the time of reporting. In the paediatric PBS/Sucrose cases, Rash and Vomiting were assessed as serious events in 177 and 334 occurrences, with an AERP of 3.4% and 5.3, respectively.

MAH's conclusion: Overall, more than 80% of the Tris/Sucrose cases was reported in paediatric subjects; the most frequently reported AEs in this population do not differ from the paediatric PBS/Sucrose formulation. 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 are listed in the approved version 4.0 of the EU-RMP adopted on 26 November 2021.

Based on the review of the cases reported with Tris/Sucrose formulation, no new safety issues were identified.

Rapporteur assessment comment:

Regarding the Tris/Sucrose formulation, 2426 AEs from 963 cases were retrieved during the reporting period. Most cases (84%) were from paediatric subjects aged ≤17 years and 4 AEs were considered SAEs (rash N=3 and vomiting N=1). 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 12th SSR (reporting period 29 Oct 2021 – 15 Dec 2021) and in the 13th SSR (reporting period 16 Dec 2021 – 15 Feb 2022), and no new important safety information was identified regarding medication errors.

Response to the PRAC request 4b from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *In the PSUR under off-label use and in other relevant sections, the MAH should assess the safety profile of Comirnaty when used in heterologous vaccination schedules with other vaccines.*

MAH's response:

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

Post-Authorisation Data:

- Number of cases: 9609 (1.5% of 657,528 cases, the total PM dataset; 37.2% of the third dose/booster dataset) of which 1299 medically confirmed cases.
- Country of incidence (≥2%): UK (7934), Netherlands (616), US (237), Brazil (208).
- Subjects' gender: female (6796), male (2392) and unknown (421).
- Subjects' age in years (n = 8278), range: 0.5 – 103, mean: 55.0, median: 56.0.
- Case outcome: fatal (54), resolved/resolving (2923), resolved with sequelae (101), not resolved (5840), unknown (691).

- Medical history (n = 4594): the most frequently (≥2%) reported medical conditions included Hypertension (526), Immunodeficiency (523), Asthma (456), Clinical trial participant and Disease risk factor (417 each), Steroid therapy (288) and Hypothyroidism (199).
- COVID-19 Medical history (n = 1080): Suspected COVID-19 (826), COVID-19 (294), Post-acute COVID-19 syndrome (20), SARS-CoV-2 test positive (5), COVID-19 pneumonia (4), Asymptomatic COVID-19 (3) and Exposure to SARS-CoV-2 (1).
- Among the 9609 cases reporting administration of heterologous third/booster doses of BNT162b2 vaccine, the previous vaccine series consisted of:
    - 5187 subjects immunised with unknown non-Pfizer-BioNTech COVID-19 Vaccine;
    - 3257 subjects immunised with AstraZeneca vaccine;
    - 595 subjects immunised with Moderna vaccine;
    - 269 subjects immunised with Coronavac vaccine;
    - 184 subjects immunised with Johnson and Johnson vaccine;
    - 49 subjects immunised with Sinopharm vaccine;
    - 42 subjects immunised with Novavax vaccine;
    - 17 subjects immunised with Sputnik vaccine;
    - 3 subjects each immunised with Curevac or Covidshield vaccine;
    - 1 subject each immunised with Convidecia or Covilo, other vaccine.
- Number of events: 66,290.
- Event seriousness: serious (36,044), non-serious (30,268).
- The most reported (≥ 2%) PTs were Interchange of vaccine products (9468), Off label use (9143), Immunisation (8969), Headache (2389), Fatigue (1991), Pyrexia (1452), Lymphadenopathy (1332), Chills (1321), Pain in extremity (1280), Nausea (1142), Arthralgia (1032), Myalgia (1029), Malaise (979), Pain (969), Vaccination site pain (841), Dizziness (604), Axillary pain (538), Diarrhoea (505), Pruritus (495), Peripheral swelling (444), Swelling (430), Rash (422), Vomiting (416), Chest pain (400), Dyspnoea (391), Palpitations (378), Asthenia and Vaccination site swelling (335 each), Vaccination site erythema (307), Influenza like illness (297), Erythema (296), Lymph node pain (263), Decreased appetite (253), Hyperhidrosis and Insomnia (248 each), Feeling cold (234), Paraesthesia (231), Tremor (223), Illness (218), Back pain (213), Vaccination site warmth (197) and Cough (194).

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

Post-Authorisation Data:

- Number of cases: 2572 (0.4% of 657,528 cases, the total PM dataset) of which 1108 medically confirmed cases.
- Country of incidence (≥2%): UK (955), US (379), Italy (173), Germany (171), France (162), Austria (74), Lithuania (63), Spain (61), Sweden (60), Israel (51).
- Subjects' gender: female (1604), male (739) and unknown (229).
- Subjects' age in years (n = 2006), range: 6 – 108, mean: 58.4, median: 59.0.

- Case outcome: fatal (108), resolved/resolving (754), resolved with sequelae (47), not resolved (806), unknown (857).
- Medical history (n = 909): the most frequently (≥2%) reported medical conditions included Hypertension (185), Asthma (59), Atrial fibrillation (54) and Type 2 diabetes mellitus (52).
- COVID-19 Medical history (n = 73): Suspected COVID-19 (47), COVID-19 (24), SARS-CoV-2 antibody test positive and SARS-CoV-2 test positive (1 each).
- Number of events: 11,318.
- Event seriousness: serious (4449), non-serious (6872).
- The most reported (≥ 2%) PTs were Immunisation (2387), Off label use (789), Pyrexia (403), Headache (371), Fatigue (295), Pain in extremity (230), Chills (210), Lymphadenopathy (191), Myalgia (174), Pain (173), Nausea (165), Arthralgia (163), Vaccination site pain (161), Malaise (155), Asthenia (126), Dyspnoea (117), Dizziness (108), Poor quality product administered (99), Diarrhoea (78), Pruritus (75), Peripheral swelling (74), Vomiting (73), Chest pain (72), Axillary pain (68), Product temperature excursion issue and Rash (66 each), Influenza like illness (63), Expired product administered (62), Palpitations (56), Hyperhidrosis, Paraesthesia and Vaccination site swelling (52 each).

Analysis booster doses versus primary vaccination series

The most frequently reported clinical adverse events in post-marketing cases of subjects who received the third/booster doses of BNT162b2 were consistent with those reported in subjects receiving primary vaccination series, as shown in **Error! Reference source not found.** (not reproduced here). A higher reporting frequency of 5 PTs (Chills, Lymphadenopathy, Pain in extremity, Axillary pain and Peripheral swelling) was noted in subjects who received the third/booster doses of BNT162b2 (11.8%, 11.7%, 11.7%, 4.4% and 3.7%, respectively) compared to subjects receiving the primary vaccination series (8.0%, 4.2%, 5.7%, 0.8% and 0.9%, respectively); of note, this is consistent, in the context of lymphadenopathy reactions, with the RSI data for participants receiving a booster dose as seen in interventional clinical studies.

MAH's conclusion: Based on the review of the cases reported with the booster/third doses, no new safety issues were identified.

Rapporteur assessment comment:

As requested the MAH assessed the safety profile of Comirnaty in a heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2) and when the third/booster doses of BNT162b2 were administered after an unspecified primary COVID-19 vaccination series. The data do not indicate that the safety profile of Comirnaty is amended when used in heterologous vaccination schedules with other vaccines as compared to a homologous vaccination schedule.

Issue solved

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Clinical trials

Completed clinical trials

No clinical trials were completed with a final CSR during the reporting interval.

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, 9 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.
    - C4591017, A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple production lots and dose levels of the vaccine candidate BNT162b2 against COVID-19 in healthy participants 12 through 50 years of age and the safety, tolerability, and immunogenicity of BNT162b2 RNA-based COVID-19 vaccine candidates as a booster dose in healthy participants 18 through 50 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, 3 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.
- 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 is ongoing. 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 9 ongoing sponsor-initiated non-interventional studies.

Safety Studies:

- PASS: Non-interventional studies C4591008 , C4591010, [redacted] and C459102232 are PASS. No clinically important information has emerged from PASS.
- Other studies where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.

Other Studies, 4 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.
- C4591035, Coronavirus Disease 2019 (COVID-19) Vaccination and Breakthrough Infections Among Persons with Immunocompromising Conditions in the United States.

During the reporting period, no new safety information regarding 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.

There were 4 cases (4 events; Febrile neutropenia, Liver transplant rejection, Respiratory failure and Syncope) originated from the non-Pfizer sponsored study "Immunological responses after vaccination for COVID-19 with the messenger ribonucleic acid (mRNA) vaccine Comirnaty in immunosuppressed and immunocompetent individuals. An open and non-randomized, phase IV multicenter study". The investigator considered all the SAEs as related to BNT162b2; the MAH agreed with the exception of Respiratory failure.

There were 2 cases (3 events; Cytomegalovirus infection, Myelitis and Thrombotic microangiopathy) originated from the non-Pfizer sponsored study "Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Allo)." The investigator considered all the SAEs as related to BNT162b2, while the MAH assessed them as unrelated.

In 1 case, originated from the non-Pfizer sponsored study "A phase 1-2 study of delayed heterologous SARS CoV 2 vaccine dosing (boost) after receipt of EUA vaccines" the SAE Fall was assessed as not related to BNT162b2 by both the investigator and the MAH.

No new safety information with regards to BNT162b2 from the review of these cases was reported.

Rapporteur assessment comment:

From the non-MAH sponsored study "Immunological responses after vaccination for COVID-19 with the messenger ribonucleic acid (mRNA) vaccine Comirnaty in immunosuppressed and immunocompetent individuals" 3 SAEs including liver transplant rejection were considered related to Comirnaty exposure. The MAH is requested to provide more detailed information regarding the methods of the study (including study size) and the SAEs considered related to Comirnaty exposure. Furthermore, it is noted that during the interval period of the current PSUR there were 2 post-marketing cases reporting liver transplant rejection. The MAH is requested to provide more detailed information regarding these 2 cases reporting liver transplant rejection including a causality assessment concerning Comirnaty exposure. **Request for supplementary information**

From the non-MAH sponsored study "Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Allo)" there were 2 cases reporting 3 SAEs (cytomegalovirus infection, myelitis and thrombotic microangiopathy) which the MAH considered unrelated to Comirnaty exposure while the investigator considered all SEAs related to Comirnaty exposure. The MAH is requested to provide a detailed explanation regarding the discrepancy between the assessment of the MAH and the assessment of the investigators concerning the causality assessment of the SEAs to Comirnaty exposure. **Request for supplementary information**

Medication errors

Clinical trial data

During the reporting period, there was 1 serious case (0.1% of 721 cases, the total CT dataset) indicative of medication error reported (PT: Accidental overdose). The accidental overdose resulting in a fatal outcome referred to fentanyl, not to BNT162b2 and it was assessed as not related by the Investigator and the Sponsor. There were no serious cases retrieved during the reporting period of the first PSUR.

Post-authorisation data

The potentially relevant medication error cases during the reporting period were 33,834 (5.1%) reporting 42,992 events, compared to 10,776 relevant cases (3.3%) analysed in the first PSUR.

Overall, among the 33,834 relevant medication error post-marketing cases, 879 cases (0.1% of the total interval cases), 2.6% of total relevant medication error cases were considered harmful, 59 of which (0.01% of total relevant cases) were serious and most of them originated from vaccine administration issues (49 cases of 59 serious cases with harm). Some medication errors are expected to occur despite written instructions for handling the vaccine (thawing, dilution, preparation) and educational activities for HCPs administering the vaccine. 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:

One serious clinical trial case indicative of a medication error was reported and considered not related to Comirnaty exposure.

During the reporting period, a slightly increased number of medication errors (N=33,834 cases with an estimated 1,430,363,611 administered doses) was reported compared to the previous PSUR (N=10,776 cases with an estimated 635,763,682 administered doses). From the 879 cases with medication errors associated with harm, 59 cases were considered serious. However, no specific trend or pattern was observed.

No new important safety information could be identified.

Errors pertaining to the new formulation of BNT162b2 – Paediatric Tris/Sucrose 10 µg/dose

During the reporting period, there was a regulatory commitment:

- *EMEA/H/C/005735/MEA/002.10 (11th SSR), The MAH should report on handling and dosing errors as a result of the different Comirnaty formulations on the market.*

MAH's response:

Overall, out of the 33,834 relevant medication error cases, there were 755 cases reporting events indicative of medication errors related to Tris/Sucrose paediatric formulation. This number is a good index of the effectiveness of the routine pharmacovigilance activities implemented by the MAH and detailed in Part III.1 of the EU-RMP in the subsection Potential Medication errors, considering that in the reporting period 47,038,200 paediatric tris/sucrose doses were shipped worldwide.

Rapporteur assessment comment:

Post-marketing cases on handling and dosing errors as a result of the different Comirnaty formulations have been monitored in the SSRs, and no new important safety information could be identified regarding 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 no studies that presented important new safety findings for BNT162b2. A literature review including 58 studies is available in Appendix 5 of the PSUR (not reproduced here).

All Other Published Sources

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

Unpublished manuscripts

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

Rapporteur assessment comment:

The MAH provided an overview of the retrieved 58 studies that presented new safety information during the reporting period by topic: Anaphylaxis (5 studies), Myocarditis and pericarditis (7 studies), Immune-mediated/Autoimmune conditions (arthritis, rheumatic diseases, diabetes) (10 studies), Neurological events (Guillain Barré syndrome, Bell's palsy, epilepsy, multiple sclerosis) (14 studies), Herpes zoster (3 studies), Mortality (1 study), Booster dose (3 studies), Heterologous vaccination (1 study), Safety in

special populations (history of COVID-19, cancer, transplant) (11 studies), and Safety profile in patients with underlying comorbidities -HIV and immunocompromised individuals (3 studies).

The presented studies were assessed in the 8th through 12th SSR during the reporting period of the current PSUR and provided no additional information as provided in the Comirnaty PI. Therefore, no new important safety information could be identified regarding literature.

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, 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.

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

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 2.0 adopted 31 May 2021:

Table 1. Ongoing Safety Concerns

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

During the reporting period, on 05 August 2021, the MAH submitted the 2.3 version of the EU-RMP including myocarditis/ pericarditis as important identified risk; this version received a positive CHMP opinion on 30 September 2021. In the first PSUR, the MAH had proposed to include myocarditis/ pericarditis in the list of safety concerns for the next reporting period, subject to the PRAC approval of the EU RMP version 2.3.

There are no further changes to propose with regard to the safety concerns.

Rapporteur assessment comment:

As per EU RMP version 2.3 myocarditis and pericarditis are important identified risks. Please refer to 'Evaluation of Important Identified Risks' in section 2.3 'Evaluation of risks and safety topics under monitoring' of this AR for the interval data for these safety concerns.

2.2. Signal evaluation

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

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
Ongoing signals							
Vasculitis	22 Nov 2021	Ongoing	NA	Enquiry from a competent authority	Lareb (Netherlands) reviewed cases of vasculitis reported to the Netherlands Pharmacovigilance Centre and suggested that the relationship between vasculitis and Comirnaty should be further investigated	Safety and Clinical database review	Ongoing
Cerebral venous sinus thrombosis	02 Dec 2021	Ongoing	NA	Enquiry from a competent authority	Swiss-medic requested Pfizer to submit a cumulative safety report on Comirnaty and cerebral venous sinus thrombosis	Safety and Clinical database review	Ongoing

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
Signals Determined Important Risks							
Myocarditis and pericarditis	15 Feb 2021 Re-opened 19 Apr 2021 Re-opened 24 May 2021 Re-opened 24 Jun 2021 Re-opened 30 Jun 2021 Re-opened 14 Oct 2021	Closed	10 Nov 2021	Enquiry from a competent authority	Signal previously reviewed in the context of ongoing discussions with a health authority (Israel MoH) and in response to a PRAC signal assessment report and several requests from other Health Authorities. The MAH has continuously monitor the emerging evidence on the association between COVID-19 mRNA vaccine Comirnaty and myocarditis and pericarditis arising from all available of sources. In October 2021, PRAC Signal procedure prompted by new data on the known risk of myocarditis, pericarditis in a preliminary report of a meta-analysis of data from Denmark, Finland, Norway and Sweden. The signal re-evaluation found that in large, controlled, pivotal study C4591001, myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis and pericarditis. The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. In aggregate, the epidemiology studies reported higher risk after Dose 2	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been confirmed. Continuous monitoring of the emerging data continues. At the request of several HAs, the events were included as adverse reactions in local product labelling and as Important Identified risk in risk management and pharmacovigilance plans. Most recently, in response to the Nordic observational study data, the PRAC requested that the frequency be changed from "Not known" to "very rare" in the SmPC.

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
					compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination. The review of the post-marketing cases of myocarditis found that although the number of cases increases as the vaccine exposure increases, the profile of cases remains largely unchanged. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration.		

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
Signals Determined NOT to be Risks							
Liver injury/Autoimmune hepatitis	10 Nov 2021	Closed	15 Dec 2021	Enquiry from a competent authority	Therapeutic Goods Administration (Australia) requested Pfizer to provide an analysis for Comirnaty associated with 'acute liver injury adverse events of special interest (AESI)' and 'autoimmune hepatitis'. The review of the clinical study data did not identify relevant cases of autoimmune hepatitis or liver injury with the vaccine. The review of the post-marketing data was conducted and identified cases with confounders or lacking proper information to support a diagnosis of the conditions under review. The O/E ratios were <1.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded based on available information. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available

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
Multisystem inflammatory syndrome (MIS) in adults (MIS-A) and children (MIS-C)	03 Sep 2021	Closed	28 Sep 2021	Enquiry from a competent authority	PRAC provided a signal assessment report for Multisystem Inflammatory Syndrome (MIS) and requested a cumulative review of MIS in children and adults. A cumulative search of the Pfizer safety database to 02 September 2021 was conducted for events that may represent potential cases of MIS-C or MIS-A using the 16 broad and specific PTs as delineated in the PRAC query of 02 September 2021. A total of 363 cases were identified and reviewed. Six cases met the BC case level definitions for MIS (one MIS-C and 5 MIS-A). A definitive causal relationship between Comirnaty and the development of MIS could not be made for the one identified MIS-C case; and the MIS-A cases contained various confounding factors that precluded a reliable assessment of Comirnaty causality. The calculated O/E ratios upper limits of the 95% CI were substantially <1 suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.	Safety database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded based on available information. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available

Uveitis	31 Aug 2021	Closed	30 Sep 2021	Scientific literature	Published article was retrieved ("Anterior uveitis onset after BNT162b2 vaccination: is this just a coincidence?", Renisi et al.). A safety database review of cases for Comirnaty coded with the PT, Uveitis, identified 142 cases amid 1,359,989,180 doses have been administered globally as of 22-Sep-2021. Given the complexity of diagnosing uveitis, the majority (53.5%) were not medically confirmed, with only 46.5% of cases categorized as medically confirmed. Almost half of the medically confirmed cases had either history of uveitis and/or no time of onset reported and thus excluded from analysis. Only 35 cases (almost 25% of the total reported cases) were medically confirmed without a medical history of an ocular pathology and had a time to onset of 30 days or less postvaccination. A review of these cases showed that while the majority did not resolve at the time of reporting, there were no dose-dependent sequence of occurrence. None of these cases resulted in hospitalization or was fatal. Nevertheless, 20 of these cases did not have a medical history reported, some did not have concomitant medications reported, clinical or laboratory investigations conducted to exclude causes for differential diagnosis, nor intensity assessment. This missing information further confounds a proper assessment of causality to the vaccine. Lastly, the O/E ratios for both 21-day and no risk windows were <1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.	Safety database review O/E analysis	A causal association between the vaccine and this event has not been concluded based on available information. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

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
Rhabdomyolysis	17 Aug 2021	Closed	01 Sep 2021	Enquiry from a competent authority	PRAC assessment report for Summary Monthly Safety Report #8 included a request for a cumulative review of rhabdomyolysis that included an O/E analysis, with sensitivity analysis to compensate for backlogged cases. Rhabdomyolysis had been spontaneously reported following vaccination with Pfizer/BNT B162b2 vaccine in the post-authorization setting. Of the total 112 cases, 2/3 of the cases were eliminated from further analysis due to insufficient clinical details and implausible latency. Subsequently, the remaining 1/3 of the cases either provided a clear alternate aetiology for rhabdomyolysis or were confounded by concurrent conditions and/or concomitant medications. The placebo-controlled clinical trial data did not provide evidence of a causal association with vaccine (one placebo recipient and no vaccine recipients reported rhabdomyolysis).	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded based on available information. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available

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
Hypoaesthesia/ Paraesthesia	26 Aug 2021	Closed	01 Sep 2021	Enquiry from a competent authority	PRAC assessment report for SMSR #7 included a request to provide an analysis of hypoaesthesia and paraesthesia and to discuss whether paraesthesia and hypoaesthesia are sufficiently covered in the product information in the context of stress-related reactions. In study C4591001 Phase 2/3 participants ≥16 years of age who received at least 1 dose of study intervention - 21,926 in the vaccine group and 21,921 in the placebo group, at the cut-off date of 13 March 2021, from dose 1 to 1 month after dose 2, a total of 22 participants in the vaccine group and 23 participants in the placebo group reported paraesthesia whilst 5 participants in the vaccine group and 7 in the placebo group reported hypoesthesia. In the context of 1,290,832,556 doses of vaccine distributed as of 25 August 2021, there have been 21,793 cases reported containing PT paraesthesia and/or hypoaesthesia. On review of data this does not appear to reflect a novel or distinct pathological process, rather the majority reflect a nuance of the description of symptomatology of existing medical concepts (e.g. stress reactions).	Safety and Clinical database review Literature review	Hypoaesthesia and paraesthesia were determined to be descriptive of symptomatology medical concepts such as stress reactions. The core datasheet was therefore not amended to include them as causally associated adverse reactions to the vaccine association. The EU SmPC was required by EMA to be updated to add the PT Hypoaesthesia and paraesthesia in section 4.4 within the symptoms of the anxiety related reactions and as adverse reactions to section 4.8 with a frequency of Not known

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
Glomerulonephritis and Nephrotic Syndrome	27 July 2021	Closed	18 Aug 2021	Enquiry from a competent authority	PRAC provided a signal assessment report for glomerulonephritis and nephrotic syndrome and based on this and the SMSR #7 assessment, MAH was requested to provide a cumulative review of Glomerulonephritis and Nephrotic Syndrome. Subsequent to SMSR #10, Health Canada requested an updated cumulative review for SMSR #11. No cases of Glomerulonephritis or Nephrotic syndrome were reported in the large placebo controlled clinical trial with over 20,000 participants vaccinated with BNT162b2 (Study C4591001, cutoff date of 13 March 2021). There were no literature reports of studies or case series presentations of these conditions following vaccination with this vaccine. The safety database contains a total of 89 potentially relevant cases that were retrieved with the aforementioned search strategy. Most reports contained limited details, and the majority of cases with more detail reported alternate etiologies and/or significant confounding comorbidities. Even when utilizing a very conservative O/E analysis, the resulting ratio is <1, including the upper limit of the 95% CI.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and these events has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

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
Erythema multiforme	27 July 2021	Closed	18 Aug 2021	Enquiry from a competent authority	PRAC provided a signal assessment report on Erythema multiforme and requested a cumulative review of all cases concerning Comirnaty and erythema multiforme. No occurrences of EM were reported in the pivotal clinical trial in which over 20,000 participants received BNT162b2 (Study C4591001, cutoff date of 13 March 2021). One occurrence of EM was reported in a study of BNT162b2 in healthy Japanese adults (Study C4591005). The safety database contains a total of 124 potentially relevant cases, the majority of spontaneous cases were reported in females, from the age of 31 years and greater, post Dose 1, and the majority of EM events occurred from Day 1 to Day 3 post vaccination. The most commonly reported outcome of EM was resolved/resolving. There were no literature reports of studies or case series presentations of EM following vaccination with this vaccine. The O/E ratios for all risk windows overall and by dose are <1.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and EM has not been concluded, ,therefore the RSI has not been amended. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available. The EU SmPC was required by EMA to be updated to include Erythema multiforme as an adverse reaction in section 4.8 with a frequency of "Not known"

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
Thrombocytopenia Thrombosis Syndrome (TTS)	06 July 2021	Closed	04 Aug 2021	Enquiry from a competent authority	Due to reports of the co-occurrence of thrombocytopenia and thromboembolism, the MAH has been closely monitoring such reports and providing updates in the Summary Monthly Safety Documents. PRAC requested close monitoring of this topic and analysis in SMSR. Of the post-marketing cases received, those meeting BC criteria consistent with the highest level of certainty are the BC Level 1 cases with PF4 antibody (ELISA) test positivity. Of these 9 cases, there is not an apparent patient profile that can be discerned. The cases consist of males and females of a wide age range. The events occur after either dose and the medical backgrounds of the patients are also varied, with some having other medical conditions that would predispose to thrombocytopenia or blood clots. Given the several hundred million doses of Pfizer-BNT vaccine administered worldwide, the numbers of concerning cases remains relatively low.	Safety database review O/E analysis	A causal association between the vaccine and this event has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

Myasthenia gravis	11 Mar 2021 (nonvalidated signal) Re-opened as a validated signal 16 Aug 2021	Closed	25 Aug 2021	Epidemiology O/E Analysis Enquiry from a competent authority	O/E finding (upper level of 95% CI exceeding 1) Health Canada Request for an updated review and analysis of myasthenia gravis in response to a Summary Monthly Safety Report inclusion of an O/E with an upper level of the 95% confidence interval exceeding 1 for both the 21-day and no risk windows in the interval period in the overall observed versus expected (O/E) analysis. The review of the post-marketing safety database found that most spontaneous cases are confounded by a medical history reporting a pre-existing MG or other significant clinical risk factors (ongoing autoimmune disease and or cancer). Overall, 10 subjects reported the diagnosis confirmed by EMG and/or autoantibodies of which 5 had underlying autoimmune condition and 3 had an ongoing neoplasm Clinical study results do not demonstrate an imbalance between placebo and vaccine. At the time of the review, statistical signal detection in the Pfizer safety database has not shown a signal of disproportionate reporting for Myasthenia gravis. Further, O/E analysis does not suggest an increased rate for this topic. In the literature a worsening of MG symptoms after vaccination has not been identified as a risk while is clearly reported that infections account for 40-70% of the exacerbations. In addition, if the patient is not medically optimized, could developed a cytokine storm, despite being on steroids. Moreover, up to 15% of patients may experience worsening MG symptoms and/or exacerbations upon initiation of oral prednisolone therapy.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and MG has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

Immune thrombocytopenia	21 Jan 2021 Re-opened 25 Feb 2021 Re-opened 14 Jun 2021 Re-opened 25 Jun 2021	Closed	04 Aug 2021	Enquiry from a competent authority Evaluation for PSUR	This topic was originally opened as a signal following a fatal case of thrombocytopenia following vaccination in the US and a subsequent FDA request. The signal re-opened following PRAC assessment for SMSR (#2 requesting cumulative overview of all cases reporting Immune thrombocytopenia / Thrombocytopenia. Signal re-opened with request of FDA Office of Biostatistics and Epidemiology that signal detection on the Center for Medicare & Medicaid Services (CMS) database showed this event as an AESIs as a signal for the Pfizer/BNT COVID-19 vaccine (any dose) with a relative risk >1. Signal re-opened for full evaluation of data for PSUR. Overall, the review of thrombocytopenia from clinical study data, post-authorisation spontaneous reports, medical literature and observed versus expected analyses did not identify sufficient information to establish a causal relationship with the vaccine. While there are spontaneous post-vaccination reports of de-novo and worsening thrombocytopenia in patients with and without known thrombocytopenia, respectively, it is not outside of the range that would be expected without BNT162b2 vaccination. While it is acknowledged that patients with a diagnostic history of immune thrombocytopenia may be the most vulnerable to thrombocytopenia if precipitated by the vaccine, the undulating nature of the disorder calls into question the vaccine as the clear cause. A hypothesis can be made about an immune response and molecular mimicry as a mechanism for thrombocytopenia, but this would be speculative in nature.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

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
Herpes zoster including Ophthalmic herpes zoster	05 Oct 2020 Re-opened 21 Feb 2021 Re-opened 26 Apr 2021 Re-opened 02 Sep 2021	Closed	30 Sep 2021	Spontaneous Reports: Non statistical Line listing;	Validated Signal Feb 2021 when cases were found on internal nonstatistical line listing review. 4/26/21 Re-opened: Signal re-opened as a result of a Swiss Medic Query received. 9/2/2021: Signal re-opened. PRAC Assessment Report for SMSR #8 requested a cumulative review of the cases reported following the publication of Bada N et al., Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting, N Engl J Med, 25 Aug 2021. The review of information from the post-marketing safety database did not support an association with the vaccine. The O/E ratio was below 1 suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. Review of the literature review did not identify a significant safety information for vaccine associated herpes zoster.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

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
Appendicitis	18 Sep 2020 Re-opened 06 May 2021 Re-opened 02 Sep 2021	Closed	22 Sep 2021	Clinical trial data Enquiry from a competent authority	Signal opened 9/18/2020: Clinical trial data Signal re-opened 05/06/2021: Health Canada HA query Signal re-opened 9/2/2021: PRAC Assessment Report for SMSR #8 with request for a cumulative review of the cases reported following the publication of Bada N et al., Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting, N Engl J Med, 25 Aug 2021. The review of information from the post-marketing safety database did not support an association with the vaccine. The O/E ratio was below 1 indicating no increased risk of appendicitis. Review of the literature review did not identify a significant safety information for vaccine associated appendicitis. Notably, a recent publication of an analysis of the Vaccine Safety Datalink (VSD) demonstrated that there was no increased risk of appendicitis.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been concluded. Routine PV monitoring will continue, and the topic will be reopened if new relevant information becomes available.

2.2.1. Post-approval regulatory requests

2.2.1.1. Exacerbation (flare-up) of pre-existing AI/Inflammatory disorders

Response to the PRAC request 5 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *The MAH should present a cumulative review of exacerbation (flare-up) of pre-existing AI/Inflammatory disorders in the next PSUR including data from, at least, the scientific literature and the post-marketing cases. A tabulated case summary to be presented, with the following columns to be included: Case ID, Eudravigilance Case ID, PTs, Patient Age, Patient Gender, First Dose to Onset, Medical History, Concomitant Medications, Case Comment, information dose, WHO causality assessment and the reasoning for the causality category*

MAH's response:

Post-marketing safety database

The MAH's safety database was searched for all BNT162b2 vaccine cases received through 18 December 2021 using the MedDRA version 24.1 using the following search criteria:

- SMQ Immune-mediated/autoimmune disorders (narrow scope, to increase specificity);
- HLGT Autoimmune disorders;
- HLGT Immune disorders NEC (Primary Path);
- HLT Neuromuscular junction dysfunction (Primary Path).

The search criteria were used in different steps:

1. The search criteria were applied to the medical history field to retrieve all cases with a medical history of autoimmune disease.
2. For the cases that reported autoimmune diseases in the medical history, the same search criteria was applied to the reported adverse events to retrieve cases reporting autoimmune disease in subjects with existing autoimmune comorbidity.
3. The cases retrieved in the search as per point 2 were reviewed for potential exacerbation/ relapse/ flare of the autoimmune disease coded both in the medical history and as an adverse event.

A total of 33,711 cases described a medical history of autoimmune disease (total cases in the safety database: 997,934). Among them, 2223 reported the same autoimmune condition as an adverse event, indicating a potential exacerbation or worsening of the underlying disorder (some cases were counted more than once because they reported more than 1 underlying autoimmune medical history and adverse event pair).

It is important to note that a spontaneous database cannot collect the medical history prospectively, rather a reporter provides both the adverse event and medical history. Thus, the number of cases that report autoimmune medical history should not be considered a denominator or indicator of that condition in a population.

In the table below, the specific autoimmune diseases reported in the medical history and after vaccination are detailed.

Table: Autoimmune Disease Reported in the Medical History and After Vaccination

Autoimmune disease	Case reporting an autoimmune disease in the medical history	Case reporting an autoimmune disease after vaccination
Thyroiditis/Basedow (autoimmune thyroid disorder, autoimmune thyroiditis, thyroiditis, autoimmune hypothyroidism, Basedow's disease)	7073	67
Rheumatoid arthritis	5155	469
Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus	3652	40
Psoriasis	2456	366
Multiple sclerosis/Multiple sclerosis relapse/Relapsing-remitting MS	2382	372
Crohn's disease	1953	119
Ulcerative colitis/autoimmune colitis	1936	228
Coeliac disease	1472	14
Systemic lupus erythematosus	1185	82
Ankylosing spondylitis	965	90
Sjogren's syndrome	955	29
Sarcoidosis	481	20
Polymyalgia rheumatica	546	50
Immune thrombocytopenia	494	89
Vitiligo	326	26
Myasthenia gravis/MG crisis	279	43
Vasculitis	190	16
Guillain-Barre syndrome	216	12
Bechet's syndrome	187	21
Alopecia areata	115	24
Uveitis	83	14
Henoch-Schoenlein purpura	73	12
Transverse Myelitis/Myelitis	61	10
Amyloidosis	43	1
Systemic scleroderma	73	1
Still's disease	48	8
Total	**32399***	**2232***

* some patients reported more than 1 autoimmune disease in medical history and/or as an adverse event

A detailed analysis, including dose sequence information, time to onset (latency), outcome and duration of the relevant adverse events for each autoimmune disease is presented for the reports below. Note that each table below considers the number of cases in which the autoimmune disorder was reported in both the medical history and as an adverse event following vaccination. Note that the number of events may not equal the number of cases (e.g., if the event occurred after more than 1 dose or if >1 PT describing the event is reported in the case).

Alopecia areata

There were 115 cases reporting the PT Alopecia Areata as relevant medical history and 24 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Alopecia Areata	Dose 1: 14 Dose 2: 13	Not Resolved: 18 Resolved/Resolving/Resolved with sequelae: 5 Unknown: 6	3-7 days: 6 14-21 days: 9 22-32 days: 4 96 days: 2	4 days: 2

Amyloidosis

There were 43 cases reporting the PT Amyloidosis as relevant medical history and one that reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Amyloidosis	Not reported	Not Resolved: Not reported Resolved/Resolving/Resolved with sequelae: Not reported Unknown: 1	Not reported	Not reported

Ankylosing spondylitis

There were 965 cases reporting the PT Ankylosing spondylitis as relevant medical history and 90 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Ankylosing spondylitis	Dose 1: 38 Dose 2: 78 Dose 3: 9	Not Resolved: 42 Resolved/Resolving/Resolved with sequelae: 40 Unknown: 16	Same day: 12 1-3 days: 31 4-9 days: 14 11-15 days: 5 16-23 days: 3 28-32 days: 2	3 days: 1 6-8 days: 4 9-12 days: 2 42 days: 1 108 days: 1

Behcet's syndrome

There were 187 cases reporting the PT Behcet's syndrome as relevant medical history and 21 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Behcet's syndrome	Dose 1: 12 Dose 2: 5 Dose 3: 2	Not Resolved: 7 Resolved/Resolving/Resolved with sequelae: 8 Unknown: 6	Same day: 3 1-3 days: 3 5-7 days: 3 10-20 days: 4	13-14 days: 2

Coeliac disease

There were 1472 cases reporting the PT Coealiac disease as relevant medical history and 14 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Coealiac disease	Dose 1: 9 Dose 2: 1 Dose 3: 2	Not Resolved: 6 Resolved/Resolving/Resolved with sequelae: 4 Unknown: 5	Same day: 2 1-2 days: 3 7 days: 1 13 days: 1	3 days: 1

Colitis ulcerative

There were 1936 cases reporting the PT Colitis ulcerative or Autoimmune colitis as relevant medical history and 228 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Colitis ulcerative and Autoimmune colitis	Dose 1: 117 Dose 2: 100 Dose 3: 4 Dose 4: 1	Not Resolved: 106 Resolved/Resolving/Resolved with sequelae: 96 Unknown: 55	Same day: 21 1-3 days: 74 4-7 days: 27 8-11 days: 13 13-24 days: 19 25-35 days: 4 44 days: 2 72-77 days: 4 87 days: 1 174 days: 1	2-9 days: 6 2 weeks: 1 20-24 days: 3 30-42 days: 2 60-69 days: 4 84 days: 2

Crohn's disease

There were 1953 cases reporting the PT Crohn's disease as relevant medical history and 119 out of them reported the disease after vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Crohn’s disease	Dose 1: 56 Dose 2: 52 Dose 3: 8 Dose 4: 1	Not Resolved: 62 Resolved/Resolving/Resolved with sequelae: 52 Unknown: 37	Same day: 8 1-3 days: 25 4-7 days: 12 8-11 days: 7 13-24 days: 9 25-30 days: 5 40-44 days: 2 88 days: 1	4-8 days: 3 12-14 days: 4

Diabetes

There were 3652 cases reporting one the PTs Diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus as relevant medical history and 40 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus	Dose 1: 24 Dose 2: 19	Not Resolved: 12 Resolved/Resolving/Resolved with sequelae: 28 Unknown: 19 Fatal: 2	Same day: 3 1-3 days: 9 7 days: 3 14-20 days: 4 77 days: 2 98 days: 1	1 day: 1 6 days: 1 15 days: 1

Diabetes fatal [redacted]

[redacted] is not reproduced here (already presented and assessed in the 10th SSR [EMEA/H/C/005735/MEA/002.9])

AER#2021527624

A 69-year-old female patient received BNT162b2 on 19Jan2021 as an initial dose and on 25Mar2021 as the second dose. Medical history included ketosis-prone diabetes mellitus, insulin-dependent diabetes, arterial hypertension, complete arrhythmia due to atrial fibrillation, kidney failure, sequelae cognitive disorders, stroke, sleep apnea, hypothyroidism, obesity, hyperuricaemia, deglutition disorder, hyponatraemia, hyperkalemia, swallowing disorders with currently rehydration by exclusive gastric tube. Concomitant medications included phenobarbital, oxazepam, mirtazapine, levothyroxine sodium, erythromycin, racecadotril, hyoscine, oxycodone hydrochloride, and insulin lispro. On 02Apr2021, the patient tested positive for COVID-19. On 06Apr2021, respiratory decompensation occurred, dextro 5.8g/l, oxygen saturation 85%, heartbeat was 65, and blood pressure was 100/60. The patient was put under hospital care with oxygen 6L/min. The patient presented on arrival in a comatose state with concomitant hypoxia linked to COVID and especially a state of hyper osmolarity linked to a decompensation of her diabetes. Treatment was performed with rehydration for hyperosmolar coma, insulin therapy, and antibiotic therapy. Palliative comfort management was initiated given the patient's condition and the patient eventually died on 08Apr2021 despite the treatment. An autopsy was not performed. The reported cause of death was COVID-19, hyperosmolar (non-ketotic) coma and decompensation of diabetes.

Guillain-Barre syndrome

There were 216 cases reporting the PT Guillain-Barre syndrome as relevant medical history and 12 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Guillain-Barre syndrome	Dose 1: 16 Dose 2: 8 Dose 3: 1	Not Resolved: 10 Resolved/Resolving/Resolved with sequelae: 13 Unknown: 8 Fatal: 1	Same day: 2 1-3 days: 7 4-8 days: 6 13-19 days: 5 24 days: 1 84 days: 1	79 days: 1

GBS fatal case AER#2021381625 is not reproduced here (already presented and assessed in the 10th SSR).

Rapporteur assessment comment:

12 out of 216 cases reported GBS following vaccination. It is assumed that the dose number column displayed the number of *events* and not the number of cases (there were 16 events reported following dose 1).

Henoch-Schoenlein purpura

There were 73 cases reporting the PT Henoch-Schoenlein purpura as relevant medical history and 12 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Henoch-Schoenleinpurpura	Dose 1: 6 Dose 2: 6	Not Resolved: 4 Resolved/Resolving/Resolved with sequelae: 8	Same day: 1 1-4 days: 5 6-7 days: 3	Not reported

Immune thrombocytopenia

There were 494 cases reporting the PT Immune thrombocytopenia as relevant medical history and 89 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Immune thrombocytopenia	Dose 1: 32 Dose 2: 49 Dose 3: 3	Not Resolved: 29 Resolved/Resolving/Resolved with sequelae: 66 Unknown: 11	Same day: 2 1-3 days: 22 4-7 days: 17 8-17 days: 14 23-29 days: 6 31-35 days: 6 40-50 days: 3 84 days: 1 92 days: 1 154 days: 1	2-4 days: 4 7-8 days: 4 10-11 days: 2 14-16 days: 2

Multiple sclerosis

There were 2382 cases reporting one of the PT's Multiple sclerosis/Multiple sclerosis relapse/Relapsing-remitting MS as relevant medical history and 183 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PTs: Multiple sclerosis/Multiple sclerosis relapse/Relapsing remitting MS	Dose 1: 183 Dose 2: 136 Dose 3: 16	Fatal: 1 Not Resolved: 167 Resolved/Resolving/Resolved with sequelae: 158 Unknown: 93	Same day: 46 1-3 days: 86 4-7 days: 40 8-12 days: 37 13-17 days: 20 18-23 days: 9 24-38 days: 28 41-67 days: 7 74-104 days: 9 134-224 days: 3	1-4 days: 12 6-8 days: 5 11-16 days: 4 21-26 days: 3 41 days: 1 69 days: 1 77 days: 1 93 days: 1

Multiple sclerosis fatal [redacted]:

A 61-year-old female received BNT162b2 in 2021 (number of doses unknown). Relevant medical history included: "Multiple sclerosis" (unspecified if ongoing). The patient's concomitant medications were not reported. On 25Apr2021 the patient experienced multiple sclerosis relapse described as a flare, subileus, cerebrovascular accident described as apoplexy, dysphagia, aspiration, and infections. "After long-term ventilation and weaning-failure, discharge from the respiratory care home, repeated aspirations, infections, final inpatient stay with subileus, apoplexy, and death on 16Sep2021. The reported cause of death was multiple sclerosis relapse. It was not reported if an autopsy was performed.

Myasthenia gravis

There were 279 cases reporting one of the PTs Myasthenia Gravis/Myasthenia Gravis crisis as relevant medical history and 43 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PTs: Myasthenia Gravis/Myasthenia Gravis crisis	Dose 1: 12 Dose 2: 23 Dose 3: 2	Not Resolved: 19 Resolved/Resolving/Resolved with sequelae: 20 Unknown: 5 Fatal: 1	Same day: 6 1-3 days: 14 4-8 days: 6 10-13 days: 7 17-22 days: 2 49 days: 1	1 hour: 1 4-11 days: 4

Myasthenia gravis fatal case AER# [redacted] is not reproduced here (already presented and assessed in the 10th SSR).

Myelitis/ Transverse myelitis

There were 61 cases reporting one of the PTs Myelitis/Transverse Myelitis as relevant medical history and 10 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PTs: Myelitis/ Transverse myelitis	Dose 1: 6 Dose 2: 4	Not Resolved: 2 Resolved/Resolving/Resolved with sequelae: 3 Unknown: 5	Same day: 1 3 days: 1 8 days: 1 39-40 days: 2 49 days: 1	Not reported

Polymyalgia rheumatica

There were 546 cases reporting the PT Polymyalgia Rheumatica as a relevant medical history and 50 out of them of the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Polymyalgia Rheumatica	Dose 1: 17 Dose 2: 27 Dose 3: 1	Not Resolved: 23 Resolved/Resolving/Resolved with sequelae: 22 Unknown: 8	Same day: 6 1-3 days: 9 4-7 days: 10 11-13 days: 3 14-22 days: 7 49 days: 1 78 days: 1 85 days: 1	2 days: 1 28 days: 1 60 days: 1

Psoriasis

There were 2456 cases reporting the PT Psoriasis as a relevant medical history and 366 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Psoriasis	Dose 1: 178 Dose 2: 144 Dose 3: 15	Not Resolved: 208 Resolved/Resolving/Resolved with sequelae: 143 Unknown: 85	Same day: 26 1-3 days: 92 4-7 days: 36 8-14 days: 45 15- 27 days: 31 28-38 days: 10 41-63 days: 10 83 days: 1 126 days: 1 131 days: 1 166-168 days: 2 792 days: 1	4 days: 1 12-19 days: 3 21 days: 1 24 days: 1 42 days: 1 77 days: 1 93 days: 1 120 days: 1

Rheumatoid arthritis

There were 5155 cases reporting the PT Rheumatoid Arthritis as a relevant medical history and 469 out of them reported the disease following vaccination with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Rheumatoid Arthritis	Dose 1: 226 Dose 2: 191 Dose 3: 18	Not Resolved: 215 Resolved/Resolving/Resolved with sequelae: 170 Unknown: 101 Fatal: 1	Same day: 40 1-3 days: 112 4-7 days: 52 8-14 days: 38 15- 29 days: 35 30-37 days: 7 44-51 days: 6 58-72 days: 4 76-78 days: 3 98 days: 1 273 days: 1 303 days: 1 527 days: 1	0-1 day: 4 2-8 days: 17 10- 18 days: 5 24-37 days: 4 6 weeks: 1 61-67 days: 3 62 days: 1 90 days: 1 146 days: 1

Rheumatoid Arthritis fatal [redacted] is not reproduced here (already presented and assessed in the 10th SSR).

Sarcoidosis

There were 481 cases reporting the PT Sarcoidosis as relevant medical history and 20 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Sarcoidosis	Dose 1: 14 Dose 2: 6	Not Resolved: 13 Resolved/Resolving/Resolved with sequelae: 2 Unknown: 6	Same day: 2 3-9 days: 5 14 days: 1 50 days: 1	Not reported

Sjogren's syndrome

There were 955 cases reporting the PT Sjogren's syndrome as relevant medical history and 29 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Sjogren's syndrome	Dose 1: 17 Dose 2: 10	Not Resolved: 9 Resolved/Resolving/Resolved with sequelae: 8 Unknown: 14	Same day: 3 1 day: 5 6 days: 1 8 days: 1 13 days: 1 21 days: 1 63 days: 2	4 days: 1 13 days: 1

Systemic lupus erythematosus

There were 1185 cases reporting the PT Systemic lupus erythematosus as relevant medical history and 82 out of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Systemic lupus erythematosus	Dose 1: 48 Dose 2: 26	Not Resolved: 29 Resolved/Resolving/Resolved with sequelae: 30 Unknown: 30	Same day: 12 1-3 days: 11 4-9 days: 22 14-28 days: 8 33 days: 1 61 days: 1 99 days: 1 126 days: 1	3 days: 1 4 days: 1 5 days: 1

Still's disease

There were 48 cases reporting the PT Still's disease as relevant medical history and 8 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Still's disease	Dose 1: 5 Dose 2: 2	Not Resolved: 2 Resolved/Resolving/Resolved with sequelae: 4 Unknown: 2	2 days: 1 6 days: 1 38 days: 1	Not reported

Systemic scleroderma

There were 74 cases reporting the PT Systemic scleroderma as relevant medical history and 1 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Systemic scleroderma	Dose 1: 1 Dose 2: Not reported	Resolved: 1	2 days: 1	Not reported

Thyroiditis

There were 5721 cases reporting one of the PTs Autoimmune Thyroid Disorder, Autoimmune Thyroiditis, Thyroiditis. Autoimmune Hypothyroidism/Basedow's disease as relevant medical history and 82 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PTs: Autoimmune thyroid disorder, autoimmune thyroiditis, thyroiditis, autoimmune hypothyroidism, Basedow's disease)	Dose 1: 32 Dose 2: 43	Not Resolved: 40 Resolved/Resolving/Resolved with sequelae: 26 Unknown: 9	Same day: 6 1-3 days: 21 4-7 days: 8 10-14 days: 4 15-18 days: 8 21-25 days: 6 34-39 days: 4 64-66 days: 4 85-93 days: 3 103-104 days: 4 173 days: 1	1 day: 1 4-5 days: 2 21 days: 1 54 days: 1 180 days: 1

Uveitis

There were 83 cases reporting the PT Uveitis as relevant medical history and 14 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Uveitis	Dose 1: 9 Dose 2: 8	Not Resolved: 8 Resolved/Resolving/Resolved with sequelae: 10 Unknown: 5	Same day: 1 1-4 days: 6 5 days: 1 12-14 days: 2 61 days: 1	10 days: 1

Vasculitis

There were 190 cases reporting the PT Vasculitis as relevant medical history and 16 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Vasculitis	Dose 1: 3 Dose 2: 10 Dose 3: 1	Fatal: 1 Not Resolved: 4 Resolved/Resolving/Resolved with sequelae: 6 Unknown: 5	2 days: 1 16-19 days: 2 56 days: 1 78 days: 1	5 days: 1

Vasculitis fatal case AER# [redacted]:

A 66-year-old male patient received the first dose of BNT162B2 on an unspecified date. Medical history included giant cell arteritis, stenosis, interstitial lung disease, tenderness, vasculitis, dehydration, headache, cortical blindness (admitted 14Aug2021), sciatica, hypoperfusion, visual disturbance, claudication, weakness, asthma and hypertension. Patient had seen Vascular in 2017 for leg pain which was atypical for intermittent claudication and diagnosed as sciatica; the ankle brachial pressure index was normal. Further investigation in May/June revealed bilateral inflammatory disease throughout his arterial extremities in lower limbs. He was referred to Rheumatology. Concomitant medications included beclomethasone dipropionate taken for asthma from 20Feb2020 to an unspecified stop date; ramipril taken for hypertension from 01Aug2018 to an unspecified stop date. The patient experienced vasculitis in Feb2021; cortical blindness on 14Aug2021. The patient experienced bilateral anterior circulation ischaemic strokes, bilateral carotid artery occlusions, exercise tolerance, inflammatory disease, temporal tenderness, hypoperfusion, visual disturbance, weakness, giant cell arteritis, vomiting, intermittent claudication, headache, diarrhoea, middle cerebral artery infarct, all on an unspecified date. The patient underwent lab tests and procedures which included COVID-19 virus test: Negative COVID-19 test on 29Mar2021. COVID-19 infection status was negative during last admission 14Aug2021 until death on 21Aug2021. The patient has possible inflammatory pathology. Carotid artery ultrasound showed thickened temporal, frontal and axillary arteries. The outcome of exercise tolerance was unknown. The outcome of other events was fatal. The patient died on 21Aug2021. An autopsy was not performed. Official cause of death was Bilateral anterior circulation ischaemic strokes and Bilateral carotid artery occlusions.

Vitiligo

There were 326 cases reporting the PT Vitiligo as relevant medical history and 26 of them reported the disease with the following features:

Autoimmune disease	Dose number	Clinical outcome	Time to onset (when reported)	AE duration (when reported)
PT: Vitiligo	Dose 1: 14 Dose 2: 9	Not Resolved: 16 Resolved/Resolving/Resolved with sequelae: 2 Unknown: 10	2-4 days: 5 5-9 days: 6 15-19 days: 3 25-28 days: 4 43 days: 1	Not reported

MAH discussion on post-marketing AE reports:

In many cases retrieved from the safety database, information on the underlying status of the autoimmune disease and/or the ongoing therapy or stressful situation that may induce a relapse of the underlying autoimmune disease is missing. Furthermore, it is unknown whether the patient is on a tapering dose of immune suppressive therapy that can by itself give rise to a flare-up. In addition, there is no information about the frequency of relapses of each patient, which is a very individual response characteristic of the disease, or of concomitant stressful factors that may induce a relapse/flare (e.g., recent infections, stressful situation). The paucity of this information makes it difficult to assess the potential contributory role of the vaccination to the relapse/flare of a pre-existing autoimmune disease.

The analysis has an intrinsic bias that is driven by the fact that the number of subjects that have been vaccinated who have an autoimmune comorbidity is not known and cannot be inferred from the spontaneous database. Therefore, an incidence or rate of a flare up/relapse cannot be calculated, and the detail showed above should be viewed with caution and the understanding of the nature of spontaneous reporting; clearly, in the database were captured only cases that reported an AE and it is not known how many patients with underlying disease were vaccinated but did not experience any adverse event/ relapse/flare.

Nevertheless, the data suggest that most cases report a potential relapse very shortly after vaccination (the same day or within 2 days of vaccination). This timing is more than likely implausible for the induction of a sufficient autoimmune response leading to a worsening of the underlying autoimmune disease.

Rapporteur assessment comment:

A cumulative search in the MAH's safety database up to 18 December 2021 revealed a total of 33,711 cases described a *medical history* of autoimmune disease (total cases in the safety database: 997,934). Among them, 2223 reported the same autoimmune condition as an *adverse event* after Comirnaty exposure, indicating a potential exacerbation or worsening of the underlying disorder.

Due to the lack of all kinds of relevant information (e.g. status of the autoimmune disease, ongoing therapy, tapering of immune suppressive therapy, frequency of relapses of the individual patient, concomitant stressful factors) it remains very challenging to properly assess the causal relationship between the vaccination and the relapse/flare of the autoimmune disease, as also discussed by the MAH. The MAH's note that most cases report a relapse (very) shortly after vaccination is acknowledged; a limited temporal relationship to the reported adverse events does not seem suggestive to induce an autoimmune response leading an exacerbation or relapse of an underlying autoimmune disease, but seems more likely events that mimic flares like fever, fatigue etc.

Clinical trial data

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 relevant adverse events. The data cutoff allows for a controlled comparison between the vaccine group and placebo group. A specific analysis of flare-ups of underlying conditions was not performed in the study.

Using the same search described in the method section and applied on the Clinical trial database, the following result was retrieved:

- 2955 (13.5%) of 21926 BNT subjects had one of the autoimmune conditions in their medical history
- 2977 (13.6%) of 21921 Placebo subjects had one of the autoimmune conditions in their medical history

- From Dose 1 to 1 month Post Dose 2, the number reporting a potential aggravation of autoimmune disease is:
  - 7 (0.2%) of 2955 BNT subjects
  - 4 (0.1%) of 2977 Placebo subjects
- From Dose 1 to unblinding date:
  - 8 of 2955 BNT subjects (IR/100PY = 0.7)
  - 8 of 2977 Placebo subjects (IR/100PY = 0.7)

MAH's discussion of clinical study data:

MAH's clinical study results do not demonstrate an imbalance between placebo and vaccine in subjects with autoimmune disorders in their medical histories who also report the autoimmune disorder following vaccination.

Rapporteur assessment comment:

Results from clinical trials did show a numerical imbalance for potential aggravation of autoimmune disease between placebo and vaccine from dose 1 to 1-month post dose 2 but not from dose 1 to unblinding date. However, this is based on 7 and 4 subjects respectively and only a limited number of subjects (13.5% study arm, 13.6% placebo arm) with one of the autoimmune conditions in their medical history were included in the clinical trials, which precludes robust data from this source.

Clinical trial data were already presented in the 10th SSR (EMEA/H/C/005735/MEA/002.9).

Ongoing epidemiology studies

The following studies include those non-interventional post-authorization safety studies that will address autoimmune adverse events of special interest (AESI).

Study C4591008

Study C4591008, HERO-Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers, their families, and their communities, is a primary data collection study of US healthcare workers, their families, and their communities.

This study includes the incidence of the following autoimmune AESI: Guillain-Barre syndrome, Multiple sclerosis, Thyroiditis, Transverse Myelitis, Single organ cutaneous vasculitis, and Arthritis and arthralgia. In addition, it includes Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus as a pre-existing baseline comorbidity.

Interim reports were submitted to FDA in June 2021 and December 2021. Additional interim reports are planned for 30 June 2022 and 31 December 2022 with a final study report for 31 December 2023.

Rapporteur assessment comment:

Note that study C4591008 is not included in the EU RMP of Comirnaty. Other studies displayed below are included as category 3 post-authorisation safety studies in the Comirnaty RMP.

Study C4591009

Study C4591009, A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States, is a post-approval observational study using real world data from the general US population within selected data sources participating in the US Sentinel System.

This study includes the incidence of the following autoimmune AESI: Guillain-Barre syndrome, Immune thrombocytopenia, Transverse Myelitis/Myelitis, and Arthritis and arthralgia. In addition, it includes Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus as a pre-existing baseline comorbidity and autoimmune disorders as a potential covariate.

Monitoring analysis reports are planned for quarter 3 (Q3) 2022 and Q3 2024, an interim report for Q3 2023, and a final study report for 31 October 2025.

Study C4591010

Study C4591010, A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the EU, is a primary data collection cohort study in Germany, Italy, and Spain.

This study includes the incidence of the following autoimmune AESI: Guillain-Barre syndrome, Multiple sclerosis, Thyroiditis, Transverse Myelitis, Single organ cutaneous vasculitis, and Arthritis and arthralgia. In addition, it includes Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus as a pre-existing baseline comorbidity.

A progress report was submitted to EMA in September 2021. Interim reports are planned for 01 March 2022, 01 September 2022, 01 March 2023, 01 September 2023, and 01 March 2024 with a final study report for 30 September 2024.

Rapporteur assessment comment:

MAH's progress report of study C4591010 was submitted (EMEA/H/C/005735/MEA/011.3, finalized) and commitments were noted. As of 31 Aug 2021, a total of 18 sites across Germany, Italy and Spain had confirmed intent to participate. Data collection was anticipated to begin on 20 Sept, 2021 in Spain and Germany, and on 29 Oct 2021 in Italy. The study is currently ongoing and on target to meet study milestones. The first interim report has been submitted to the EMA on 01 Mar 2022, the assessment is ongoing (PAM-MEA-011.5).

A protocol amendment of study C4591010 was submitted (EMEA/H/C/005735/MEA/011.4, ongoing) in response to the need to monitor Comirnaty safety in a landscape of updated COVID-19 vaccine recommendations and changing COVID-19 vaccine distribution. Accordingly, the MAH proposes to evaluate the safety of Comirnaty in a real world setting where dynamic COVID-19 vaccine recommendations result in a heterogenous source population of vaccinees exposed to Comirnaty, heterologous primary, or heterologous booster COVID-19 vaccine courses.

Study C4591011

Study C4591011, Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization, is a secondary data

collection study using data from the US Department of Defense military and civilian personnel and their families in the Military Health System.

This study includes the incidence of the following autoimmune AESI: Guillain-Barre syndrome, Multiple sclerosis/Multiple sclerosis relapse/Relapsing-remitting MS, Thyroiditis/Basedow, Transverse Myelitis/Myelitis, Arthritis and arthralgia, and Hematologic thrombocytopenia. In addition, it includes Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus as a pre-existing baseline comorbidity and autoimmune disorders as a potential covariate.

Per delays in study start up communicated with EMA on 20 December 2021, amended report milestone dates have been proposed and preliminarily endorsed by EMA.

Study C4591012

Study C4591012, Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine, is a secondary data collection study that uses real-world data on US veterans to conduct comparative analyses using self-controlled risk interval and active comparator approaches.

This study includes the incidence of the following autoimmune AESI: Guillain-Barre syndrome, Multiple sclerosis, Autoimmune Thyroiditis, Transverse Myelitis, and Arthritis and arthralgia. In addition, it includes Diabetes mellitus as a pre-existing baseline comorbidity.

Interim reports were submitted to EMA and FDA in June 2021 and December 2021.

Additional interim reports are planned for 30 June 2022 and 31 December 2022 with a final study report for 31 December 2023.

Rapporteur assessment comment:

The second interim report of study C4591012 (MEA/010.3, ongoing) concluded that no safety events of interest were found to be increased after Comirnaty exposure when compared with the defined control groups (i.e., the vaccine recipients who were concurrently in their comparison interval for myocarditis/pericarditis and the seasonal influenza vaccine sample for the rest of the safety events).

The first interim report (August 2021) did not include any safety results at that time.

Study C4591021

Study C4591021, Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine, is a secondary database analysis of observational data among the EU general population.

This study includes the incidence of the following autoimmune AESI: Diabetes mellitus/Type 1 diabetes mellitus/Type 2 diabetes mellitus, Guillain-Barre syndrome, Thyroiditis/Basedow, Transverse Myelitis/Myelitis, and Cutaneous vasculitis. In addition, it includes autoimmune disorders as a potential covariate.

A progress report was submitted to EMA and FDA in September 2021. Interim reports are planned for 31 March 2022, 30 September 2022, 31 March 2023, 30 September 2023, and 31 March 2024 with a final study report for 30 September 2024.

Rapporteur assessment comment:

The first interim report of study C4591021 (former ACCESS/VAC4EU) has been submitted on 31 Mar 2022, the assessment is ongoing (PAM-MEA-017.3).

Study C4591022

Study C4591022, Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry, will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to Comirnaty using an established pregnancy registry in the US and Canada. This study includes autoimmune disorders as potential covariates or exclusion criteria.

Interim reports are planned for 31 January 2022, 31 January 2023, and 31 January 2024 with a final study report for 31 December 2024.

Rapporteur assessment comment:
Study C4591022 is an ongoing non-interventional post-approval safety study in the US/Canada addressing the safety concern Use in pregnancy.

Literature review

The MAH search literature through 16 December 2021 and discussed the most relevant articles that bring new information and overview on the topic.

Please note that published studies by *Rotondo et al*, *Sattui et al*, *Geisen et al*, *Barbhaiya M et al*, *Yang K et al*, *Bixio et al*, *Watad A et al*, *Alfayadh N.M. et al*, *Boekel L et al*, *Furer V et al*, *Connolly CM et al*, *Achiron et al* and *Izmirly et al* are not reproduced in this report, as these studies were already presented in the 10th SSR (MEA 002.9).

Machado et al report published the results of the EULAR COVID-19 Vaccination(COVAX) Registry that is an observational registry launched on 5 February 2021. Data are entered voluntarily by clinicians or associated healthcare staff; patients are eligible for inclusion if they have a rheumatic and musculoskeletal diseases (RMDs) and have been vaccinated against SARS-CoV-2. As of 27 April 2021, 1519 patients were reported to the registry for a total of 28 countries, with France (60%) and Italy (13%) as the highest contributors. The majority (91%) had inflammatory RMDs. Inflammatory joint diseases accounted for 51% of cases, connective tissue diseases 19%, vasculitis 16%, other immune mediated inflammatory diseases 4%, and noninflammatory/mechanical RMDs 9%. The most frequent individual diagnoses were rheumatoid arthritis (30%), axial spondyloarthritis (8%), psoriatic arthritis (8%), systemic lupus erythematosus (SLE, 7%) and polymyalgia rheumatica (6%). At the time of vaccination, 45% were taking conventional synthetic DMARDs, 36% biological DMARDs, 31% systemic glucocorticoids, 6% other immunosuppressants (azathioprine; mycophenolate; cyclosporine; cyclophosphamide; tacrolimus), and 3% targeted synthetic DMARDs. The most frequent individual DMARDs were methotrexate (29%), TNF inhibitors (18%), antimalarials (10%) and rituximab (6%). The vaccines administered were: 78% Pfizer, 16% AstraZeneca, 5% Moderna and 1% other/unknown; 66% of cases received two doses and 34% one dose. Mean time from 1st and 2nd dose to case report was 41 days and 26 days, respectively. COVID-19 diagnosis after vaccination was reported in 1% of cases. Disease flares were reported by 5% of patients with inflammatory RMDs, with 1.2% classified as severe flares (vaccine type was not specified). Mean time from closest vaccination date to inflammatory RMD flare was 5 days (SD 5). The most common flare types were arthritis (2.5%), arthralgia (2.1%), cutaneous flare (0.8%) and increase in fatigue (0.8%). Potential vaccine side effects were reported by 31% of patients. The majority were typical early adverse events within 7 days of vaccination, namely pain at the site of injection (19%), fatigue (11%) and headache (7%). The author conclude that the majority of patients tolerated their vaccination well with rare reports of inflammatory RMD flare (5%; 1.2% severe) and very rare reports of severe adverse events (0.1%).

Rapporteur assessment comment:

The study by *Machado et al* included 5,121 participants from 30 countries, 90% with inflammatory/ autoimmune rheumatic and musculoskeletal disease (I-RMDs, n=4604, 68% female, mean age 60.5 years) and 10% with non-inflammatory RMD (NI-RMDs, n=517, 77% female, mean age 71.4). For patients with I-RMDs, information about flares was collected, namely: (1) type of flare (fever, weight loss, increase in fatigue, increase in dryness, enlarged lymph nodes, arthralgia, arthritis flare, etc.); (2) severity of flare (mild/minor, moderate, severe/major without hospitalisation and severe/major with hospitalisation); (3) information about changes in medication due to the flare; and (4) period of time between vaccination and the flare.

Flare following vaccination with SARS-CoV-2 vaccines was reported in 4.4% (n=204) of I-RMD cases (4,604), though these data were unknown or missing in 15% of cases. The percentage of cases reporting a flare, flare severity and medication changes due to the flare were consistent among different vaccines. The authors discussed that regarding flares, the data suggest that the risk of I-RMD flare following vaccination is low and not more strongly associated with any particular type of vaccine, with observed percentages being compatible with the natural history of the disease rather than necessarily caused by vaccines against SARS-CoV-2. Strengths of this study include the rapid dissemination via European networks (EULAR, ERN ReCONNET and ERN RITA) that resulted in a large number of cases reported by rheumatologists, internists or associated healthcare professionals over a short period of time. Limitations of the study include among others possible selection bias due to voluntary case submission; dissemination was more effectively achieved in certain European countries (e.g., France, Italy and Portugal); reporting was also influenced by differences in vaccine availability and access across European countries, which has resulted in a significantly higher proportion of cases vaccinated with the Pfizer vaccine, limiting comparisons between vaccines; control group of patients with I-RMDs is not available, and the sample size of patients with NI-RMDs is substantially smaller. The authors also discussed that for some signs or symptoms, it can be difficult to determine if the event should be considered an I-RMD flare or simply a transient side effect of the vaccine (e.g., polyarthralgia). The authors noted that no causal conclusions regarding vaccination and the development of flares/AEs can firmly be drawn from this dataset.

Tzioufas A.G et al report a study result that investigated humoral responses and safety of mRNA SARS-CoV-2 vaccines in systemic autoimmune and autoinflammatory rheumatic disease (SAARD) patients subjected or not to treatment modifications during vaccination. From February 1st, 2021, until June 30th, 2021, 2411 SAARD patients were eligible for recruitment in the study of whom 960 patients were enrolled. Among them, 737 had completed vaccination up to June 30th, 2021. Most patients (n = 659) were vaccinated with either Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273 vaccines. Patients with extended treatment modifications responded to vaccines similarly to controls as well as SAARD patients without immunosuppressive therapy (97.56% vs 100%, p = 0.2468 and 97.56% vs 97.46%, p > 0.9999, respectively). In contrast, patients with partial or without therapeutic modifications responded in 87.50% and 84.50%, respectively. Furthermore, SAARD patients with extended treatment modifications developed higher anti-SARS-CoV-2 antibody levels compared to those without or with partial modifications (median:7.90 vs 7.06 vs 7.1, p = 0.0003 and p = 0.0195, respectively). Mycophenolate mofetil (MMF), rituximab (RTX) and methotrexate (MTX) negatively affected anti-SARS-CoV-2 humoral responses. In 10.5% of vaccinated patients, mild clinical deterioration was noted; however, no differences in the incidence of deterioration were observed among the distinct treatment modification SAARD subgroups. Side-effects were generally comparable between SAARD patients and controls. Overall, the authors concluded that SAARD patients, mRNA SARS-CoV-2 vaccines are effective and safe, both in terms of side-effects and disease flares. Treatment with MMF, RTX and/or MTX compromises anti-SARSCoV-2 antibody responses, which are restored upon extended treatment modifications without affecting disease activity.

Rapporteur assessment comment:

In this nationwide, multicenter study, *Tzioufas A.G et al* investigated humoral responses and safety of mRNA SARS-CoV-2 vaccines in systemic autoimmune and autoinflammatory rheumatic disease (SAARD) patients subjected or not to treatment modifications during vaccination. The authors note that disease activity status as provided by the caring physician and disease course as self-reported by the patients before and after the vaccination was provided. The authors discussed among others that a slight clinical deterioration (usually mild, not requiring hospitalization or radical therapeutic adjustments) of the underlying SAARD was observed in one out of ten patients. Given the fact that at least some of these patients were expected to flare spontaneously during the study period, disease exacerbations after vaccination occur at low rates and were easily manageable. The authors noted the limitations of the study, e.g. data regarding disease deterioration rates within a 6-month period before vaccination were missing and as such a direct comparison between exacerbation rates before and after vaccination was not feasible. The authors concluded that disease exacerbations presented in a few patients were rare and mild.

Fan et al conducted a real-world survey to evaluate the safety profiles and disease flare in patients with AIIRDs (autoimmune inflammatory rheumatic diseases) who received any dose of inactivated COVID-19 vaccines in China. From 1 Aug 2021 to 15 Oct 2021, eligible participants completed a predefined 25-question-based questionnaire by invitation on social media or visiting the outpatient department. In total, 1507 adult patients with AIIRDs who received inactivated COVID-19 vaccine participated in this study. Systemic lupus erythematosus (SLE) (614, 40.7%) was the most common AIIRD among participants, followed by rheumatoid arthritis (RA) (434, 28.8%), Behcet's disease (BD, 122, 8.1%), psoriatic arthritis/psoriasis (PsA/PsO) (76, 5.0%), primary Sjogren's syndrome (74, 4.9%) and ankylosing spondylitis (44, 2.9%). Among all participants, 29.9% participants experienced adverse events (AEs) after vaccination. Local AEs, such as pain, redness or swelling at injection site, were reported to occur in 19.0% participants. Systemic AEs after vaccination were reported by 17.3% patients mainly fatigue or sleepless (8.2%), headache (5.4%) and skin rash (3.6%). Most AEs were mild to moderate and self-limiting. Overall, 1.9% patients self-reported severe AEs. No one reported AE of interests or fatal AE, including myocarditis, idiopathic thrombocytopenic purpura, anaphylactic shock or death. Flare of existing AIIRDs was reported by 10.5% participants, with requirement of treatment escalation in 3.5% patients. Joint pain (38.6%) and swelling (19.6%) were the most common manifestations of disease flare, followed by skin rash (17.1%), morning stiffness (12.7%) and febrile recurrence (8.9%). Interestingly, the frequencies of AE and flare of AIIRDs were generally lower in inflammatory arthritis patients (RA or PsA/PsO) than those in patients with systemic AIIRDs (eg, SLE and BD). Multivariable logistic analyses demonstrated that elderly, allergic history was the risk factor for disease flare of their underlying AIIRDs, while stable disease of AIIRDs was the negative predictor for self-reported disease flare only. The data from Fan et al confirmed the safety profiles, and for the first time demonstrated the disease flare after inactivated COVID-19 vaccination in patients with AIIRDs indicating the well tolerability of inactivated COVID-19 vaccines in AIIRDs population. These results aligned with a large real-world study supported by European League against Rheumatism (EULAR) COVID-19 database (83% mRNA vaccines), whose vaccine-related AEs were observed in 31% of patients.

Rapporteur assessment comment:

The study by *Fan et al* conducted a real-world survey to evaluate the safety profiles and disease flare in patients with AIIRDs who received any dose of inactivated COVID-19 vaccines in China. Flare of existing AIIRDs was reported by 158 (10.5%) participants, with requirement of treatment escalation in 53 (3.5%). No episode of severe flare needing emergent hospitalisation was reported. The authors noted that the incidence of AEs and AIIRD flares was generally comparable among all COVID-19 vaccines and

referred to the publications of Machado et al and Felten et al (VACOLUP study, see below under subsection SLE).

Adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases were studied by Heshin-Bekenstein M et al and Maritsi D et al. The authors performed a prospective multicenter study and examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. Details of the studies are reported below.

Maritsi et al evaluated the safety and tolerability of the BNT162b2(Pfizer-BioNTech) COVID-19 vaccine in adolescent and young adult patients with juvenile idiopathic arthritis (JIA) on TNFi treatment. The study involved 21 subjects aged 16- 21 years (median 17 years) with stable JIA who have been diagnosed and treated for at least 1 year with TNFi. The patients received two doses of the COVID-19 vaccine (Pfizer-BioNTech) intramuscularly at 0 and 3 weeks. In addition to the visits for vaccine administration, further visits were planned at 2, 6 and 12 months after enrolment. Disease activity was evaluated by using the JADAS-27 score at all planned assessments performed. All participants tolerated both doses of the vaccine well. Local reactions were frequent (74%) in the majority of participants, no difference was noted between patients on etanercept (71%) versus adalimumab (75%) (p=0.09). Localized erythema (73%), pain (72%) and swelling (68%) were among common side effects. There were no differences noted in patients with different JIA types. The type of JIA or medication received did not reveal any differences in the rates of systemic reactions. Most localized and systemic reactions were noted after the second dose of the vaccine (p= 0.02). There were no significant changes in 27-JADAS or laboratory tests as noted at the 2 months' follow-up. The authors conclude that the mRNA vaccine seemed safe and well tolerated in adolescents with JIA on TNFi. Although our sample size was small, it can be concluded that the vaccine assures an adequate safety and tolerability profile and not provoking disease flare.

Heshin-Bekenstein M et al evaluated the safety and immunogenicity of the BNT162b2 mRNA vaccine in adolescents with autoimmune inflammatory rheumatic disease (AIIRD) treated with immunosuppressive medications compared with healthy adolescents. The prospective multicenter study examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. Patients were evaluated 2-10 weeks after the second dose of the vaccine. Overall, 71 adolescents with AIIRD patients and 28 controls from 2 countries, 4 centers, participated in the study. The most common diagnosis in the AIIRD cohort was JIA (N=27), followed by SLE (N=14). The mean disease duration was 5.1±4.48 years (N=70). A total 84.5% (N=60) of the patients were treated with immunomodulatory medications. Post vaccination disease activity remained stable in 96.88% of the adolescents with AIIRD, and post vaccination treatment change was made in the minority of the patients (N=3, 4.84%). Both patients and controls have tolerated the vaccine well, with minimal side effects. There were no severe adverse events in both groups. No post vaccination infection with COVID-19 was documented in both groups. Seropositivity rate was 90.32% in adolescents with AIIRD and 100% in the healthy controls (N=28/31 vs. N=14/14; p=0.54). The level of the S1/S2 antibodies was significantly reduced in adolescents with AIIRD compared to controls.

Rapporteur assessment comment:

Adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases were studied by *Heshin-Bekenstein M et al* and *Maritsi D et al*. No disease flare was observed in the study by Maritsi et al. In the study by Heshin-Bekenstein et al. post vaccination disease activity remained stable in the vast majority

(97%) of the adolescents with AIIRD. It should be however noted that the sample size in both studies was considered relative small.

Systemic lupus erythematosus (SLE)

Tang et al published a review on patients with SLE and concludes that AIIRD patients are not at greater risk of disease flares nor have a higher incidence of side effects following vaccination. There is no significant safety concern for the use of COVID-19 vaccines in patients with AIIRD and benefits of vaccination far outweigh the risks in patients with AIIRD, including SLE.

Rapporteur assessment comment:

Tang et al reviewed the published data on SARS-CoV-2 vaccination in SLE patients. Regarding safety the authors referred to publications by Geisen et al, Izmirly et al, Furer et al, Connoly et al, Boekel et al, Felten et al and Watad et al which were, with the exception of the publication by Felten et al (see below), already presented and assessed in the 10th SSR (MEA 002.9).

Felten R et al performed a study where the primary objective was to assess the tolerance of COVID-19 vaccines in patients with SLE, including the risk of incident flare, from the patients' perspective (international vaccination against COVID in systemic lupus (VACOLUP) study). VACOLUP was a cross-sectional study based on a 43-question web-based survey, which took place between March 22, 2021, and May 17, 2021. The study included 696 participants from 30 countries. All patients received at least one dose of vaccine and 343 (49%) patients received a second dose. The most common vaccines were Pfizer-BioNTech (399 [57%] participants), Sinovac (156 [22%] participants), AstraZeneca (73 [10%] participants), and Moderna (57 [8%]). Side-effects were reported by 316 (45%) patients after the first vaccine dose and by 181 (53%) of 343 patients after the second vaccine dose, with no difference according to gender, age, or vaccine type. Patients who received both vaccine doses and reported side-effects after the first dose were more likely to report side-effects after the second dose than those who did not. An important finding of the study is that side-effects after COVID-19 vaccination in patients with SLE are common (around 50%) but do not impair daily functioning in most cases. No difference were found in the occurrence of side-effects after receipt of mRNA vaccines compared with vaccines with other modes of action. The number of medically confirmed flares reported after COVID-19 vaccination was low. The short median time between vaccination and flare onset suggests that it might be difficult to distinguish actual SLE flares from common and expected postvaccine side-effects, and therefore the 3% figure could be an overestimation of the actual flare rate. Vaccination is recommended for patients with rheumatic and musculoskeletal diseases according to the American College of Rheumatology, irrespective of disease activity and severity, except for those with severe and life-threatening illness (e.g., a patient receiving treatment in the intensive care unit for any condition). In conclusion, the VACOLUP study suggests that COVID-19 vaccination appears well tolerated in patients with SLE, with only a minimal risk of flare, if any, including after the mRNA vaccines.

Rapporteur assessment comment:

Felten at al performed a survey studying the tolerance of COVID-19 vaccines in SLE patients (n=696). SLE flare after vaccination was reported in 21 patients (3%). Of the SLE flare manifestations musculoskeletal symptoms (e.g., arthralgia, myalgia), and fatigue were the most reported events (19/21 [90%], 18/21 [86%] respectively). As noted by the authors, the short time between vaccination and flare onset suggests that it is difficult to distinguish actual flares from expected events after vaccination. The authors noted that the self-reported and subjective nature of the outcomes and the absence of a control group are main limitations of the study.

Note that the authors received consultancy fees from the MAH (unrelated to the VACOLUP study).

Zavala-Flores E et al studied post SARS-CoV-2 vaccine BNT162b2 (BioNTech & Pfizer) side effects in patients with systemic lupus erythematosus (SLE) immunized with the BNT162b2 vaccine from May 21 to June 30, 2021 performing a descriptive observational study. Of the total number of patients seen in the service, 100 received the vaccine's 1st dose, and 90 patients received the 2nd dose; 90% and 92.2% presented symptoms within 10 days after immunization (1st and 2nd doses, respectively), being pain at the inoculation site the most frequent (87%); most of the symptoms presented were of mild intensity. There were 27 episodes of post-immunization flare, 9% and 20% after the 1st and 2nd doses, respectively; the predominant type of flare was articular (85.1%), followed by dermal (18.5%). It was found that a history of renal involvement was associated with the risk of developing flare RR 0.38 (0.15–0.91) and the use of hydroxychloroquine and azathioprine prior to immunization 0.20 (0.06–0.63) and 7.96 (2.70–23.43) respectively. In 100 SLE patients immunized with BNT162b2 vaccine against SARS-CoV-2, 27% of SLE reactivation episodes occurred, two patients were hospitalized for flare severity, and none died. This study report similar results to those reported by Izmirly et al. who reported, in a multiethnic study, up to 11.5% of flare episodes in patients with lupus after SARS-Cov-2 immunization.

Rapporteur assessment comment:

Zavala-Flores et al conducted a descriptive observational study in patients with SLE in a public hospital in Peru. A total number of 100 patients were studied, 20 patients presented post-immunization flares including 27 flare episodes (7 patients had flare episodes both after 1st and 2nd dose). The authors noted that a higher proportion (27%) of flare episodes (mostly mild) was found in this study compared to the VACOLUP study (mostly European/US population), which could be due to the known difference in SLE activity in relation to ethnicity.

In addition, *Sen, P et al* have designed a specific protocol to analyse efficacy and safety data of COVID-19. The study proposed is an ongoing international collaborative study involving 29 countries and over 110 investigators of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study. The result of the study will shed additional light on the safety profile of COVID-19 vaccines available in the market in patients with autoimmune diseases.

Rapporteur assessment comment:

The COVAD study is a long-term ongoing global patient self-reported survey study, with the goal of evaluating the long-term efficacy, as well as the short and long-term adverse effects and disease flares in patients with systemic autoimmune rheumatic diseases (AIRD) vaccinated against COVID. The authors developed an extensive self-report e-survey to assess the safety of the COVID-19 vaccine in idiopathic inflammatory myopathies and other AIRDs, and non-autoimmune controls. The survey was first launched in the first half of 2021 and was open until the 31st of December 2021. As of August 2021, 16,327 responses had accrued. The authors note that results will be disseminated in peer-reviewed journals, via the media, online, and at academic conferences.

References

1. Machado, P.M., et al., *Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry*. Ann Rheum Dis, 2021.
2. Tzioufas, A.G., et al., *A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with systemic autoimmune and autoinflammatory rheumatic diseases*. J Autoimmun, 2021. 125: p. 102743.
3. Fan, Y., et al., *Safety and disease flare of autoimmune inflammatory rheumatic diseases: a large real-world survey on inactivated COVID-19 vaccines*. Ann Rheum Dis, 2021.
4. Heshin-Bekenstein, M., et al., *Safety and immunogenicity of the BNT162B2 mRNA COVID-19 vaccine in adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases*. Pediatric Rheumatology 2021. 19 (SUPPL 1).

5. Maritsi, D., et al., *Safety and tolerability of the biontech COVID-19 vaccine in adolescent patients with JIA on TNFi*. Pediatric Rheumatology 2021. 19 (SUPPL 1).
6. Tang, W., et al., *The Use of COVID-19 Vaccines in Patients with SLE*. Curr Rheumatol Rep, 2021. 23(11): p. 79.
7. Felten, R., et al., *Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study*. The Lancet Rheumatology, 2021. 3(9): p. e613-e615.
8. Zavala-Flores, E., et al., *Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus*. Clin Rheumatol, 2021.
9. Sen, P., et al., *COVID-19 vaccination in autoimmune disease (COVAD) survey protocol*. Rheumatol Int, 2021.

MAH conclusion:

The review of **post-marketing adverse event reports** in patients with autoimmune disorders offers limited information on the risk of flares following vaccination. Unfortunately, most cases do not report information on the underlying status of the autoimmune disease (active versus dormant) nor the ongoing therapy or other conditions that may induce a relapse of the underlying autoimmune disease. The lack of this crucial information makes it difficult to perform a meaningful causality assessment.

The **scientific literature** regarding patients with systemic rheumatic disease who received COVID-19 vaccination, showed that patient-reported adverse events in this population were typical of those reported in the general population. Overall, most studies showed that flares appear rare. Interestingly, another hypothesis mentioned is that patients with autoimmune and inflammatory disease experience and report adverse events following SARS-CoV-2 vaccination that may mimic flares (as fever, fatigue, arthralgia).

It should be taken into consideration that some autoimmune diseases treatments, specifically immunomodulatory therapy (methotrexate, Jak inhibitor, abatacept, rituximab and cyclophosphamide), are recommended from American college of rheumatology guidance guidelines to be discontinued shortly before vaccination. Clearly this **temporary discontinuation may influence a temporary flare up** of the underlying autoimmune disease due to change of immunomodulatory therapy rather than vaccination.

MAH's **clinical study results** do not demonstrate an imbalance between placebo and vaccine.

The etiology of autoimmune disorders is multi-factorial, involving an individual's genetic risk factors, exposure to environmental triggers and underlying immune dysregulation. Exacerbations are likely also multi-factorial.

Overall, given the totality of the available information, especially the multiple real-world studies involving subjects with autoimmune disorders, exacerbations of disease cannot be concluded to be causally associated with BNT162b2. Changes in the risk minimisation measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favourable. The topic will continue to be monitored through routine pharmacovigilance activities.

Rapporteur assessment comment:

The MAH provided an evaluation of exacerbation (flare-up) of pre-existing autoimmune/inflammatory disorders from all available sources, as requested.

A cumulative search in the MAH's safety database up to 18 December 2021 revealed a total of 33,711 cases described a *medical history* of autoimmune disease (total cases in the safety database: 997,934). Among them, 2,223 reported the same autoimmune condition as an *adverse event*, indicating a potential exacerbation or worsening of the underlying disorder after Comirnaty exposure. The MAH's note that most cases report a relapse (very) shortly after vaccination is acknowledged; a limited temporal relationship to the events does not seem suggestive to induce an autoimmune response leading an exacerbation or relapse of an underlying autoimmune disease, but seems more likely events that mimic flares like fever, fatigue etc.

Results from clinical trials did show a numerical imbalance between placebo and vaccine from dose 1 to 1-month post dose 2 but not from dose 1 to unblinding date. However, this is based on 7 and 4 subjects respectively and only a limited number of subjects (13.5% study arm, 13.6% placebo arm) with one of the autoimmune conditions in their medical history were included in the clinical trials, which precludes robust data from this source.

No new important safety information on this topic could be identified from the ongoing non-interventional post-authorization safety studies.

The MAH provided a literature review on this topic through 16 December 2021. The presented literature did not support a safety issue.

European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2 were updated November 2021.

The ACR (American College of Rheumatology) *COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases* (version 5, revised February 2022) notes that a theoretical risk exists for autoimmune and inflammatory rheumatic disease flare or disease worsening following COVID-19 vaccination. However, the benefit of COVID-19 vaccination for RMD patients outweighs the potential risk for new onset autoimmunity.

This topic had been discussed with the MEB Board including experts in clinical practice and patient representative. Dutch clinical experts recognize that some patients experience exacerbation of their chronic autoimmune disease, following vaccination in general, hence not limited to COVID-19 vaccination. Furthermore, our clinical experts question the added value to include information on this topic in the product information of the COVID-19 vaccines, neither for patients. Patients with such chronic autoimmune diseases are generally very adherent to their medication and motivated to consult their healthcare professional about any topic related to their disease. Finally, professional patient organizations also communicate information on this topic via their websites.

Given the course of the diseases it is not unexpected that cases of flare up of autoimmune diseases are reported and will be reported in future. To assess causality based on spontaneous reports will remain very challenging, since information on baseline disease activity and/or information on history of relapses is often not reported. We still consider, to be able to determine the increased frequency of flare up of autoimmune disorders following Comirnaty vaccination, compared to background incidences of flare ups, that more data is needed and will arise from literature and from the ongoing PASS's.

Overall, the MAH's conclusion is supported. Based on the available data no new important safety information could be identified and no regulatory action is needed at this time. This topic should be continuously monitored through routine and additional pharmacovigilance activities.

Issue solved

2.2.1.2. Pregnancy and Lactation

Response to the PRAC request 7 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

Regarding pregnancy and lactation, the MAH is requested to:

a) define the strategies put in place to identify, manage and prioritize the pregnancy cases among the unlocked cases.

b) include all relevant publications during the reporting interval.

c) make all efforts to complete the follow-up of the pregnant woman cases.

d) describe with detail the relevant cases evaluated under signals or health authorities requests that concern breastfed children in section 'Use in pregnant/lactating women' of the PSUR.

MAH's response (not fully reproduced here):

Clinical Trial Data

Cumulative review (Pregnancy Cases)

- Number of pregnancy cases: 443 (25.1% of the total 1766 cases from the CT dataset). These 443 cases represent 421 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 22 pregnancies). Cases originated from clinical studies BNT162-01 (1), C4591001 (205), C4591006 (132), C4591015 (98), C4591017 (1), C4591020 (2) and C4591031 (4) study treatment was reported as BNT162b2 (226), blinded therapy (175), and placebo (42).

Cumulative review (Lactation cases)

- Number of lactation cases: 49 (2.8% of the total 1766 cases from the CT dataset). Of these 49 cases, 48 cases non-serious cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk, Maternal exposure during breast feeding) without the occurrence of any clinical events. In the remaining 1 serious case the clinical events were coded to PTs Hyperbilirubinaemia neonatal and Hypoglycaemia neonatal (1 each). 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: 113 (15.7% of the total 721 cases from the CT dataset). These 113 cases represent 100 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 13 pregnancies). Cases originated from clinical studies C4591001 (20), C4591015 (89), C4591020 (1) and C4591031 (3) and study treatment was reported as blinded therapy (86), BNT162b2 (18), and placebo (9).

Post-Authorisation Data

Incremental review (Pregnancy)

- Number of pregnancy cases: 5239 (0.8% of 657,528 cases, the total PM dataset), compared to 1661 cases (0.5%) retrieved in the PSUR #1. These 5239 cases represent 4896 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 343 pregnancies).

Incremental review (Lactation)

- Number of lactation cases: 2670 (0.4% of 657,528 cases, the total PM dataset), compared to 966 cases (0.3%) retrieved in the first PSUR.

Literature

Review of the literature cumulatively through 30 December 2021 about the use of BNT162b2 in pregnant and lactating women was included. The review of the safety information from literature reports of use of BNT162b2 in pregnant women did not reveal a new safety signal or concern. There is, however, limited information for long term post-natal outcomes, therefore no definite conclusions can be drawn.

MAH's conclusion

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

Rapporteur assessment comment:

Please refer to section 1.3.4 for the assessment of the general measures that were put in place by the MAH to manage the volume of reported cases. Here it is described that the AESIs (incl. pregnancy and lactation AESIs) were given priority. Furthermore, the MAH describes the method used to identify the pregnancy cases from the dataset.

The provided literature review was already, as agreed upon, assessed within procedure EMEA/H/C/005735/LEG LEG/045 as part of the review of COVID-19 vaccination in pregnant and breastfeeding women. Following the assessment in this separate procedure with data as of December 2021, the product information was updated to reflect that Comirnaty can be safely used during pregnancy and breastfeeding.

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.

Issue solved

2.2.1.3. Chronic urticaria/worsening of pre-existing chronic urticaria

Response to the PRAC request 8 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *The MAH should perform a cumulative review on the association between Comirnaty and chronic urticaria/worsening of pre-existing chronic urticaria. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.*

MAH's response:

MAH's safety database was searched for all cases cumulatively to 18 December 2021 using MedDRA 24.1. the search was performed in 2 steps: 1) All cases reporting the PT: urticaria chronic in the medical history, 2) All cases retrieved from the previous listing were selected for the PT urticaria chronic as adverse event.

Post-marketing data

A total of 497 cases reported chronic urticaria in the medical history. Fifteen cases among the 497 reported an adverse event of chronic urticaria. There were 11 females and 4 males. Age was reported as ranging from 21 to 73 years of age (mean: 43.3 years). Most cases (12) were reported by adults (≥ 18-<65 years) and 2 cases were reported by elderly (≥65) subjects. Most cases were reported from United Kingdom (6) followed by France, Japan (2 cases each), Germany (1 case) and Lithuania (1 case). Ten cases were reported as non-serious and 5 as serious. Ten cases were not medically confirmed and 5 were medically confirmed. Eight cases did not report concomitant medication, the other cases reported either antihistamine and/or corticosteroid therapy.

Four cases reported the flare after the 1st vaccine dose, 4 after the 2nd vaccine dose, 2 after the 3rd booster dose and the dose number was not reported for 5 cases. Time to onset was reported for 11 cases and ranged between the same vaccination day to 16 days after vaccination (one additional case reported it as few days after vaccination and from the date may be from day 1-5). Time to onset was reported as:

- same vaccination day: 6 cases,
- day 1-2: 2 cases,
- day 6: 1 case,

- day 10: 1 case,
- day 16: 1 case.

Details on the 15 relevant cases:

AER Number Age/Sex Country	Dose / Time to onset	Medical History Concomitant medication	Events
[redacted] 47/M [redacted]	Dose 2/Not reported	Relapsing multiple sclerosis / Rheumatoid arthritis / Urticaria chronic Cortisone / glatiramer acetate	Relapsing multiple sclerosis, Urticaria chronic, Disease recurrence
[redacted] 23/F [redacted]	Dose 2/ same vaccination day	Fexofenadine / prednisolone	Hypersensitivity, Urticaria, Urticaria chronic, Condition aggravated, Dermatitis allergic, Vaccination site urticaria
[redacted] 32/F [redacted]	Dose 2/10 days	Suppressed lactation / Urticaria chronic Fexofenadine	Peripheral swelling, Urticaria chronic
[redacted] 61/M [redacted]	Dose 2/ same vaccination day	Hypertension / Urticaria chronic Not reported	Urticaria chronic
[redacted] 26/F [redacted]	Unknown/ 1	Asthma / Urticaria chronic Not reported	Angioedema, Urticaria chronic, Dizziness, Nausea, Pyrexia, Headache, Lip swelling, swelling face, Swelling
[redacted] 56/F [redacted]	Dose 3/ same vaccination day	Idiopathic angioedema / Immunodeficiency / Urticaria chronic Fexofenadine / omalizumab	Off label use, Interchange of vaccine products, Immunisation, Swelling, Lip swelling, Swelling face, Urticaria chronic
[redacted] 60/F [redacted]	Dose 1/unknown	Back pain / Inguinal hernia / Osteoarthritis / Osteoporosis / Urticaria chronic	Disease recurrence, Urticaria chronic
[redacted] 46/F [redacted]	Dose 3/ same vaccination day	Urticaria chronic Not reported	Off label use, Interchange of vaccine products (Patient exhibited flare-up of her chronic urticaria during a previous vaccination with SPIKEVAX), Immunisation, Disease recurrence, Urticaria chronic, Influenza like illness, Vaccination site pain
[redacted] 36/F [redacted]	Unknown/unknown	Migraine / Suppressed lactation / Urticaria chronic Not reported	Migraine, Urticaria chronic
[redacted] 71/F [redacted]	Unknown/2	Urticaria / Urticaria chronic Fexofenadine / gabapentin	Vaccination site erythema, Vaccination site pruritus, Urticaria chronic, Urticaria
[redacted] 34/F [redacted]	Dose 1/ same vaccination day	Dermatitis contact / Migraine / Urticaria chronic Not reported	Anaphylactic reaction, Lip swelling, Pruritus, Urticaria chronic
[redacted] 21/M [redacted]	Unknown /few days	Idiopathic angioedema / Urticaria chronic Beclometasone / cetirizine	Rash, Urticaria, Dermatitis, Pain, Urticaria chronic, Condition aggravated
[redacted] 73/F [redacted]	Dose 1/6	Angioedema / Urticaria chronic Not reported	Angioedema, Rash, Oedema peripheral, Urticaria, Disease recurrence, Eyelid oedema, Urticaria chronic
[redacted] 39/M [redacted]	Unknown/16	Urticaria chronic Not reported	Urticaria chronic
[redacted] 30/F [redacted]	Dose 1/same vaccination day	Food allergy / Urticaria chronic Not reported	Urticaria chronic

Clinical trial data

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 cut-off date 13 March 2021) was also reviewed for the adverse event Chronic urticaria. In the Phase 2/3 safety population, Chronic Urticaria was reported in 0 of 21926 participants in the BNT162b2 group compared with 0 of 21921 participants in the placebo group. Four subjects reported Chronic urticaria in the medical history and none of these subjects reported a flare up of the underlying disease.

MAH's conclusion

A total of 15 cases reported chronic urticaria relapse in subject that presented urticaria as underlying disease. Eight among the 11 cases reporting the time to onset report a time to onset ranging from the same vaccination day to 2 days after vaccination suggesting an allergic reaction to vaccine more than a relapse of chronic urticaria. This is evident also in some literature cases reported where the symptoms (lips edema) appeared 30 minutes after vaccination and disappear within half an hour (Alflen C et al 2021).

There has been hesitancy to vaccination for the patients with underlying Chronic urticaria. In addition, low adherence to therapy, nervousness as well as worsening of urticaria was frequently reported in these patients.

Overall, during the COVID-19 pandemic, chronic urticaria patients presented more frequently new episodes of emotional stress and these were a factor associated with worsening urticaria and greater use of corticosteroids. Overall, the number of cases reporting a relapse of chronic urticaria is low and the short time to onset suggest more an allergic response to the vaccine.

Urticaria is recognised as a causally associated reaction to Comirnaty. Based on the abundance of literature regarding the stress induced by the SARS-CoV-2 pandemic and chronic urticaria and given the very low number of cases (15) reporting worsening of chronic urticaria after more than 2 billion doses of BNT162B2 administered worldwide, chronic urticaria is not considered a signal and safety updates to the product information and/or the risk management plan are not warranted at this time. The benefit risk profile of the vaccine remains favourable. The topic will continue to be closely monitored with routine pharmacovigilance.

Rapporteur assessment comment:

Urticaria is labelled in section 4.8 of the Comirnaty SmPC under hypersensitivity reactions in SOC immune system disorders with frequency rare.

In the placebo-controlled phase 2/3 study C4591001 no (relapse of) chronic urticaria was reported in both the BNT162b2 group and placebo group.

The MAH only reported and discussed the cases reporting worsening of pre-existing chronic urticaria and not the cases reporting chronic urticaria after Comirnaty exposure, which is not accepted. Therefore, the MAH is requested to perform a cumulative review on the association between Comirnaty and chronic urticaria. 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 supplementary information**

Fifteen of the total 497 post-marketing cases reporting chronic urticaria in their medical history, reported an adverse event of chronic urticaria after Comirnaty exposure. TTO was reported for 11 cases and ranged between the same vaccination day to 16 days after vaccination, and 8 cases among these 11

cases reported a TTO ranging from the vaccination day to 2 days after vaccination suggesting an allergic reaction to the vaccine more than a relapse of chronic urticaria. No more detailed information or causality assessment of the remaining 3 cases was provided. However, MAH's conclusion is accepted that given the very low number of cases (N=15) reporting worsening of chronic urticaria after more than 2 billion doses of BNT162B2 administered worldwide, worsening of pre-existing chronic urticaria is not considered a safety signal.

Issue partly solved

2.2.1.4. Polymyalgia rheumatica and exacerbation or flare-up

Response to the PRAC request 9 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *The MAH should perform a cumulative review on the association between Comirnaty and Polymyalgia Rheumatica and exacerbation or flare-up hereof. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.*

MAH's response:

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease of the elderly characterised by pain and stiffness in the neck and pelvic girdle. It is the second most common inflammatory rheumatic condition in people aged over 50 years, after rheumatoid arthritis (RA). Polymyalgia rheumatica can occur independently or in association with giant cell arteritis (GCA), the most common primary vasculitis in this age group.

MAH's safety database was searched for all BNT162b2 vaccine cases received through 18 December 2021 using the MedDRA version 24.1 search criteria: PT: Polymyalgia rheumatica. To analyze exacerbations (flares) of PMR, a two-step approach was used:

1. Retrieve all cases reporting in the medical history the PT: Polymyalgia rheumatica.

2. Using the line listing with cases reporting PMR in the medical history, all cases reporting the AE of PT Polymyalgia rheumatica were retrieved.

Results - PMR cases reported after BNT162B2 vaccination

A total of 628 cases were identified from the database using the search criteria mentioned above. Most cases were spontaneous reports (619, 98.6%) except for seven literature case reports (1.1%) and one clinical study report (0.2%). All cases were serious. A total of 323 cases (51.4%) were medically confirmed, while the remaining 305 cases (48.6%) were non-medically confirmed. The reported age ranged from 34 years to 95 years (mean 70.9 years, median 72.0 years).

Of the 628 reports, 357 (56.8%) were females, 265 (42.2%) males, and in 6 (1.0%) cases sex was not reported. Most of the cases were reported from France (138, 22%), followed by United Kingdom (91, 14.5%) and Germany (83, 13.2 %).

When reported, the clinical outcome of the selected PT 'Polymyalgia rheumatica' was reported as not resolved in 272 cases (43.3%), resolved/resolving/resolved with sequelae in 256 cases (40.8%), unknown in 101 cases (16.1%).

Time to onset was reported in 483 cases (77%) and in 85 cases (13.5%) it was reported as the same vaccination day or the day after, in 216 cases (34.3%), time to onset ranged between 2 to 14 days post vaccination, in 82 cases (13.1%) time to onset ranged between 15- and 30-days post vaccination and in 100 cases (16%), time to onset was reported as more than 30 days post vaccination (up to more 192 days). In 147 cases (23.4%) time to onset was not reported.

Out of the 628 cases, 424 cases were excluded from further analysis because they were reported at an implausible time to onset. An implausible time to onset was considered to be either the day of vaccination day or over 28 days after vaccination. In addition, cases with the event occurring from 1 to 3 days after vaccination were excluded from further analysis based on the possibility that the event may have been representative of expected reactogenicity events (confounders). In addition, all cases reporting a relevant medical history of diseases considered confounders (SOCs Endocrine, Immune, Musculoskeletal, Neoplasms) and all cases that co-reported events in SOC Infections or Neoplasms that can mimic PMR were excluded from analysis.

The remaining dataset comprised 204 cases which were further analyzed by laboratory data provided, to identify those cases in which both CRP and ESR levels were elevated (CRP greater than 5 mg/L and ESR greater than 30 mm/hour). Although there are no clear diagnostic criteria for PMR, the CRP is nearly always elevated in PMR patients. The medical literature supports that an elevated ESR (greater than 30 mm/hour) occurs in >92% of patients at the time of diagnosis of PMR, while 99% of such patients have an increased serum CRP level (greater than 5 mg/L).

- *Cases providing c-reactive protein and sedimentation rate values*
    - Out the 204 reports, only 16 provided both CRP and ESR levels, increasing the likelihood that the cases are accurately assessed as PMR. Each case has been assessed based on the WHO-UMC causality assessment categories. Case detail for each report is provided in Table 6 (not fully reproduced here, only the cases considered possible related to Comirnaty exposure):

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 65/M [redacted] Dose 1 Not Recovered/Not Resolved 7 Days	Polymyalgia rheumatica, Gait inability, Inflammation, Pyrexia, Arthralgia, Myalgia Not Reported Not Reported	Pt received dose 1 on 20 June 2021. 7 days after vaccination he experienced pyrexia and pain in the right shoulder and right hip joint on the opposite side of the vaccination left arm. Blood tests on 19 July 2021 showed high inflammatory response, white blood cell (WBC): 9500, C-reactive protein (CRP): 12.24 mg /dL, Erythrocyte sedimentation rate (ESR): 80 mm/h. The diagnosis of polymyalgia rheumatica was made Corticosteroid treatment was started. Outcome was reported as not recovered. *Symptoms reported, lab data, CRP and ESR decreased following steroid initiation and plausible time to onset support the diagnosis of PMR. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*
[redacted] 69/F [redacted] Dose 1 Unknown Not Reported	Polymyalgia rheumatica Not Reported Not Reported	This is a literature report describing a woman who complained of sudden bilateral pain in the shoulder and pelvic girdles associated with morning stiffness lasting > 2 hours, fever, and general malaise on an unspecified date after 1st dose vaccination. X-ray of the chest, shoulders, and pelvic region, revealing no pathologic findings; an abdominal ultrasound (US) showing mild hepatomegaly, and an 18-fluorodeoxyglucose positron emission tomography (18-FDG/PET) associated with total body computed tomography (CT) that excluded pathological findings in other sites. PMR was diagnosed. She was started on corticosteroid and her clinical manifestations and ADL quickly improved. *Symptoms reported and lab data along with the improvement after prednisone therapy may support a PMR diagnosis. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*

[redacted] 46/M [redacted] Dose 1 Not Recovered/Not Resolved 16 Days	Giant cell arteritis, Impaired work ability, CSF protein increased, Polymyalgia rheumatica, Haematuria, Vasculitis Not Reported Not Reported	Pt received dose 1 on 14 June 2021. 16 days after vaccination pt experienced neck, shoulders, and head soreness that extended then to legs and arms. These symptoms lasted for 2-3 weeks and then pt also felt feverish and had elevated heart rate. A central nervous system infection was suspected, but no confirmation from cerebrospinal fluid was obtained for this. Mainly proteins were elevated in cerebrospinal fluid, but there was no sign of viral infection. Upon admission, CRP was 180 (unspecified unit) and urinary microhematuria and normocytic anemia were found. Body CT was performed on 22 July and no signs of malignancy or infection were found. During that time, neck-shoulder pain eased, but the pain migrated to the thighs and hip area. Lab data showed CRP at 257 (unspecified unit) and ESR up to 110. Rheumatoid serum, ANCA antibodies and myositis antibodies were negative. Prostate-specific antigen was normal. A muscle biopsy was performed from the left thigh and did not show abnormality. In a PET-CT scan, fluorodeoxyglucose-positive lymph nodes in both groins, somewhat pronounced glucose metabolism of large vessels in the proximal area of the thighs, and mild vasculitis were considered possible. Corticosteroid treatment was started, and the inflammatory values started to decrease. *Possible PMR case in the context of vasculitis. Patient age is not typical for PMR. In addition, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*
[redacted] 83/M [redacted] Dose 2 Recovering/Resolving 5-7 Days	Polymyalgia rheumatica Aortic aneurysm / Hyperlipidaemia / Hypertension / Intra-thoracic aortic aneurysm repair Atorvastatin / metoprolol fumarate	Pt received dose 2 on an unspecified date in March 2021. The patient presented with pelvis and shoulder myalgia, difficulty standing from a sitting position and difficulty in raising hands, 5-7 days after the second dose of vaccine. The patient's laboratory tests included anaemia (Hct 37%), ESR 61 and CRP 8. There was great improvement after 2 days of cortisone (Medrol 24mg). The outcome of the event was recovering. *The case is possibly related with vaccine administration.* *WHO-UMC Causality Assessment: Possible*

- *Cases providing c-reactive protein and no sedimentation rate values*
    - Of the 204 reports, 26 provided CRP values only. These are described in more detail in Table 7 (not fully reproduced here, only the cases considered possible related to Comirnaty exposure):

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 71/M [redacted] Dose 1 and 2 Recovering/Resolving 14 Days	Polymyalgia rheumatica Atrial fibrillation / Obesity / Prosthesis implantation / Vascular graft Not Reported	This literature report describes a 71-year-old man patient with grade 1 obesity, atrial fibrillation, bypass surgery and aortic bioprosthesis that received BNT162B2 (dose 1) on 09 April 2021. On 23 April 2021, he developed a mild pain in his left shoulder. One month later, he got his second dose (on 07 May 2021). Pain was persistent, but CRP was normal (7.5 mg/). Slowly, pain worsened with involvement of both shoulders and morning stiffness lasting at least 2 hours. He also developed thigh, neck and lumbar pain. CRP increased at 55 mg/L (in 2021). Ultrasound showed subdeltoid bursitis and biceps tenosynovitis. Thoraco-abdominal-pelvic computed tomography (TAP-CT) did not show any carcinologic process or large vessel arteritis. The patient met the EULAR 2012 classification criteria of PMR and prednisone was started at 15 mg/day, increased at 20 mg/day after 7 days (54% of improvement of PMR-AS) with good efficiency. CRP was 24 mg/L (in 2021). *This case describes a man with elevated CRP and PMR symptoms confirmed by ultrasound. The time to onset is plausible with a temporal relationship.* *WHO-UMC Causality Assessment: Possible.*
[redacted] 79/F [redacted] Dose 1 Recovering/Resolving 7 Days	Polymyalgia rheumatica Bronchitis bacterial / Tobacco user / Varicose vein / Varicose vein operation Not Reported	A 79-year-old female patient, long- term smoker with chornic mucopurulnet bronchitis and with a varicose vein operation in an unspecified date. The patient's concomitant medications were not reported. She received BNT162B2 (dose 1) on 25 March 2021 and one week after, she experienced rheumatic polymyalgia. Around 01 April 2021, she had pain in her left shoulder and in both hips. She began to wake up at night due to pain and in the mornings, she felt stiff for at least 30 minutes. There was no oedema, no headache or fever. Elevated inflammatory parameter was identified: s-CRP (12 April 2021): 108.9 mg/l on 12 April 2021. On 14 April 2021, the diagnose of polymyalgia rheumatica was confirmed and Medrol 16 mg was started, and pain began to abate. Supportive therapy with Oleovit, Actonel and Calcium was added. The outcome of the event was recovering. *Symptoms reported, lab data, time to onset and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR. Of note, concomitant meds were not reported.* *WHO-UMC Causality Assessment: Possible.*
[redacted] 82/F [redacted] Dose 2 Recovered/Resolved 16 Days	Polymyalgia rheumatica Hypertension Lercanidipine / valsartan	A 82-year-old female patient with a medical history on hypertension treated with valsartan and lercanidipine, received BNT162b2 (dose 2) on 15 March 2021. On 31 March 2021, she experienced pseudopolyarthritis (myalgias and arthralgias mainly in the hips and shoulders) with a CRP: >100 mg/l on an unspecified date. Treatment with Cortancyl between 20 and 40 mg/day resulted in disappearance of pain on 26 May 2021. *Symptoms reported, lab data, time to onset and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR.* *WHO-UMC Causality Assessment: Possible.*

- *Cases providing sedimentation rate values and no c-reactive protein*
    - Of the 204 reports, 6 provided ESR values (no CRP values provided). They are described in more detail in Table 8 (not reproduced here, no cases considered possible related to Comirnaty exposure).

All cases were assessed based on WHO-UMC causality assessment. Overall, the majority of the cases (30 cases) reporting valuable lab data (both CRP and ESR, only CRP and only ESR) were considered unclassifiable due to the lack of information. Eleven cases were confounded by underlying medical history or alternative aetiology and seven cases represented possible PMR cases after vaccination.

Out of the 16 cases providing both CRP and ESR values, four cases met the criteria to be classified as 'possible' based on WHO-UMC causality assessment. Six cases reported a possible differential diagnosis of giant cell arteritis or vasculitis or were confounded by pre-existing medical condition and concomitant treatment (previous RA disease, concomitant use of Apixaban) and were assessed as 'unlikely' and the remaining six cases did not report sufficient information to confirm the diagnosis of PMR or reported insufficient information to perform a meaningful causality assessment.

In all six cases reporting only elevated ESR, the paucity of the reported information precluded a meaningful causality assessment and therefore all of them were considered 'unclassifiable'.

Out of the 26 cases reporting only elevated CRP, eighteen cases did not report sufficient information and were considered unclassifiable as per WHO-UMC causality assessment. Five cases were confounded by

possible alternative aetiology and were assessed as unlikely, and three cases met the criteria to be considered 'possible' as per WHO-UMC causality.

Rapporteur assessment comment:

From the retrieved 628 post-marketing cases reporting PMR after Comirnaty exposure, 424 cases were excluded because they reported an implausible time to onset (<3 days after vaccination or over 28 days after vaccination). Out of the remaining 204 cases:

- 16 cases provided both CRP and ESR levels of which 4 cases were considered possible related to Comirnaty exposure, 6 cases unlikely related and 6 cases unclassifiable;
- 26 cases provided CPR levels only of which 3 cases were considered possible related to Comirnaty exposure, 4 cases unlikely related and 19 cases unclassifiable.
- 6 cases provided ESR levels only of which all 6 cases were considered unclassifiable.

In total 7 cases reporting PMR after Comirnaty exposure were considered possibly related to Comirnaty exposure. Only in 2 of these 7 cases medical history and concomitant treatment was provided, in 3 of the 7 cases medical history and concomitant medication was not provided, and in the remaining 2 of the 7 cases concomitant medication was not provided. Therefore, the provided post-marketing data does not suggest a causal association between Comirnaty exposure and PMR.

Results – PMR exacerbation cases reported after BNT162B2 vaccination

A total of 54 cases, among 565 cases that report PMR in the medical history, report PMR as an adverse event following vaccination, potentially indicating an exacerbation or flare of underlying PMR. Among these 54 cases there are 35 (64.8%) females and 19 (35.2%) males.

Age was reported as ranging from 51 to 88 years (mean: 70.9; N: 51). The majority of cases were reported from the United Kingdom (50%), followed by France (13%), Netherlands (11.1%) and Germany (7.4%).

A total of 46 cases reported the dose number: 16 cases reported PMR after dose 1, 27 after dose 2 and 3 after dose 3. The 3 subjects that reported PMR after dose 3 received Astra-Zeneca COVID-19 vaccine as the primary series vaccine.

A total of 15 subjects did not report concomitant medication, among the subjects that report medication a total of 23 reported corticosteroid or other immunosuppressant as concomitant medication. Ten patients reported one or more additional autoimmune disease in addition to PMR. Of note, are 3 subjects who reported immunodeficiency, neoplasm and renal failure, respectively.

Case outcome was reported as follows: recovered/recovering in 23, not recovered in 20 and unknown in 11 cases.

Among the 54 cases, 3 subjects reported it in the context of giant cell arteritis (GCA: known to be often present as concomitant disease with PM), 1 in the context of Herpes Zoster, 1 in the context of urinary infection and 1 in the context of tapering down corticosteroid to have a better immune response to vaccination.

Time to onset ranged from the day of vaccination to >30 days. Among the 18 cases with a time to onset between 4 and 30 days, there were 7 subjects that did not report concomitant medications, additional 7 were under corticosteroid /immunosuppressive therapy indicative of an instable disease; among them 2 that had underlying other autoimmune disease and the subject that was on tapering down corticosteroid, 1 was in the context of urinary tract infection and 1 case in the context of GCA.

Three cases presented a worsening of PM after both the first and the second vaccination dose:

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 51/F [redacted] Dose 1 and 2 Recovering 7 Days (after each dose)	Polymyalgia Rheumatica Polymyalgia Rheumatica Not Reported	A 51-year-old female patient received bnt162b2 and 7 days after each vaccination the patient had polymyalgia rheumatica complaints. Outcome is reported as recovering. *The subject is under continuous corticosteroid treatment indicating an unstable disease. Is not mentioned whether the treatment was suspended shortly before vaccination or "scaled down". Lack of these crucial information preclude a final diagnosis of relapse.*
[redacted] 72/F [redacted] Dose 1 Unknown 15 days and reported as pain and stiffness worsened after the 2nd vaccine dose without a specific timing reported.	Polymyalgia rheumatica, Disease recurrence, Musculoskeletal stiffness, Myalgia, Pain Polymyalgia rheumatica Not reported	A 72-year-old female patient received and about 2 weeks after first vaccination the patient started to experience stiffness and muscle soreness. After the second dose these symptoms worsened. He was diagnosed with polymyalgia rheumatica and started corticosteroids. *The information is confusing as it was reported as polymyalgia rheumatica in the medical history, but the subject now refers to it as a new disease. Lack of information on medical history and concomitant medication preclude a final diagnosis of relapse.*
[redacted] 74/M [redacted] Dose 2 Recovering Unknown	Polymyalgia rheumatica, Arthralgia, Mobility decreased, Abdominal pain upper, Insomnia, Inappropriate schedule of product administration Polymyalgia rheumatica, Immunodeficiency, heart attack, B12 deficiency anemia, Esophageal acid reflux, autoimmune disorder Acetylsalicylic acid / atorvastatin calcium / diastase, magnesium carbonate, sodium bicarbonate / hydroxocobalamin / omeprazole / prednisolone / sacubitril, valsartan.	A 74-year-old male patient received BNT162B2 and after unknown time experienced polymyalgia rheumatica, extreme pains in shoulder, wrists and knees, lack of mobility, sleep disturbances and diabetes. After the second dose, on unknown date, the patient experienced the same symptoms. He performed blood exams, but the results were not reported. Outcome is reported as recovering. *The subject is under continuous corticosteroid treatment indicating an unstable disease. It is not mentioned whether the treatment was suspended shortly before vaccination or scale down. Lack of these crucial information preclude a final diagnosis of relapse. Time to onset of flare is not reported.*

In summary, among the 54 cases reporting a flare of PMR after vaccination, 25 cases reported a time to onset between the same vaccination day and 3 days after vaccination suggesting the possibility of reactogenicity event(s) to vaccination rather than a PMR flare; 4 cases reported a time to onset not suggestive of a causal association with vaccination (34, 60, 60 and 69 days after vaccination respectively); 7 cases did not report the time to onset making an assessment impossible. Among the 18 cases reporting a plausible time to onset, 7 subjects did not report any concomitant medication for the treatment of PMR or information about the stability of the disease, rendering difficult a proper assessment, 7 were under corticosteroid/immunosuppressive therapy indicating an instable disease (2 had also additional underlying autoimmune disease and 1 patient was tapering down corticosteroid that may have been the reason of the flare) and 1 case was reported in the context of GCA that could be the consequence of the reported relapse. Overall, 3 subjects did not report alternative explanation to the flare. Among these 3 only 1 performed laboratory examination during the symptomatology and confirmed the increased ESR and CRP.

Rapporteur assessment comment:

From the retrieved 54 post-marketing cases reporting a flare of PMR after Comirnaty exposure, 36 cases were excluded because they reported an implausible time to onset (<3 days or over 30 days after vaccination) (N=29) or did not report the time to onset (N=7). Out of the remaining 18 cases, only 3 cases did not report an alternative explanation of the flare of PMR. A causality assessment with Comirnaty exposure was not provided by the MAH for these 3 cases reporting a flare of PMR after vaccination. However, only 1 of the 3 cases provided laboratory examination (confirmation of increased ESR and CRP) which hampers causality assessment. Therefore, the provided post-marketing data does not suggest a causal association between Comirnaty exposure and a flare of PMR.

Clinical trial data

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 cut-off 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.

Literature

A literature search was conducted using Database: Database: OVID MEDLINE(R) 1946-present, OVID MEDLINE(R) In-Process & Epub Ahead of Print, Embase <1974 to 2022 January 21 for vaccination and Polymyalgia Rheumatica. Search strategy: 1) polymyalgia rheumatica.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, bo, bt, tn, dm, mf, dv, dq] (10383), 2) vaccination.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, bo, bt, tn, dm, mf, dv, dq] (616225).

A total of 76 articles were retrieved and the most relevant are described below:

A potential link between vaccination and new onset or relapse of PMR/giant cell arteritis was previously described with influenza vaccine. The role of the adjuvant was suspected to induce inflammatory cytokine production such as interleukin-6 or tumor necrosis factor- α leading a flare of the disease.[1]

Yang et al.[2] described a prospective observational study (70 patients) examining the immunogenicity and safety profile of the SARS-CoV-2 vaccine in patients with immune-mediated diseases taking immunomodulatory medications. Adults with an immune-mediated disease scheduled to receive either a Pfizer or Moderna SARS-COV-2 vaccine were enrolled in this study. The authors concluded that patients with autoimmune and inflammatory disease experience adverse events following SARS-CoV-2 vaccination as fever, fatigue and arthralgias mimicking flares with both frequency and severity appearing slightly greater than that of the reported results from the vaccine clinical trials.

Spinelli et al.[3] reported a study including 126 patients with rheumatic Musculo-skeletal diseases (RMD) (all under therapy). Overall, 5 cases reported a flare of the disease (0.007 person/month). After excluding other possible causes, and confirming the temporal relationship with the vaccination, only 3 out of the 126 evaluated patients showed a mild disease flare probably attributable to the vaccination. All disease reactivations consisted in mild articular flares lasting 7 days on average and requiring just symptomatic treatment. The authors conclude that the low incidence rate of disease reactivation and the similar adverse event following vaccination occurrence compared to controls reassure on mRNA vaccine safety in RMD patients.

Bixio et al.[4] performed a study focusing on COVID-19 vaccines safety and immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs), they have estimated an incidence of between 5% and 17% for RMD flares after COVID-19 vaccination. The results showed a low flare rate after the BNT162b2 COVID 19 vaccine in patients with RA in remission (7.8% of which 83% after the 2nd dose and all resolved within 2 weeks). Of note, 83% of the patients with flares withdrew or delayed anti-rheumatic therapies in the proximity of vaccination according to ACR guidelines. The data were consistent with previous findings about Varicella-zoster virus (6.7%) and Hepatitis B virus (2.2%) vaccinations.

Watad A et al.[5] evaluated immune-mediated diseases (IMDs) flares or new disease onset within 28-days of SARS-CoV-2 vaccination at five large tertiary centers in countries with early vaccination adoption, three in Israel, one in UK, and one in USA. Of the relapsed cases, 75% were mild to moderate in severity and over 80% of cases had excellent resolution of inflammatory features, mostly with the use of corticosteroid therapy. They concluded that, despite the high population exposure in the regions served by these centers, IMDs flares or onset temporally associated with SARS-CoV-2 vaccination appear rare.

Boekel L et al.[6] describe the results of a questionnaire that assessed adverse events following COVID-19 vaccinations in patients with autoimmune diseases and healthy controls. The questionnaire was sent to patients with systemic autoimmune diseases who were enrolled in two ongoing prospective cohort studies (Netherlands Trial Register, trial ID NL8513 and NCT04498286). Between April 26, 2020 and March 1, 2021, all adult patients with systemic autoimmune diseases from the Amsterdam Rheumatology and Immunology Center (Amsterdam, Netherlands), and all adult patients with multiple sclerosis from the Amsterdam Multiple Sclerosis Center of Amsterdam UMC (Amsterdam, Netherlands) were invited to participate. Patients enrolled in the first study were asked (but not obliged) to recruit their own healthy control participant who was of the same sex and of comparable age (age difference <5 years). Data were collected via online questionnaires distributed via email. Analysis of the results of our questionnaire demonstrate that adverse events of COVID-19 vaccinations in patients with autoimmune diseases are comparable with controls, independent of the type of vaccine. Subjects were requested to send all adverse events reported within the first 7 days after vaccination, in addition patients with rheumatic diseases and healthy controls were asked whether they experienced an increased number of joint complaints in the first 2 months after vaccination. The observed adverse events consisted of expected transient local or systemic reactions that were mostly self-limiting. The frequency of participants who reported adverse events was lower than that reported in clinical trials, but similar to a nationwide observational study on adverse events of COVID-19 vaccinations in the general population done in the UK. The data were consistent with previous studies that reported higher frequencies of adverse events in women and younger people. The authors conclude that COVID-19 vaccinations do not seem to trigger autoimmune disease flares, which is in accordance with data from previous small studies that assessed consequences of mRNA vaccines in patients with autoimmune diseases.

Many published studies showed reassuring results after COVID-19 vaccination with no increase of autoimmune diseases nor flares in subjects with underlying autoimmune diseases.[2,4,5,6,7,8] Interestingly, Yang et al.[2] suggest that patients with autoimmune and inflammatory disease experience adverse events following SARS-CoV-2 vaccination as fever, fatigue and arthralgias that mimicking flares. When the time to onset of flare is reported in the literature article is reported as a mean of 4 days after vaccination which suggest the possibility of a reactogenicity event from the vaccine instead of a real flare of the underlying disease.

The authors from the French Pharmacovigilance Network used the WHO global individual case safety report database, VigiBase, to look for signals of disproportionate reporting for events of PMR and GCA reported in association with COVID-19 vaccine. They compared the events reported with COVID-19 vaccines with all drugs in the database and with influenza vaccine as comparators. The reporting odds ratio (ROR) of PMR using all drugs as a comparator was elevated for COVID-19 vaccines (ROR 2.3, 95% CI: 2.0, 2.6) and specifically for mRNA COVID-19 vaccines (4.1 (3.6, 4.7). The ROR of PMR using influenza vaccine as a comparator was not elevated for COVID-19 vaccines (ROR 0.2, 95% CI: 0.2, 0.2) including mRNA COVID-19 vaccines (0.4 (0.4, 0.5). The median time to event was 6 days, 52.4% of the patients were women and the median patient age was 72 years. Although the pathophysiology of PMR is not fully understood, this was taken to be a potential safety signal requiring confirmation, with the caveats of the known limitations of a spontaneous report database.[9]

A French rheumatology service at the University of Paris Hospital described a series of 10 patients fulfilling ACR/EULAR criteria for PMR following COVID-19 vaccination (7 were new-onset and 3 were relapses). Nine of the patients were vaccinated with BNT162b2 and one with mRNA-1273. The median time to symptoms was 10 days, 70% of the patients were women and the median patient age was 74.5 years. All patients were PCR negative for SARS-CoV-2 and had elevated C-reactive protein levels (median 26 mg/l) and PET scans indicative of inflammation in the PMR-related joint sites. All responded favorable to treatment with systemic (n=9) or local (n=1) glucocorticoids (+/- methotrexate [n=3] or tocilizumab [n=1]). The authors also describe that during the period of May to October 2021, 12 patients were

diagnosed with PMR while from May to October in previous years (2020) and (2018 and 2019), PMR diagnoses were lower at 3 and 6, respectively. While the authors postulate a causal association, they concede that this data cannot exclude the possibility that these patients would have developed PMR without vaccination.[1]

Rapporteur assessment comment:

No important new safety information could be identified from the provided literature concerning Comirnaty exposure and reports of PMR and exacerbation or flare-up hereof.

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Observed versus expected analysis of spontaneously reported events

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 628 new onset cases of polymyalgia rheumatica reported through 18 December 2021. O/E analyses using 21- and 42-day risk windows are provided in Table 9 overall and by gender for all cases reported globally, and by age for the United States (US) and European Economic Area (EEA) countries only because these regions make detailed information about vaccine administration publicly available.

Table 9. Observed to Expected (O/E) Ratios for Polymyalgia Rheumatica through 18 December 2021

Events	Observed Cases	Person-Years[a]	Background Rate Per 100,000 Person-Years[b]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
Global – all ages							
21 day risk period	460	88,917,877.7	95.90	85,272.2	0.005	0.005	0.006
42 day risk period	507	132,927,707.4	95.90	127,477.7	0.004	0.004	0.004
By Age – EEA and US							
<=11 years							
21 day risk period	0	785,983.1	0.00	0.0	NA	NA	NA
42 day risk period	0	1,113,755.0	0.00	0.0	NA	NA	NA
12-17 years							
21 day risk period	0	2,558,968.5	0.00	0.0	NA	NA	NA
42 day risk period	0	3,737,127.5	0.00	0.0	NA	NA	NA
18-24 years							
21 day risk period	0	3,601,697.5	0.00	0.0	NA	NA	NA
42 day risk period	0	5,262,763.4	0.00	0.0	NA	NA	NA
25-49 years							
21 day risk period	12	15,484,028.8	3.20	495.5	0.024	0.013	0.042
42 day risk period	13	22,700,554.0	3.20	726.4	0.018	0.010	0.031
50-59 years							
21 day risk period	42	7,236,785.4	27.60	1,997.4	0.021	0.015	0.028
42 day risk period	44	10,620,266.2	27.60	2,931.2	0.015	0.011	0.020
60-69 years							
21 day risk period	95	6,262,999.7	105.70	6,620.0	0.014	0.012	0.018
42 day risk period	107	9,165,352.6	105.70	9,687.8	0.011	0.009	0.013
70+ years							
21 day risk period	196	9,337,505.6	293.50	27,405.6	0.007	0.006	0.008
42 day risk period	220	13,961,488.5	293.50	40,977.0	0.005	0.005	0.006
By Gender – EEA and US							
Females							
21 day risk period	192	23,992,023.4	125.20	30,038.0	0.006	0.006	0.007
42 day risk period	216	35,277,492.8	125.20	44,167.4	0.005	0.004	0.006
Males							
21 day risk period	153	21,275,945.3	64.40	13,701.7	0.011	0.009	0.013
42 day risk period	168	31,283,814.4	64.40	20,146.8	0.008	0.007	0.010

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Rapporteur assessment comment:

In the O/E analysis of the 628 new onset cases of PMR reported through 18 December 2021, all O/E ratios are well below 1.

MAH's conclusion

A total of 628 reports were identified via the search strategy. Of these reports, 424 were excluded from further analysis because included confounders such as co-reported events in SOC Infections or Neoplasm may mimic PMR and a relevant medical history of previous auto-immune disorders, endocrine and musculoskeletal diseases and neoplasms.

Out of the remaining 204 cases, only 16 co-reported elevated CRP and ESR levels, while 26 cases report only elevated CRP and 6 reported only elevated ESR. Most of the reports (30 cases) did not report

sufficient information to confirm the PMR diagnosis or reported it in the context of alternative diseases that could cause elevation of CRP or ESR (11 cases). Seven reports described possible PMR cases after vaccination.

The number of cases reporting flare of PMR after vaccination are extremely low also taking in consideration that we know only the number of cases with a history of PMR that report an AE after vaccination, but we are not aware of how many patients with underlying PMR were vaccinated. Even considering only the reported relapse they are less than 10% of the cases with a history of PMR that reported an AE (overestimated for the reason mentioned above) and this is aligned with the data available from scientific literature, as described above. These low numbers of cases and lack of important information in most cases do not support of a causal association with vaccine.

The number of cases reported versus an expected rate in an unvaccinated population (O/E ratio) is below 1 suggesting the number of reports observed is not unexpected. Furthermore, clinical study results do not demonstrate evidence for an imbalance between placebo and the vaccine group.

Considering that more than 2 billion doses of COVID-19 vaccine has been administered worldwide and given the available data, the totality of the data does not suggest a causal association between BNT162b2 and PMR; therefore, the signal is refuted.

Safety updates to the product information and/or the risk management plan are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored with routine pharmacovigilance.

Rapporteur assessment comment:

Considering the safety information provided (post-marketing cases, clinical trial data, literature, O/E analyses) concerning Comirnaty exposure and reports of PMR and exacerbation or flare-up hereof, MAH's conclusion is accepted that the data does not suggest a causal association between Comirnaty and PMR.

Issue solved

2.2.1.5. Subacute Thyroiditis

Response to the PRAC request 10 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *The MAH should perform a cumulative review on the association between Comirnaty and subacute thyroiditis. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the possibility of flare up in cases with any form of thyroiditis in the medical history. The following terms should be used to identify cases: Atrophic thyroiditis, Autoimmune thyroiditis, Hashimoto's encephalopathy, Immune-mediated thyroiditis, Silent thyroiditis, Thyroiditis, Thyroiditis acute and Thyroiditis subacute, Hyperthyroidism. The MAH should consider the need for an update of the product information and/or RMP.*

MAH's response:

The MAH has searched their database for all Pfizer-BioNTech COVID-19 vaccine (BNT162B2; BNT162B2S01) cases reported cumulatively through 18 December 2022 for MedDRA v 24.1 PTs of Autoimmune thyroiditis, Thyroiditis and Thyroiditis subacute.

A total of 498 cases (2394 events) were retrieved using the search strategy above reporting the following relevant PTs as specified below in Table 1. Some cases reported multiple PTs. The majority of cases were spontaneous (488); majority (358 cases) were serious.

There were 388 females, 100 males, and gender not reported in 10 cases.

Table 1. Safety Database Search: Relevant Thyroiditis PTs and Respective Number of Cases

PT	Number of Cases
Thyroiditis subacute	189
Autoimmune thyroiditis	163
Thyroiditis	155

When provided, the age ranged as shown in Table 2 below. The mean and median ages were 47.9 and 47, respectively (n=460).

Table 2. Reported Age in 498 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	4	0.80%
18 - 30 years	34	6.80%
31 - 50 years	246	49.40%
51 - 64 years	124	24.90%
65 - 74 years	39	7.80%
Greater than or equal to 75 years	14	2.80%
Unknown	37	7.40%

Out of the 498 cases, 114 cases reported a pre-existing medical history relevant to thyroid disorders or the potential for thyroid disorders including thyroid condition, immunodeficiency, auto-immune disorder, pregnancy, viral infections, malignancies, and/or concomitant medications (e.g., thyroid hormone replacement, antibiotics, immunomodulators) which could precipitate thyroiditis or thyroiditis-like events; 19 of these 114 cases reported a pre-existing COVID-19 illness.

Rapporteur assessment comment:

The MAH identified a total of 498 thyroiditis cases (thyroiditis subacute, n=189; autoimmune thyroiditis, n=163; thyroiditis, n=155). Of these, 358 cases (72%) were considered serious and reported in females in 388 cases (78%). The majority of the cases was identified in the age category from 31 to 50 years (n=246, 49%). In 114 of the 498 cases, pre-existing medical history relevant to thyroid disorders or the potential for thyroid disorders were reported. Pre-existing COVID-19 infection was reported in 19 of these 114 cases.

Cases describing a medical history of thyroiditis

Fifty-four (54) out of the 114 cases reported a pre-existing medical history of Autoimmune thyroiditis, thyroiditis, and/or thyroiditis subacute. There were 61 relevant PTs reported as AEs in these 54 cases: Autoimmune thyroiditis (36 cases); Thyroiditis (14), and Thyroiditis subacute (5); some cases reported multiple PTs. The most commonly reported MedDRA Lower-Level Terms (LLTs) in these cases were: Hashimoto's thyroiditis (16 cases); Hashimoto's disease (15); and Thyroiditis (14).

When dose sequence was provided for the 61 events, it was following Dose 1 for 20 events, Dose 2 for 29 events: and Dose 3 for 2 events. When provided, the outcome of the events at the time of reporting was resolved/resolving for 23 events and not resolved for 30 events. The most commonly reported latency in

these 54 cases was the day of vaccination (for 7 events) and 1 day post vaccination (for 8 events). The duration of the relevant events was provided only for 4 events ranging from 1 days to 14 days.

Out of 54 cases, 48 of the 61 thyroiditis events were serious. The most commonly co-reported PTs in these 54 cases were: Condition aggravated (17 cases), Fatigue (14), Headache (10), and Pyrexia (9).

Only 11 of the 54 cases reported thyroid laboratory data including 8 cases reporting either decreased TSH, increased T3 and increased free T4, 1 case reporting decreased TSH and increased CRP, supporting diagnosis of subacute thyroiditis, one with ongoing Hashimoto's thyroiditis reported increased TSH and the last case reported thyroid functions within reference range. Four (4) of these 54 cases reported patients complaining of "inflammation/enlargement" of thyroid gland; none of cases reported biopsy information.

Rapporteur assessment comment:

In the 114 cases pre-existing medical history relevant to thyroid disorders or the potential for thyroid disorders were reported. Of these, 54 (61 events) reported a pre-existing medical history of Autoimmune thyroiditis, thyroiditis, and/or thyroiditis subacute. Of the 61 events, 20 occurred after the first dose, 29 after the second dose, and 2 after the third dose. TTO was reported as the day of vaccination for 7 events, 1 day after vaccination for 8 events, and for 4 additional events ranging from 1 to 14 days. In 11 of the 54 cases, thyroid laboratory data were provided.

Cases not describing a medical history of thyroiditis

Of the remaining 384 cases in the overall dataset of 498 cases, 15 cases were lacking necessary information on reported dose sequence, latency, clinical outcome and other datapoints precluding meaningful assessment.

Of the remaining 369 cases, 57 cases co-reported the following adverse events post vaccination in addition to reported relevant events: anaphylaxis, hypersensitivity, infections including Covid 19, auto-immune conditions, vasculitis, myocarditis, pericarditis, and/or hypothyroidism. These co-reported events confounded an assessment of the relevant events.

Out of the remaining 312 cases, further analysis was concentrated on 161 cases (reporting 174 relevant events of Thyroiditis subacute [75 cases], Thyroiditis [53], and Autoimmune thyroiditis [37]), with a most plausible latency of 3 to 42 days post vaccination. Some cases reported multiple relevant events.

The most commonly reported LLTs for the thyroiditis events in these 161 cases were: Thyroiditis (50 cases), Subacute thyroiditis (33), De Quervains thyroiditis (22), and Thyroiditis subacute (19).

The most commonly co-reported PTs in the 161 cases are in Table 4 below:

Table 4. Commonly Co-Reported PTs

PTs	Number of cases
Pyrexia	33
Fatigue	18
Neck pain	18
Headache	15
Asthenia	12
Hyperthyroidism	11
Malaise	11
Oropharyngeal pain	11
Palpitations	11

When dose sequence was provided, it was following Dose 1 for 70 relevant events, Dose 2 for 60 events: and Dose 3 for 3 events.

When provided, the outcome of the relevant events at the time of reporting was resolved/resolving for 63 events; not resolved at the time of reporting for 89 events; and resolved with sequelae for 4 events.

The most commonly reported latency in these 161 cases was Day 3 to Day 15.

The duration of the relevant events in 161 cases was provided only for 11 of the events ranging from 9 days to 4 months and 26 days.

Further analysis concentrated on 91 cases that specified the thyroiditis event as serious. Sixty-six (66) of these 91 cases reported laboratory work up and/or diagnostic procedures, and 38 of the 66 cases reported thyroid function specific diagnostic test such as decreased TSH, increased T3 and increased free T4 and/or increased CRP, supporting diagnosis of subacute thyroiditis. One of these 38 cases reported inflammation of the thyroid gland; none of 38 cases reported biopsy information.

Rapporteur assessment comment:

Of the 384 cases that did not report pre-existing medical history relevant to thyroid disorders or the potential for thyroid disorders, 15 lacked information for a causality assessment. The MAH further focusses on the 161 cases that did not co-report relevant events that confound the assessment and that reported TTO between 3 to 42 days post vaccination. These were reported after the first dose in 70 events, after the second dose in 60 events and after the third dose for 3 events. Duration of the event was reported in 11 events and ranged from 9 days to more than 4 months. Of the 161 cases, 91 were reported as serious of which 66 reported laboratory work up and/or diagnostic procedures.

Clinical trial data

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 cut-off date 13 March 2021) was also reviewed for the adverse events Autoimmune thyroiditis, Thyroiditis and Thyroiditis subacute. In the Phase 2/3 safety population, 1 case of autoimmune thyroiditis was reported among 21926 participants in the BNT162b2 group compared with 1 case of autoimmune thyroiditis among 21921 participants in the placebo group.

Rapporteur assessment comment:

Within the clinical trials, one case of autoimmune thyroiditis was observed in the Comirnaty group as well as in the placebo group.

O/E analysis

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the subacute thyroiditis cases reported to the safety database through 18 December 2021. This condition was defined with PTs thyroiditis subacute, thyroiditis, and autoimmune thyroiditis. O/E analyses using 21- and 42-day risk windows are provided in Table 5 overall for all cases reported globally, as well as by age, gender, and dose for the United States (US) and European Economic Area (EEA) countries only because these regions make detailed information about vaccine administration publicly available.

Expected subacute thyroiditis cases for the O/E analyses were derived using background incidence rates reported by a US study in Olmsted County, Minnesota. Cases were ascertained from review of medical records and ranged in age from 14-87 years. The incidence rate during 1990-1997 was 3.6 cases per 100,000 persons per year overall; 4.6 /100,000 for females; 2.8/100,000 for males. No age-specific rates

were provided and so we used the overall incidence rate of 3.6/100,000 persons per year for all ages. Based on the background rates from this study, all O/E ratios and upper limits of the 95% confidence intervals (CI) were below 1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.

Table 5. Observed to Expected (O/E) Ratios for Subacute Thyroiditis through December 18, 2021

Category *	Observed Cases through 18 DEC 2022	Time at Risk (PY) through 18 DEC 2022	Background Rate Per 100,000 PY**	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-Day Risk Window							
<11 years	0	785,983.10	3.600	28.30	0.000	0.000	0.106
12-17 years	3	2,558,968.50	3.600	92.12	0.033	0.007	0.095
18-24 years	6	3,601,697.50	3.600	129.66	0.046	0.017	0.101
25-49 years	147	15,484,028.80	3.600	557.43	0.264	0.223	0.310
50-59 years	78	7,236,785.40	3.600	260.52	0.299	0.237	0.374
60-69 years	22	6,262,999.70	3.600	225.47	0.098	0.061	0.148
70+ years	16	9,337,505.60	3.600	336.15	0.048	0.027	0.077
Male	54	21,275,945.30	2.800	595.73	0.091	0.068	0.118
Female	218	23,992,023.40	4.600	1103.63	0.198	0.172	0.226
Dose 1	143	21,070,123.20	3.600	758.52	0.189	0.159	0.222
Dose 2	123	19,189,615.30	3.600	690.83	0.178	0.148	0.212
Dose 3	6	5,008,230.20	3.600	180.30	0.033	0.012	0.072
Overall Global	338	88,917,877.70	3.600	3201.04	0.106	0.095	0.117
42-Day Risk Window							
<11 years	0	1,113,755.00	3.600	40.10	0.000	0.000	0.075
12-17 years	3	3,737,127.50	3.600	134.54	0.022	0.005	0.065
18-24 years	7	5,262,763.40	3.600	189.46	0.037	0.015	0.076
25-49 years	184	22,700,554.00	3.600	817.22	0.225	0.194	0.260
50-59 years	96	10,620,266.20	3.600	382.33	0.251	0.203	0.307
60-69 years	31	9,165,352.60	3.600	329.95	0.094	0.064	0.133
70+ years	22	13,961,488.50	3.600	502.61	0.044	0.027	0.066
Male	69	31,283,814.40	2.800	875.95	0.079	0.061	0.100
Female	274	35,277,492.80	4.600	1622.76	0.169	0.149	0.190
Dose 1	171	21,070,123.20	3.600	758.52	0.225	0.193	0.262
Dose 2	166	37,875,785.60	3.600	1363.53	0.122	0.104	0.142
Dose 3	6	7,615,398.50	3.600	274.15	0.022	0.008	0.048
Overall Global	422	132,927,707.40	3.600	4785.40	0.088	0.080	0.097

*Age, gender, and dose specific results are for EEA/US only
**Background rate source: Fatourechi V, et al. J Clin Endocrinol Metab. 2003 May;88(5):2100-5. doi: 10.1210/jc.2002-021799. PMID: 12727961

Rapporteur assessment comment:

The MAH has provided O/E analyses for subacute thyroiditis. The O/E ratios were <1 for all of the analyses, including those stratified for age, gender, and dose.

Literature review

COVID-19 and thyroid dysfunction

COVID-19 infection extra-pulmonary manifestations may include endocrine forms involving pancreatic, pituitary, gonadal and finally thyroid disorders. Various thyroid disorders, including inflammatory thyroiditis, subacute or de Quervain's thyroiditis, chronic lymphocytic thyroiditis or Hashimoto's disease, painless (silent) postpartum thyroiditis have been described after COVID-19 infection.

With the identification of SAT cases associated with COVID-19 infection, studies on how the virus can cause subacute thyroiditis have been performed. It has been shown that angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2) play a role in the entry of SARS-CoV-2 into host cells. In addition, the presence of ACE-2 and TMPRSS2 expression in thyroid gland cells, suggest that the thyroid may be one of the target tissues during SARS-CoV-2 viremia. An interesting study by Lui W et al reported that around 15% of patients with mild to moderate COVID-19 had thyroid dysfunction. The authors suggest that there may be a direct effect of SARS-CoV-2 on thyroid function, potentially

leading to exacerbation of pre-existing autoimmune thyroid disease. Their study also proposes that low fT3, associated with systemic inflammation, may have a prognostic significance.

Subacute thyroiditis and COVID-19 vaccination

An interesting study on subacute thyroiditis (SAT) has been performed by Bahcecioglu AB et al that evaluated prospectively all cases of SAT in a tertiary center and their relationship with SARS-CoV-2 during 16 months of the pandemic (between March 2020 and July 2021). Cases during a similar pre-pandemic period were recorded for comparison.

Study group of all cases diagnosed with SAT was divided into three as: CoV-SAT, patients who had or still have COVID-19, Vac-SAT, patients diagnosed within three months after SARS-CoV-2 vaccination and NonCoV-SAT, those not associated with COVID-19 or vaccination. Out of 64 patients, 18.8% (n = 12) was classified as CoV-SAT, 9.3% (n = 6) as Vac-SAT and 71.9% (n = 46) as NonCoV-SAT. CoV-SAT and NonCoV-SAT groups were similar in terms of clinical, laboratory, and treatment characteristics. However, symptoms were milder and treatment was easier in Vac-SAT group ($p = 0.006$). The authors concluded that the number of SAT cases during the pandemic period was comparable to pre-pandemic period. However, a considerable rate of SARS-CoV-2 exposure in SAT patients was established. COVID-19 presented with SAT, as the first manifestation in three cases. There was no difference between the groups in terms of age, gender, frequency of fever, asthenia and sweating, ESR, CRP level and thyroid ultrasound findings. Neck pain was significantly less frequent in Vac-SAT compared to NonCoV-SAT. TSH level was significantly lower in Vac-SAT when compared to the other groups. Median time between COVID-19 and the onset of SAT symptoms in CoV-SAT was 10 weeks and 4 weeks in Vac-SAT indicating that vaccine-related cases developed in a shorter time period, clinical presentation was milder, and only a few patients required corticosteroids.

Various case reports of SAT after COVID-19 vaccination have been reported with all commercialized COVID-19 vaccines. Some case reports are described below.

Capezzone et al reported young health care people (wife and husband) who received a first dose of SARS-CoV-2 vaccine (Moderna vaccine), and few weeks later developed clinical manifestations of thyroid hyperactivity, with increased thyroid hormone levels on thyroid function tests, suppressed TSH and negative antithyroid antibodies, despite being healthy before vaccination. They were diagnosed at the 4th week after first dose of SARS-Cov-2 vaccine as silent thyroiditis and followed without treatment, since their symptoms were not severe. At the 6th week, the patients became wholly asymptomatic and their thyroid function returned to normal.

The authors concluded that thyrotoxicosis can occur after SARS-CoV-2 vaccination probably related to silent thyroiditis.

Bostan H et al describe two cases who developed SAT three days after BNT162b2 and six days after the inactivated COVID-19 vaccine (CoronaVac). The patients were female aged between 30-42 and the complaints of the patients initiated within the first 2-7 days following vaccination.

Pla Peris B et al describe a single-center case series based on all the information collected in the hospital medical records, as well as the temporal sequence between the onset of symptoms and COVID-19 vaccination. They reported 8 cases with thyrotoxicosis after SARS-CoV-2 vaccination (4 cases of Graves' disease (GD), 2 cases of subacute painful thyroiditis (SAT), 1 case of concurrent GD and SAT and 1 case of atypical subacute thyroiditis). Five patients received BNT162b2 mRNA vaccine, and 3 patients 1273 mRNA vaccine. The onset of symptoms following vaccination ranged from 10 to 14 days in six of eight patients and from 7 to 8 weeks in two patients. Several hypotheses have been proposed to explain the potential correlation between SARS-CoV-2 vaccination and thyrotoxicosis, including immune system hyper-stimulation, molecular mimicry and Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants.

Khan F et al presented the case of a 42-year-old female healthcare worker who was diagnosed with subacute thyroiditis 4 days after receiving her second dose of Pfizer-BioNTech vaccine. Her clinical course followed the classical pattern for thyroiditis with spontaneous return to euthyroidism at 6 months post-presentation. They conclude that subacute thyroiditis should be considered in all patients who receive any kind of vaccine for COVID-19 and subsequently develop symptoms or signs of hyperthyroidism or neck pain. Subacute thyroiditis is a self-limiting condition, and recognizing it is important as no specific thyroid treatment is necessary for most patients.

Pandya M et al described three patients without a history of thyroid disease who presented with symptomatic, biochemical, and radiological evidence of thyroiditis with thyrotoxicosis, 10-20 days after receiving either the Pfizer Bio-NTech or the Moderna COVID-19 mRNA vaccine. All presented with thyrotoxicosis, but with negative thyroid stimulating immunoglobulins for Graves' disease and no autonomous nodules. Two patients underwent thyroid uptake and scan which confirmed thyroiditis. One patient had significantly increased erythrocyte sedimentation rate (ESR) and Interleukin-6 (IL-6). All had improvement in symptoms with non-steroidal anti-inflammatory drugs (NSAIDs), with one patient eventually requiring steroids for symptom control. The authors concluded that mRNA vaccine for SARS-COV-2 was associated with thyroiditis and presented with thyrotoxicosis. Elevated proinflammatory markers and cytokines after vaccines may play a major role.

Sozen M et al describe the clinical, laboratory and imaging features of five cases of subacute thyroiditis after COVID-19 mRNA vaccine (Pfizer/BioNTech R). The cases reported subacute thyroiditis with clinical findings typical of classic subacute thyroiditis such as fever, neck pain, weakness, and tremor within a few days following vaccination and responded quite well to non-steroidal anti-inflammatory therapy.

Oyibo S et al reported a case of a female patient who developed subacute thyroiditis soon after receiving the adenovirus-vectored COVID-19 vaccine. The patient presented with severe neck pain and her blood results demonstrated an initial thyrotoxic phase followed by a hypothyroid phase. The author concludes that subacute thyroiditis occurring after COVID-19 vaccination is rare but also probably underreported.

Plaza-Enriquez L et al described the case of a patient who developed subacute thyroiditis after administration of Moderna mRNA COVID-19 vaccine. A 42-year-old female, with a past medical history of stage IIIB pT3N1aM0 right adenocarcinoma of colon status, after right hemicolectomy on 01/2020, followed by adjuvant chemotherapy, paroxysmal supraventricular tachycardia, iron deficiency anemia, chemotherapy-induced neuropathy, and lumbar radiculopathy, presented to theclinic with anterior neck pain that started 6 days after the second dose of Moderna mRNA COVID-19 vaccine. She was diagnosed with subacute thyroiditis and treated conservatively with pain medications. The authors concluded that subacute thyroiditis could represent one of the side effects of Moderna mRNA COVID-19 vaccine.

Soltanpoor P et al reported another case of SAT after the first dose of COVAXIN (The Bharat Biotech COVID-19 Vaccine) in a 34-year-old woman, with negative history of previous proven or suspicious COVID-19 infection. The subject reported expected symptoms of fatigue, myalgia, and mild fever about 12 hours post-injection, gradually resolving over the next 72 hours. During the 5th–7th day post-vaccination, she experienced gradual onset of intermittent mild fever, palpitation, and radiating anterior neck pain and following diagnostic analysis was diagnosed with subacute thyroiditis.

Siolos A et al describe two female patients with thyroiditis after vaccination against SARS-CoV-2. The first patient presented with fever and pain in the thyroid area typical of SAT two weeks after vaccination with the BNT162B2 mRNA (Pfizer-BioNTech) COVID-19 vaccine. The second patient presented with biochemical and imaging features consistent with silent thyroiditis three weeks after vaccination with the ChAdOx1-S (AstraZeneca) vaccine. Both patients were asymptomatic prior to vaccination and PCR of nasopharyngeal swab for SARS-CoV-2 and other respiratory viruses associated with SAT was negative. Antibody titer against spike S protein of SARS-CoV-2 was measured for both patients and was indicative of adequate post vaccination antibody response. Two months after initial assessment, both patients were

euthyroid and asymptomatic. The authors concluded that subacute as well as silent thyroiditis may rarely occur after vaccination against COVID-19.

Yorulmaz G et al report a case series of 11 patients that developed SAT after different COVID-19 vaccination (BNT162b2 Pfzer/BioNTech and Coronavac). The authors discuss further the mechanism that could trigger the SAT after COVID-19 vaccination and they suggest that, as the spike protein is a common stimulant for cellular and humoral immune responses in the functioning of both mRNA vaccines and whole virus vaccines, the mRNA vaccines enable our cells to produce spike protein, and the whole virus vaccines contain it in an inactive form. Therefore, is possible that the spike protein can trigger SAT in susceptible individuals by binding to the HLA-B35 molecule in macrophages and activating cytotoxic T lymphocytes. This activation may be the reason for the destruction in thyroid follicular cells, rich in ACE-2 receptors to which spike protein binds. The neutralization of spike protein by the antispike antibodies may have a role in the self-limitation of thyroid damage.

References literature review

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Siolos A, Gartzonika K, Tigas S. Thyroiditis following vaccination against COVID-19: Report of two cases and review of the literature. Metabol Open. 2021 Dec; 12:100136.

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Rapporteur assessment comment:

The MAH has provided a literature review describing articles related to subacute thyroiditis and COVID-19 infection and COVID-19 vaccination.

Regarding subacute thyroiditis and COVID-19 infection, potential underlying mechanisms have been reported including the presence of ACE-2 and TMPRSS2 expression in thyroid gland cells, suggesting that the thyroid may be one of the target tissues during SARS-CoV-2 viremia. Also, it is suggested that there may be a direct effect of SARS-CoV-2 on thyroid function, potentially leading to exacerbation of pre-existing autoimmune thyroid disease.

Regarding subacute thyroiditis and COVID-19 vaccination, in a study in patients with subacute thyroiditis it was concluded that the number of relapse cases during the pandemic period (including those vaccinated) was comparable to the pre-pandemic period although a considerable rate of SARS-CoV-2 exposure in those patients was observed. The MAH also describes multiple case reports that also include case reports for the other COVID-19 vaccines. It is described that some cases resolved without treatment and that the condition is generally self-limiting although also cases are described that required treatment with corticosteroids. Authors conclude that subacute thyroiditis may occur (rarely) after COVID-19 vaccination. Also, potential mechanisms are described that include stimulation of the immune system and the importance of elevated proinflammatory markers and cytokines.

MAH's summary and conclusion

Statistical and disproportionality analysis in the Pfizer safety database has not shown a signal of disproportionate reporting for subacute thyroiditis.

Subacute thyroiditis has been spontaneously reported following vaccination. However, most cases do not report relevant information (medical history, laboratory and other diagnostic data) to allow a proper evaluation.; the majority of reports do report underlying thyroid disorder or concomitant disease that represent a confounding factor. The details of 38 cases reporting relevant events and laboratory work up confirming hyperthyroid activity, did not provide enough relevant information in order to confirm the causal association with the vaccine.

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

A large double-blind placebo-controlled study of the Pfizer/BioNTech COVID-19 vaccine did not demonstrate any increased risk of subacute thyroiditis between placebo and vaccine administered subjects.

Literature analysis did not reveal an increased risk of developing subacute thyroiditis after Pfizer/BioNTech COVID-19 vaccine administration. While single case reports have been received, a full comprehensive prospective study concludes that the number of SAT cases during the pandemic period was comparable to pre-pandemic period.

Overall, given the totality of the available information, 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:

As requested by PRAC, the MAH has provided a cumulative review of subacute thyroiditis. A total of 498 cases were identified of which 114 reported pre-existing medical history relevant to thyroid disorders or the potential for thyroid disorders were reported. In a limited number of cases, laboratory work up and/or diagnostic procedures were provided. The provided O/E ratios for subacute thyroiditis were all <1, including the stratified analysis for age, gender, and dose. In the clinical trials, in both the Comirnaty group as the placebo group, one case of autoimmune thyroiditis was observed. Literature review identified multiple case reports of subacute thyroiditis following COVID-19 vaccination.

Overall, based on the information provided on the post-marketing and clinical trial cases, O/E analyses, and despite of some case reports were considered possible related by the authors, we agree with the MAH that no new safety concern was identified. Closure of the signal is accepted.

Issue solved

2.2.1.6. Glomerulonephritis and Nephrotic Syndrome

Signal assessment report on Glomerulonephritis and nephrotic syndrome with tozinameran EMA/PRAC/416198/2021 EPITT 19722:

> *"Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of the COVID-19 mRNA vaccine (nucleoside-modified) COMIRNATY (BioNTech Manufacturing GmbH) should closely monitor the issue of 'glomerulonephritis/nephrotic syndrome', including exacerbations, and present a cumulative review of cases from all sources and relevant literature in the upcoming PSUR submissions. However, if new relevant information becomes available earlier that would support an association with the vaccine, the MAH should propose updates of the product information accordingly and without delay".*

MAH's response:

The MAH has performed a literature search and analysed their safety database regarding glomerulonephritis and nephrotic syndrome for the period between 26 July 2021 through 18 December 2021.

Literature data

The literature search retrieved a total of 16 publications, of which 4 articles were already presented in the original PRAC response. Of the remaining 12 publications, 6 presented information relevant to the topic under analysis and are therefore described in further detail below:

The first article by Nakazawa et al[1] was a case report of a 15-year-old male patient from Japan without underlying disease who newly developed nephrotic syndrome after SARSCoV-2 vaccination with BNT162b2, and due to absence of history of infection disease or other vaccination during several months prior to vaccination, the authors considered that the vaccine 'may have triggered the onset of nephrotic syndrome'. The case reports that patient responded to conventional therapy as per Japanese guidelines (prednisolone), and whereas extensive information about patient's state and investigations are presented, there is no information to support objective exclusion of other infectious or autoimmune risk factors for the event. In the discussion section, the authors present that a potential mechanism could be via immune systemic immune activation, as revealed by sporadic reports of such event after other vaccines (e.g. influenza, Hepatitis B, etc). The authors considered that BNT162b2 vaccination induces a broad immune response with SARS-CoV-2 S-specific neutralizing antibodies, poly-specific CD4+ and CD8+ T cells, and various cytokines such as IFN-γ and IL-2, however they state that a causal relationship between vaccination and the development of nephrotic syndrome cannot be proven on basis of observation of nephrotic syndrome after vaccination alone.

Rapporteur assessment comment: The article of Nakazawa et al. describes a case report of newly developed nephrotic syndrome in a 15-year old male from Japan. Symptoms occurred four days after first dose of Comirnaty. The diagnosis was not confirmed by biopsy. Regarding potential confounding factors, the authors only state that history of infection or other vaccination in the months prior to vaccination was absent without reporting on potential specific infections substantiated with laboratory findings. Also, only information was provided on S-specific SARS-CoV-2 antibodies, therefore previous COVID-19 infection cannot be excluded. Therefore, causality with Comirnaty exposure is considered possible.

The second article, Izzedine et al[2], was a commentary of case series on development of nephrotic syndrome and vasculitis following SARS-CoV-2 Vaccine. The authors provided a summary of reported cases from literature sources following COVID-19 vaccination and discuss proposed mechanisms or

explanations for the observed events, in form of part publications of the same events with other vaccinations (notably influenza), or suspected trigger role of the immune response to vaccination. However, authors recognize that such mechanisms remain to be elucidated, stating that 'it is also possible that these phenomena are completely circumstantial and unrelated'. The discussion on potential role of environmental factors, such as infections, is relevant and based on temporal and spatial clustering of cases. The authors also noted that reported cases of glomerulonephritis (GN) do not provide evidence of exclusion of COVID-19 infection, and thus, whether the reported cases could be attributed to SARS-CoV-2 warrants investigation.

Rapporteur assessment comment:

The article of Izzedine et al. is a commentary on 11 published nephrotic syndrome cases (5 new onset, 6 relapsed). Of these, 7 were vaccinated with Comirnaty. Additionally, 6 cases of new onset crescentic glomerulonephritis were described (Comirnaty, n = 2). The authors discussed several potential underlying mechanisms for the events. No specific causality assessment of the individual literature cases discussed was performed.

The third article, Abdulgayoom M et al[3], was a case report of a 45-year-old female patient with a medical history of hypothyroidism, atopic dermatitis, and a heterozygote factor V mutation and no history of kidney disease, who developed minimal-change disease with symptom onset 4 days after receiving the first dose of BNT162b2. Although the case provides information about exclusion of associated viral infections (SARS-CoV-2, adenovirus, EBV, CMV), and autoimmune diseases, there is no information about testing or exclusion of bacterial infections, as these are well known triggers of GN. The authors considered a potential relationship with the vaccine based on the temporal association, absence of viral or autoimmune etiologies, and historical information about the same event with this or other non-COVID-19 vaccines (influenza). The authors propose a hypothesis regarding mechanism to be related to T cell response, and question whether dosing after such event poses a risk of triggering a more severe disease, however, this information is presented purely on theoretical grounds and there is no evidence provided to substantiate such mechanism or risk in the case itself or data described by the authors.

Rapporteur assessment comment:

The article of Abdulgayoom et al. presented a case report of (new onset) minimal-change disease in a 45-year old female. Symptoms occurred four days after first Comirnaty dose and diagnosis was confirmed by biopsy. Multiple other (viral) factors that could confound the assessment were excluded. Therefore, causality with Comirnaty exposure is considered probable.

The fourth article, Davidovic et al[4], discuss 2 case reports of vasculitis GN, of which one patient was thought to have a pre-existing yet undiagnosed GN. The authors discuss the potential role of withdrawing immunosuppression with rituximab in one of these 2 cases, as due to the pandemic situation and the reported higher risk of COVID-19 mortality in patients treated with immunosuppressives, there was a decision to withdraw rituximab treatment until improvement of the pandemic situation or patient vaccination. The patient had started showing evidence of vasculitis relapse one month prior to vaccination. The authors propose a number of mechanisms, all proposed on theoretical grounds, take into account prior cases reported with influenza vaccination, and discuss the challenges in establishing a therapeutic conduct for patients treated with immunosuppressive treatments in view of the pandemic situation and timing of vaccination.

Rapporteur assessment comment:

The article of Davidovic et al. described one case of de novo and one case of relapsing glomerulonephritis that both occurred after second Comirnaty dose in patients with vasculitis. In the relapse case, treatment with rituximab for vasculitis was withdrawn given the pandemic situation and the patient developed a

relapse two months after the second Comirnaty dose. Given these factors, causality with Comirnaty exposure is considered unlikely. The other case is reported as a de novo case, however, it is reported that histopathological findings suggest that this patient had renal flares prior to Comirnaty vaccination. Causality with Comirnaty exposure is in this case considered unlikely.

The fifth article, Mancianti et al[5], was a case report of a 39-year-old Caucasian male with a history of biopsy-proven minimal change disease with nephrotic syndrome 38 years before (at age on 1, who remained on been on regular follow-up for 37 years) and who developed MCD and AKI 3 days after first dose of the BNT162b1. The patient recovered after standard treatment (prednisolone). Similar to earlier publications, this article also presents a suspicion of association with the vaccine due to temporal relationship and includes a presentation of the role of immune response to vaccination in inducing T-cell mediated response based on theoretical and animal model consideration, also proposing that dosing is not continued in patients who experience such events.

Rapporteur assessment comment:

The article of Mancianti et al. described a case report of a minimal change disease and acute kidney injury that occurred three days after first Comirnaty dose in a 39-year old male. Diagnosis was confirmed by biopsy. Medical history included minimal change disease at age 1. It is reported that common causes of renal failure were excluded and that no infectious or relevant conditions occurred in the weeks prior to vaccination. No information was, however, provided on the exact other causes that were excluded and the methods to support these. Therefore, causality with Comirnaty exposure is considered possible.

The last sixth article[6] reported 2 paediatric patients with IgA nephropathy (IgAN) presenting with macroscopic hematuria <24 hours after Pfizer COVID-19 vaccination. The authors cautionary conclude that patients, including children, with IgAN should be monitored closely following COVID-19 vaccine, and COVID-19 vaccination may unmask previously undiagnosed glomerulonephritis in paediatric patients.

Rapporteur assessment comment:

The article of Hanna et al. presented two cases of relapse of IgA nephropathy in paediatric patients that both occurred within 24 hours after second Comirnaty dose. The first case report described a 13-year old boy with an initial diagnosis of IgA nephropathy 6 months prior to the event. In the second case it was reported that, although the patient was not yet diagnosed with IgA nephropathy, biopsy results suggest an acute exacerbation of pre-existing IgA nephropathy. For both patients it was described that they had no COVID-19 infection (method to exclude not provided) before vaccination nor any history of reactions to any vaccinations. In both cases, causality with Comirnaty exposure is considered possible.

References

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Literature summary

Most (5) out of 6 relevant literature articles were published case reports with most of them reporting a relapse of the disease, and some authors provided insight on possible mechanisms for occurrence of a relapse. However, all authors mentioned that further evidence is required to confirm if this is an adverse effect associated with SARS-CoV-2 vaccines; in addition, there might be various other factors involved.

There was no literature publication providing a high strength of evidence, such as meta-analysis, systematic review of controlled clinical trial. All articles were publications of case reports or case series of patients who experienced GN or NS following COVID-19 vaccination (incl. BNT162b2). For the assessment of relationship with the vaccine, authors generally accounted for the prior reports with other vaccines (mainly influenza) and a theoretical concern on the role of the immune response to the vaccine; however due to the nature of the evidence provided in form of clinical observations, such hypotheses do not benefit from substantial data to support or prove a relationship. In terms of confounders to account for the interpretation of such cases, articles discussed the importance of excluding SARS-COV-2 infection (and how some literature reports do not offer such proof of exclusion), the potential role of other environmental factors (such as infections) based on observed seasonality and clustering of cases, as well as discussed the role of prior pandemic driven withdrawal of immunosuppressive therapies in patients with pre-existing autoimmune diseases that poses risk of relapses and aggravation.

Rapporteur assessment comment:

It is acknowledged that the literature articles only provide case reports and, in some cases, possible underlying mechanisms. However, given the incidence of glomerulonephritis and nephrotic syndrome, estimated as approximately 40 cases per 100,000 PYs, it is not unexpected that within the clinical trial program these events have not been observed and therefore currently no meta-analysis or systematic reviews are available. Besides, the literature articles that provided case reports are well-described post-marketing cases that could provide valuable information for the assessment of the potential signal. For the provided case reports, the MAH however did not specifically assess the causality with Comirnaty exposure. Also, it is noted that not all relevant articles were included in the literature review. For example, the articles by Gueguen et al. (doi: 10.1016/j.kint.2021.08.006) and Da et al. (10.1016/j.kint.2021.07.016) were published in August 2021 and described persons that developed membranous nephropathy following vaccination with Comirnaty. These may have been included in MAH's safety database but given the data provided (see below) this could not be determined. It is furthermore noted that case reports continue to be published [e.g. Nihei et al. (doi: 10.2169/internalmedicine.8787-21); Niel et al. (doi: 10.1007/s00467-021-05351-x)]. The MAH should therefore provide an updated literature review (DLP: 9 May 2022) concerning glomerulonephritis and nephrotic syndrome and for the identified case reports the MAH should include a WHO-UMC causality assessment per case regarding Comirnaty exposure. **Request for supplementary information.**

Cases from MAH's safety database

As a comprehensive cumulative review of the cases from the safety database was provided in the previous response to PRAC, the safety database was searched for all BNT162b2; BNT162b2S01 cases reported from 26 July 2021 through 18 December 2021 using MedDRA v 24.1 PTs within HLT Glomerulonephritis and nephrotic syndrome.

A total of 226 cases were retrieved. Some cases were coded with more than one of the relevant events in the HLT. Table 1 below lists relevant PTs reported in this dataset and a respective number of cases.

Table 1. Safety Database Search: Relevant PTs and Respective Number of Cases

PT	Number of Cases
Nephrotic syndrome	138
Glomerulonephritis	27
IgA nephropathy	27
Glomerulonephritis rapidly progressive	18
Glomerulonephritis minimal lesion	14
Focal segmental glomerulosclerosis	8
Glomerulonephritis membranous	7
Glomerulonephritis acute	5
Granulomatosis with polyangiitis	4
Nephritic syndrome	3
Glomerulonephritis chronic	2
Glomerulonephritis membranoproliferative	2
Mesangioproliferative glomerulonephritis	2
Pulmonary renal syndrome	2
Anti-glomerular basement membrane disease	1
Glomerulonephritis proliferative	1
Goodpasture's syndrome	1
Henoch-Schonlein purpura nephritis	1
Microscopic polyangiitis	1

The majority of cases (197) were spontaneous; 225 cases were serious. There were 115 females, 106 males, and gender was not known in 5 cases.

When provided, the age ranged as shown in Table 2 below. The mean and median ages was 46.5 and 45 years, respectively (n=216).

Table 2. Reported Age in 226 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	28	12.40
18 - 30 years	35	15.50
31 - 50 years	63	27.90
51 - 64 years	35	15.50
65 - 74 years	24	10.60
Greater than or equal to 75 years	32	14.20
Unknown	9	4.00

The top countries from where these cases were reported is presented in Table 3 below.

Table 3. Reporting Country in 226 Cases

Country	Number of Cases	% of Total Cases
Japan	47	20.80
France	42	18.60
Germany	27	11.90
Spain	13	5.80
United States	13	5.80
Italy	12	5.30
United Kingdom	9	4.00
Australia	8	3.50
Netherlands	5	2.20
New Zealand	5	2.20

In the review of these cases consideration was given to the various causes of glomerulonephritis and nephrotic renal disease.

Out of the 226 cases, 102 cases described a pre-existing medical condition and/or use of co-suspect/ concomitant medication representing a reasonable alternative cause of the relevant events; some examples of conditions are autoimmune disorders, immunodeficiencies, infections, diabetes, and some examples of medications are NSAIDs, immunosuppressants, cephalosporins. Six (6) out of these 102 cases reported COVID-19 or Suspected COVID-19. Out of these 102 cases, 61 cases reported a pre-

existing glomerulonephritis, nephrotic syndrome related events and/or acute kidney injury, renal impairment, renal transplant, chronic kidney disease, renal cancer. These 61 cases reported a total of 69 relevant events from HLT Glomerulonephritis and nephrotic syndrome. When dose sequence was provided in these 61 cases, it was following Dose 1 for 25 relevant events, Dose 2 for 39 events and Dose 3 for 4 events. The outcome of the relevant events at the time of reporting was resolved/resolving for 35 events; not resolved for 12 events; resolved with sequelae for 3 events, and unknown for 19 events. The time to onset (latency) from time of the vaccination until the development of the relevant event was reported as: from within the same day of vaccination to 3 days post vaccination for 15 relevant events, from day 5 to day 10 for 13 events, from day 13 to day 24 for 9 events, and post day 24 for 10 events.

Forty-eight (48) out of these 61 cases were healthcare professional/medically confirmed; and 24 of these 61 cases reported "aggravation, exacerbation, and/or worsening" of the renal events; in 19 of these 24 cases laboratory workup for renal function was provided.

Out of the remaining 124 cases, in 4 cases limited information was provided; the cases lacked multiple datapoints, including medical history, co-suspect and concomitant medications, dose, outcome, latency, and other details supporting the diagnosis.

The last 120 cases reported a total of 150 relevant events. Eighty-three (83) of these 120 cases were healthcare medically confirmed. The most commonly co-reported PTs in these 120 cases were: Proteinuria (21), Oedema peripheral (17), Haematuria (16), Oedema (13), and Acute kidney injury (10).

Sixty-eight (68) out of 120 cases reported hospitalization, and information related to laboratory values was present in 87 of the 120 cases: a need for dialysis was reported in 4 out of 120 cases. Out of 120 cases, renal failures was reported in 2 cases.

Out of these 120 cases, 18 cases with a total of 20 relevant events reported paediatric patients with age of less or equal to 17 years.

When dose sequence was provided in these 120 cases, it was following Dose 1 for 42 relevant events, Dose 2 for 86 events and Dose 3 for 2 events. The outcome of the relevant events at the time of reporting was resolved/resolving for 55 events; not resolved for 50 events; resolved with sequelae for 6 events, and unknown for 39 events. The time to onset (latency) was reported as: from within the same day of vaccination to 3 days post vaccination for 24 relevant events, from day 4 to day 10 for 45 events, from day 11 to day 14 for 5 events, from day 15 to day 20 for 13 events, from day 21 to day 31 for 9 events, from post day 31 for 18 events.

When reported, the duration of the relevant event was 8 hours (for one event), 8 days (for one event), from 30-33 days (for 6 events) and longer than 33 days (for 6 events).

Upon a detailed review of the 120 cases, based on the dose and latency information, in 6 cases there was no information about dose and latency to event, precluding temporal analysis of the event relative to the vaccination, and in other 25 cases, the reported latency of the same day as vaccination or more than 21 days after last dose make an association with the vaccine implausible. In 21 cases, the co-reported events supported the GN or NS occurring as a result or in association with other conditions, such as infection (pneumonia, enterocolitis, etc.), auto-immune disorders (lupus, vasculitis), etc. Therefore, in these total 47 unique cases, the role of the vaccine in inducing the renal event is implausible.

Rapporteur assessment comment:

Within the interval from 26 July 2021 through 18 December 2021, a total of 226 cases were reported. The majority of the cases reported nephrotic syndrome (n = 138), followed by glomerulonephritis (n = 27), and IgA nephropathy (n = 27). All but one case were reported to be serious. Median age in the reported cases was 46.5 years, 28 were reported in persons <18 years.

The MAH describes that in 102 of the 226 cases alternative causes of the relevant events were reported that include pre-existing medical conditions (incl. COVID-19 infection) and concomitant medications. In 61 (69 events) of these 102 cases, the pre-existing medical condition concerned glomerulonephritis, nephrotic syndrome related events and/or acute kidney injury, renal impairment, renal transplant, chronic kidney disease, and/or renal cancer. For these, the event was reported to have occurred after the first dose in 25 events, after second dose in 39 events and third dose in 4 events. When available, TTO was reported as within 24 days post vaccination for 37 events. 48 of the 61 cases were medically confirmed, 24 reported "aggravation, exacerbation, and/or worsening" of the renal events of which in 19 cases laboratory work-up was provided.

Of the 124 cases that did not report alternative causes, 4 reported insufficient information for an assessment. Of the remaining 120 cases (reporting 150 events), 83 were medically confirmed, 68 required hospitalization (4 needed dialysis), and in 87 cases information on laboratory values was present. 18 of the 120 were reported to have occurred in persons <18 years. The event was reported to have occurred after the first dose in 42 events, after second dose in 86 events and third dose in 2 events. When available, TTO was reported as within 21 days for 87 events. The MAH further reports that for 47 of the 120 cases, the role of the vaccine in inducing the renal event is implausible given the reported TTO and/or co-reported events.

For none of the cases, the MAH has provided WHO-UMC causality assessments. Although this may not be required for all of the identified cases, the MAH should report on the potentially supportive cases. For example, medically confirmed cases with plausible TTO that provide information on laboratory work-up. The MAH is therefore requested to provide an updated review (DLP: 9 May 2022) of cases reporting glomerulonephritis / nephrotic syndrome from their safety database and, when applicable, provide the WHO-UMC causality assessment per case regarding Comirnaty exposure. **Request for supplementary information.**

O/E analysis

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 226 new onset cases of glomerulonephritis and nephrotic syndrome reported from 26 July 2021 to 18 December 2021 defined using MedDRA v 24.1 PTs within HLT Glomerulonephritis and nephrotic syndrome.

Table 4. Observed to Expected (O/E) Ratios for Glomerulonephritis and Nephrotic Syndrome, Interval Time Period July 26, 2021 – December 18, 2021

Stratification	Observed Cases	Person-Years (PY)[a]	Background Rate Per 100,000 PY[b]	Expected Cases	O/E Ratio	95% CI Lower Limit	95% CI Upper Limit
Global – all ages							
Overall processed cases							
14 day risk window	143	46,278,258.0	38.50	17,817.1	0.008	0.007	0.009
21 day risk period	172	61,214,970.0	38.50	23,567.8	0.007	0.006	0.008
42 day risk period	197	89,749,700.0	38.50	34,553.6	0.006	0.005	0.007
Overall processed + backlog cases (Note 0 cases in the backlog)							
14 day risk window	143	46,278,258.0	38.50	17,817.1	0.008	0.007	0.009
21 day risk period	172	61,214,970.0	38.50	23,567.8	0.007	0.006	0.008
42 day risk period	197	89,749,700.0	38.50	34,553.6	0.006	0.005	0.007
By dose - EEA and US							
All ages Dose 1							
14 day risk window	33	3,247,087.0	38.50	1,250.1	0.026	0.018	0.037
21 day risk period	43	4,982,393.6	38.50	1,918.2	0.022	0.016	0.030
42 day risk period	49	4,982,393.6	38.50	1,918.2	0.026	0.019	0.034
All ages Dose 2							
14 day risk window	46	4,184,495.0	38.50	1,611.0	0.029	0.021	0.038
21 day risk period	56	6,551,217.7	38.50	2,522.2	0.022	0.017	0.029
42 day risk period	69	14,798,341.0	38.50	5,697.4	0.012	0.009	0.015
All ages Dose 3							
14 day risk window	6	3,655,235.5	38.50	1,407.3	0.004	0.002	0.009
21 day risk period	6	5,008,070.3	38.50	1,928.1	0.003	0.001	0.007
42 day risk period	6	7,615,135.2	38.50	2,931.8	0.002	0.001	0.004
By Age – EEA and US							
<=11 years							
14 day risk window	0	494,578.3	20.00	98.9	0.000	-	-
21 day risk period	1	734,938.9	20.00	147.0	0.007	0.000	0.038
42 day risk period	1	1,054,139.0	20.00	210.8	0.005	0.000	0.026
12-17 years							
14 day risk window	12	1,111,690.7	20.00	222.3	0.054	0.028	0.094
21 day risk period	14	1,669,840.0	20.00	334.0	0.042	0.023	0.070
42 day risk period	16	2,561,798.6	20.00	512.4	0.031	0.018	0.051
25-49 years							
14 day risk window	31	3,964,417.9	20.00	792.9	0.039	0.027	0.055
21 day risk period	39	6,042,786.8	20.00	1,208.6	0.032	0.023	0.044
42 day risk period	42	10,347,398.0	20.00	2,069.5	0.020	0.015	0.027
50-59 years							
14 day risk window	8	1,313,630.2	20.00	262.7	0.030	0.013	0.060
21 day risk period	9	1,955,385.1	20.00	391.1	0.023	0.011	0.044
42 day risk period	14	3,475,172.8	20.00	695.0	0.020	0.011	0.034
60-69 years							
14 day risk window	5	1,219,547.6	57.00	695.1	0.007	0.002	0.017
21 day risk period	11	1,749,620.6	57.00	997.3	0.011	0.006	0.020
42 day risk period	12	2,829,307.6	57.00	1,612.7	0.007	0.004	0.013
70+ years							
14 day risk window	21	1,810,495.3	57.00	1,032.0	0.020	0.013	0.031
21 day risk period	21	2,612,252.5	57.00	1,489.0	0.014	0.009	0.022
42 day risk period	26	4,252,073.7	57.00	2,423.7	0.011	0.007	0.016

Table 4. Observed to Expected (O/E) Ratios for Glomerulonephritis and Nephrotic Syndrome, Interval Time Period July 26, 2021 – December 18, 2021

By Gender - Global							
Females							
14 day risk window	46	5,876,013.2	32.50	1,909.7	0.024	0.018	0.032
21 day risk period	58	8,767,091.2	32.50	2,849.3	0.020	0.015	0.026
42 day risk period	65	14,519,811.0	32.50	4,718.9	0.014	0.011	0.018
Males							
14 day risk window	39	5,210,804.2	46.50	2,423.0	0.016	0.011	0.022
21 day risk period	47	7,774,590.3	46.50	3,615.2	0.013	0.010	0.017
42 day risk period	59	12,876,059.0	46.50	5,987.4	0.010	0.008	0.013

a. Age-stratified exposure time estimates were derived from the European Centre for Disease Prevention and Control (ECDC) data on COVID-19 vaccination in the EU/EEA[8] and Our World Data (OWD)[9] data and CDC data[10] in the US. Vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine.

b. Mean of the overall Medicare and Employer Group Health Plan primary glomerulonephritis rates in Table 1 of Reference: Wetmore JB, Guo H, Liu J, et al. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney Int. 2016 Oct;90(4):853-60. doi: 10.1016/j.kint.2016.04.026. Epub 2016 Jul 15. PMID: 27425855.[7]

Rapporteur assessment comment:

The MAH has provided overall O/E analyses and stratified by dose, age, and gender. All of the O/E ratios were <1.

MAH's conclusion

Based on the nephrology related literature, William G, et al, the current evidence suggests that infections may initiate many of the autoimmune or other reactions in genetically susceptible individuals, which lead to glomerular disease through numerous simultaneous and/or sequential pathways that begin with activation of the innate immune response. These pathways vary depending on the nature of the infectious pathogen and the genetically regulated immune response of the host. These mechanisms include immune dysregulation, adjuvant or bystander effects, epitope spreading, molecular mimicry, epitope conformational changes, and antigen complementarity. Infections may also have direct effects on podocytes and other glomerular cells, either due to direct infection or the induction of innate immune responses. Continued efforts are essential to clarify the genetic basis for susceptibility to GN, as are efforts to improve therapy."

Most (5) out of 6 relevant literature articles were published case reports with most of them reporting a relapse of the disease, and some authors provided insight on possible mechanisms for occurrence of a relapse. However, all authors mentioned that further evidence is required to confirm if this is an adverse effect associated with SARS-CoV-2 vaccines; in addition, there might be various other factors involved.

There were a total of 226 cases reported from the safety database including 18 paediatric cases, and 102 of these cases were confounded by pre-existing medical history and/or co-suspect/concomitant medications. Sixty-one (61) out of the 102 cases reported pre-existing renal condition, and 24 of these 61 cases reported "aggravation, exacerbation, and/or worsening" of the renal events. Four (4) cases were limited and for the remaining 120 cases, more cases reported an occurrence of the relevancy event post Dose 2 with latency from day 4 to day 10. In 47 of these 120 cases, the role of the vaccine in inducing the renal relevant event was implausible.

The MAH does not consider that the currently available information supports a causal association between these renal disorders and the vaccine. Pfizer/BioNTech will continue to monitor. No updates to current labelling are warranted at this time.

Rapporteur assessment comment:

As requested within the separate signal procedure (EPITT ref. 19722), the MAH provided an updated cumulative review of glomerulonephritis/nephrotic syndrome. Given that the information provided did not

reflect the complete body of evidence and additional data has become available after the DLP of the current PSUR, the MAH is requested to provide an updated cumulative review with DLP 9 May 2022 and incorporate the PRAC requests above.

2.2.1.7. Multisystem Inflammatory Syndrome in Children and Adults

Signal assessment report on multisystem inflammatory syndrome in children for COVID vaccines EMA/PRAC/473788/2021 EPITT 19732:

> *"The MAH should continue to closely monitor this safety issue and new cases of MIS-C/A should be reported in the MSSRs and PSURs. Regarding TTO, a risk window of at least 6 to 8 weeks after COVID 19 vaccination is considered reasonable. The MAH should include, but not limit to, the following: information on prior or current SARS CoV 2 infection, laboratory markers of inflammation, measures of disease activity, the duration of fever and information excluding differential diagnosis (e.g. other infectious agents). A dedicated questionnaire should be implemented to retrieve an appropriate level of information to facilitate the assessment of the cases of suspected MIS."*

MAH's response:

MAH's safety database was searched for all cases reporting the following MedDRA preferred terms, as delineated in the PRAC request: Multisystem inflammatory syndrome in children, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, Kawasaki's disease, toxic shock syndrome, distributive shock, hypotensive crisis, vaccine associated enhanced disease, vaccine associated enhanced respiratory disease, cytokine release syndrome, cytokine storm, haemophagocytic lymphohistiocytosis, macrophage activation, macrophages increased, septic shock, autoinflammatory disease, multisystem inflammatory syndrome in adults, multisystem inflammatory syndrome

A total of 440 cases were retrieved, using the search criteria above for the PSUR reporting period, 19 June through 18 December 2021.

MIS-C

Of the 440 cases retrieved, 60 cases reported patients of age < 21 years and all these cases have been previously discussed in the original PRAC response, MSSR #11 and 1st Bimonthly Summary Safety report.

Table 1 presents the classification of these 60 cases per the BC case definition criteria.

Table 1. Cases reviewed for MIS-C, presented by BC Level

BC Level	Number of cases
1	5
2	9
3	2
4	23
5	11
Cases with insufficient information for classification	10

Of the 60 cases, the following is notable on the below case, because follow-up information was received post DLP of the previous reviews (within the reporting period of the PSUR) that changed case's previous classification.

AER [redacted] was analyzed in the 1st summary bimonthly report. On the available reported information at the time, it was classified as BC level 4. Follow-up information received in the interim allows re-classification as a BC level 2b case which is summarized below.

A 12-year-old male patient, reporting country; [redacted]

Reported event PTs: Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome, Kawasaki's disease, Altered state of consciousness, Delirium febrile, Thrombocytopenia, Pyrexia, Inflammation, Mucosal disorder, Gastrointestinal disorder, Diarrhea, Headache, Blood pressure decreased, Brain natriuretic peptide increased, Ocular hyperemia, Erythema

The patient had no medical history and reported no other vaccines within four weeks prior to Dose 1 nor any concomitant medications in the two weeks before event onset. Dose 1 was received 13 November 2021. It is reported that the patient developed pyrexia approximately 3 weeks later and was described to have an inflammatory reaction which persisted despite antibiotics. Additional symptoms reported include diarrhea, headache and altered consciousness (described as "febrile delirium") and mucocutaneous involvement including ocular hyperemia, redness of the lips and palmar-plantar redness. The patient was hospitalized on 30 November 2021 for 11 days. He was found to be hypotensive (BP 94/52 mmHg). Normal brain imaging on CT and MRI.

No history of COVID-19 infection (serology confirmed on 02 December 2021 with IgG 'S' antibody 4113.90 and IgG 'N' antibody 0.03 [units not reported]). Negative SARS-CoV-2 PCR test on 30 November 2021.

30 November 2021: White blood cells 6300 (lymphocytes 8.2%, neutrophils 86.7%), hemoglobin 13.2 g/dL, platelets 93000, fibrinogen 595, BNP 66.9, CRP 17.63.

Echocardiography: "increased brightness around the coronary arteries".

02 December 2021: IL-6 95.5 (units not reported)

Treatment comprising intravenous immunoglobulins (IVIG), steroids and aspirin was initiated.

MAH comment: As the duration of fever cannot be confidently determined from the reported information this case is reclassified as BC level 2b – a probable case of MIS-C. Although the case now provides sufficient clinical detail to meet the criteria for clinical features, inflammation and disease activity and occurred within the required time-frame (12 weeks following COVID-19 vaccination) there remains a paucity of information on other relevant work-up which may identify alternative etiologies for the reported clinical features.

Rapporteur assessment comment:

The MIS-C cases that were identified by the MAH were all previously discussed in the initial signal procedure and following SSRs. For one case additional follow-up information was received based on which the case was reclassified from BC level 4 to BC level 2b. In this case previous COVID-19 infection was excluded based on negative IgG N antibody. No information was available on alternative etiologies. Causality is therefore considered to be possible.

MIS-A

Of the 440 cases identified in the PSUR review period, 362 cases reported age ≥ 21 years and as such analyzed in consideration of MIS-A.

Table 2 presents the classification of these cases per the BC case definition criteria

Table 2. Cases reviewed for MIS-A, presented by BC Level

BC Level	Number of cases
1	2
2	3
3	3
4	14
5	240
Cases with insufficient information for classification	100

A total of 8 cases reporting this age category were identified in the PSUR review period for analysis for MIS-A which were not previously analyzed/discussed.

One case was closed after the DLP for the PSUR and the reported event PTs updated to include MIS-A (previously not coded with a term included in the search strategy). This case is classified as BC Level 4, as it reports MIS however does not provide the supporting evidence to meet Level 1-3 criteria. The remaining 7 cases retrieved with the new data lock point of 18 December 2021 were all classified as BC level 5.

Rapporteur assessment comment:

Of the 440 cases identified in the reporting period, 8 were not previously discussed. These were classified as BC level 4 (n =1), and BC level 5 (n = 7).

Cases reported with "unspecified age"

A total of 16 further cases in unspecified age category were not previously discussed. Six of the cases do not present sufficient information to allow a meaningful analysis of the case, and a further eight cases are classified as BC level 5. Two cases are retrieved on the reported term MIS however the clinical information available is insufficient to meet the level 1-3 criteria and as such they are classified as BC level 4.

Rapporteur assessment comment:

Of the cases that did not report age and could therefore not be classified as either MIS-C or MIS-A, 16 were not previously discussed. These could not be classified according to the BC criteria since insufficient information was available (n = 6), were classified as BC level 4 (n = 2), and BC level 5 (n = 8).

Cumulative analysis of MIS

A cumulative analysis of cases through 18 December 2021 using the database search strategy described in section 3 retrieved 76 cases in those aged <21 years (MIS-C), of which 16 cases have been classified as BC Levels 1-3.

The same cumulative search for reports in those aged ≥ 21 years retrieved 572 cases, of which just 9 are classified as BC Level 1-3.

These cases provide sufficient information to meet the criteria to be determined as "definite", "possible" or "probable" cases of MIS-C/A, however, even these well described cases have lacked relevant clinical information on preceding COVID-19 infection or exposure, detailed work-up of other potential causes of the clinical picture which compromises an assessment of vaccine causality.

MAH's summary and conclusion

In summary, for the interval PSUR period covering 19 June through 18 December 2021, 440 cases were retrieved for the search strategy to identify potential cases of MIS-C/A. There are no cases identified as

BC level 1-3 in this period which have not previously been presented in the original PRAC signal response, MSSR #11 or 1st Summary bimonthly safety report.

Newly available follow-up information has allowed re-classification of a previously analyzed BC Level 4 case as Level 2b, however the increased diagnostic certainty does not conclude vaccine causality and there remains missing clinical information to exclude other alternative etiologies.

Recent publications on MIS-C/A and COVID-19 mRNA vaccination provide some real-world insights which merit consideration when considering the benefit-risk of Comirnaty.

Although limited by small numbers Levy et al, suggested a lower incidence of MIS-C in vaccinated than unvaccinated adolescents in France. A case-control study in the United States identified that 95% of patients age 12-18 years hospitalized with MIS-C were unvaccinated; 39% of those unvaccinated MIS-C patients required respiratory or cardiovascular life support compared with 0% of vaccinated patients with MIS-C.

Considering the totality of the data, including the number of reports received in the context of the hundreds of millions 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:

No new MIS-C/A cases of BC level 1-3 that were not previously discussed in the initial signal procedure or SSRs were identified. One MIS-A case that was previously classified as BC level 4 was within the reporting period reclassified as BC level 2b since updated information has become available. Although in this case previous COVID-19 infection was excluded, no information was provided on alternative etiologies.

It is agreed with the MAH that based on the information provided no new safety concern was identified. The MAH should continue to closely monitor this safety issue as outlined in PRAC's signal recommendation (EPITT 19732). All new cases of MIS should be reported in the SSRs and PSURs.

2.2.1.8. Erythema Multiforme

Signal assessment on Erythema multiforme EMA/PRAC/398391/2021 EPITT 19721 Procedure no: SDA 034:

> *The MAH for Comirnaty should closely monitor any new cases, patterns or trends of reporting erythema multiforme (and also the severe cutaneous adverse reactions) through routine pharmacovigilance.*

MAH's response:

Signal detection activities for the COVID-19 mRNA vaccine occurs on a weekly basis. Published literature is reviewed weekly for individual case reports and broader signal detection purposes. In addition, observed versus expected analyses is conducted as appropriate as part of routine signal management activity. The MAH closely monitors monitor any new cases, patterns or trends of reporting erythema multiforme. A specific review is provided within the section on dermatological AESIs.

Rapporteur assessment comment:

Please refer to section 2.3 Evaluation of risks and safety topics under monitoring for the assessment of the dermatological AESIs including erythema multiforme.

2.2.2. Evaluation of closed signals

2.2.2.1. Evaluation of closed signals during the reporting interval assessed under any regulatory procedure

Signals determined to be Important Identified Risks

Myocarditis and Pericarditis (EMA/PRAC/575791/2021 EPITT no: 19712 Procedure no: SDA 032.2)

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in the first PSUR.

During the reporting interval, the signal was re-opened and closed twice. The first date the signal was re-opened during the reporting interval was on 30 June 2021 due to regulatory queries as a reflection of the earlier signal assessment prior to the reporting interval. The MAH has considered that although the new queries do not change the MAH assessment of the signal, the core data sheet will be revised to reflect a warning regarding myocarditis and pericarditis in section 4.4 Special warnings and Precautions for Use.

The signal was re-opened on 14 October 2021 due to a PRAC notification of signal assessment procedure following the results of the Nordic registries study. The MAH conducted an updated evaluation of myocarditis and pericarditis from clinical studies, post-marketing data, literature and O/E analyses. In the large, controlled, pivotal study C4591001 myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis or pericarditis events. Efforts are ongoing to evaluate the background rate of troponin abnormalities in healthy study participants prior to vaccination, to inform whether or not troponin may represent a useful biomarker for presence of subclinical myocarditis or pericarditis (if such conditions exist). The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. Further, animal models of myocarditis or pericarditis are not well established and therefore do not serve as a viable model to perform additional nonclinical assessments. In the interpretation of the epidemiology data, it is important to note that data described above reflect rates from different regions, different data sources (e.g., spontaneous reports, registries, administrative), and using different methodologies. This could explain, at least partially, the variability in the reported rates between studies. Therefore, an integrated or side-by-side analysis is not appropriate, and it is not possible to use the available data to provide a single estimate of risk. Overall, in aggregate, the studies reported higher risk after Dose 2 compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination. The review of the post-marketing cases of myocarditis found that although the number of cases reported has increased with vaccine exposure increases, the profile of cases remains largely unchanged. Within this profile, a minority of cases (10%) qualify for BC level 1 classification, and thus provide a high degree of diagnostic accuracy. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-

marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration. Overall, no new or significant information regarding myocarditis or pericarditis became available. The reported data continues to align with the information presented in the EU SmPC. Therefore, no changes to the product information or risk management strategy are warranted. Myocarditis and pericarditis are important identified risks in the EU RMP and subject to close monitoring and extensive pharmacovigilance activities, routine and additional. This signal was closed on 10 November 2021 and the complete evaluation provided to PRAC in procedure EPITT: 19712. After the signal closure date, the PRAC requested the MAH to revise the EU SmPC to update the frequency of myocarditis and pericarditis to 'Very rare'. No new or significant safety information became available after the closure of the PRAC signal assessment procedure.

Rapporteur assessment comment:

The signal myocarditis, pericarditis for Comirnaty (EPITT ref. 19712) was initially confirmed on 08/06/2021 following the review of the 5th MSSR. Following the review of all available data within the signal procedure, the PRAC recommended on 08/07/2021 to update section 4.4 and 4.8 of the Comirnaty PI, and the dissemination of a DHPC.

The signal was reopened on 07/10/2021 following new data. After review of all available data, the PRAC recommended on 09/12/2021 to update section 4.4 and 4.8 of the Comirnaty PI: the warning in section 4.4 was considered adequate, however the wording was refined; the frequency category in section 4.8 was amended from 'not known' into 'very rare', including additional information in subsection 'Description of selected adverse reactions'.

Please refer to paediatric persons ≥5 years and ≤ 11 years of age, and paediatric persons ≥12 years in section 'Evaluation of special situations' of this AR for the interval data of the safety concerns myocarditis and pericarditis in paediatrics.

Signals determined not to be risks

Liver Injury/Autoimmune Hepatitis

The signal was opened on 10 November 2021 as a result of a notification from Australia TGA. The MAH conducted an analysis of the signal using clinical, post-marketing, literature and O/E analyses.

Autoimmune hepatitis has been infrequently reported following vaccination. However, most cases do not report sufficient relevant information (medical history, laboratory and other diagnostic data) to allow a proper evaluation. Among the cases that provided a medical history, the majority do report underlying hepatic disorders or concomitant autoimmune diseases that are known to have an increased incidence of developing autoimmune hepatitis independently of the trigger; in other cases, the diagnosis was a hypothesis or as part of a differential diagnosis. Even taking a conservative approach and including all 63 cases (irrespective of diagnostic certainty or causality), O/E ratios and the upper limit of the 95% CIs were well below 1 overall and for all ages assuming both 21- and 42-day risk windows, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. In a large double-blind placebo-controlled study of the vaccine there were zero (0) cases of autoimmune hepatitis in the Pfizer-BioNTech COVID-19 vaccine arm. Thus, the study results do not support an increased risk of autoimmune hepatitis between placebo and vaccine. The literature analysis did not reveal an increased risk of developing autoimmune hepatitis after Pfizer BioNTech COVID-19 vaccine administration. 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 that has not been realised until after hospitals resumed more normal operations following the initial months of the COVID-19 pandemic. Regarding liver injury AESIs, almost half of the cases (732/1680 received until 31 October 2021) were confounded by pre-existing hepatic

medical history, concurrent illnesses and/or co-suspect/concomitant medications which could predispose patients to a hepatic event. Thirty-one (31) cases reported liver injury, acute hepatic failure and/or hepatic failure. Most of these 31 cases reported a relevant event without any supporting clinical, diagnostic procedures, and/or laboratory values confirming the diagnosis. The remaining cases in the overall dataset reported PTs that in themselves were not reflective of a clinically significant hepatic impairment as they presented only isolated LFT laboratory abnormalities, or signs and symptoms that may be related to the liver. For liver injury, O/E ratios and the upper limit of the 95% CIs were well below 1 overall and for all ages assuming 21- and 42-day risk windows, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. In a large double-blind placebo-controlled study of the vaccine (21926 participants in the BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and 21921 participants in the placebo group) there were zero (0) cases of autoimmune hepatitis or liver injury in the Pfizer-BioNTech COVID-19 vaccine arm. Thus, the study results do not support an increased risk of autoimmune hepatitis or liver injury between placebo and vaccine. The MAH does not consider that the currently available information supports a causal association between the relevant conditions and the vaccine. The signal was closed on 15 December 2021.

No new or significant safety information about this closed signal was received after its signal evaluation and closure date.

Rapporteur assessment comment:

Please refer regarding the evaluation of the signal of autoimmune hepatitis to the separate procedure EPITT ref. 19749.

Thrombocytopenia Thrombosis Syndrome (TTS) (EMEA/H/C/005735/MEA/002.6)

The signal of TTS was opened on 6 July 2021 at the request of PRAC in the Assessment Report of 6th SSR.

Thrombosis with thrombocytopenia syndrome is a term coined by Brighton Collaboration to define the potential new clinical syndrome reported with COVID-19 vaccines. It should be noted, however, that thrombosis and thrombocytopenia may occur in patients for a variety of medical reasons that may not be related to vaccination at all. Additionally, anti-PF4 antibodies are thought to possibly assist with the diagnosis of this potential new clinical syndrome, however, the presence or absence of anti-PF4 antibodies should not be considered to be diagnostic of TTS associated with vaccination outside of the clinical presentation of the case. The Pfizer safety database was searched for BNT162b2 reports cumulative to 31 July 2021 using MedDRA (v 24.0) and the following search strategy: cases within the SMQ Embolic and thrombotic events were obtained, then the resulting dataset was searched for PTs in either the HLT Thrombocytopenias or HLT Platelet analysis to obtain the final dataset of cases with either thrombotic or embolic events plus thrombocytopenia, which revealed a total of 349 reports. Of the cases reviewed, those meeting BC criteria consistent with the highest level of certainty are the BC Level 1 cases with PF4 antibody (ELISA) test positivity. Of these 9 cases, there is not an apparent patient profile that can be discerned. The cases consist of males and females of a wide age range. The events occur after either dose and the medical backgrounds of the patients are also varied, with some having other medical conditions that would predispose to thrombocytopenia or blood clots. Given the several hundred million doses of Pfizer-BNT vaccine administered worldwide, the numbers of concerning cases remains relatively low. The signal was closed as refuted on 04 August 2021 and its complete evaluation was provided in 8th SSR (and subsequent reports as a safety topic).

No new or significant safety information about this closed signal was received after its signal evaluation and closure date.

Rapporteur assessment comment:

Within the 8th SSR, it was concluded that based on the information provided no new safety concern was identified and that it was acceptable that the MAH would not provide an update of the new cases in the following SSRs. Currently, the MAH described that no new significant safety information was identified after closure of the signal.

Myasthenia gravis (EMEA/H/C/005735/MEA/002.8)

The signal was initially opened as a non-validated signal due to an O/E >1 prior to the reporting interval and reported accordingly in the first PSUR.

During the reporting interval, the signal was re-opened and validated at the request of Health Canada following review of SMSR #7 considering that the upper level of the 95% CI exceeded 1 for both the 21-day and no risk windows in the interval period in the overall O/E analysis. The MAH conducted an analysis of the signal using clinical, post-marketing, literature and O/E analyses. 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 cut-off date 13 March 2021) found that MG was reported in 0 of 21926 participants in the BNT162b2 group compared with 0 of 21921 participants in the placebo group. The safety database search for PT myasthenia gravis cases reported up to 15 August 2021 using MedDRA 24.0 revealed a total of 56 cases which were reviewed in detail. Most spontaneous cases are confounded by a medical history reporting a pre-existing MG or other significant clinical risk factors (ongoing autoimmune disease and or cancer). Overall, 10 subjects reported the diagnosis confirmed by EMG and/or autoantibodies of which 5 had underlying autoimmune condition and 3 had an ongoing neoplasm. In the literature a worsening of MG symptoms after vaccination has not been identified as a risk while it is clearly reported that infections account for 40-70% of the exacerbations. In addition, if the patient is not medically optimised, s/he could develop a cytokine storm, despite being on steroids. Moreover, up to 15% of patients may experience worsening MG symptoms and/or exacerbations upon initiation of oral prednisolone therapy.

Further, O/E analysis does not suggest an increased rate for this topic. Based on the totality of the data, myasthenia gravis is not determined to be a causally associated adverse effect of the vaccine. This signal was closed on 25 August 2021 and the complete evaluation provided in 9th SSR.

No new or significant safety information about this closed signal was received after its signal evaluation and closure date.

Rapporteur assessment comment:

Within the 9th SSR, it was concluded that based on the information provided no new safety concern regarding myasthenia gravis was identified and that the signal could be closed. Currently the MAH described that no new significant safety information was identified after closure of the signal.

Immune Thrombocytopenia (EMEA/H/C/PSUSA/00010898/202106)

The signal was ongoing during the preparation of the last PSUR, and as its evaluation became available before the date of PSUR finalisation, it was provided in the first PSUR and it is herein summarised briefly for completeness. During the reporting interval, the signal was re-opened on 25 June 2021 at the request of FDA Office of Biostatistics and Epidemiology due to the Center for Medicare & Medicaid Services database showed this event as an AESIs as a signal for the Pfizer/BNT COVID-19 vaccine (any dose) with a relative risk >1, and also at the request of PRAC to provide the analysis in the first PSUR.

Phase 2/3 data from Study C4591001 placebo-controlled period (Dose 1 to 1 month after dose 2) for participants 16 years of age and older (data-lock date 13 March 2021) had 1 report of thrombocytopenia in the BNT162b2 group (N=21,926) and 1 in the placebo group (N=21,921). The Pfizer safety database was searched for BNT162b2 adverse event reports using MedDRA v 24.0 search strategy HLT Thrombocytopenias, received cumulatively to 18 June 2021. A total of 760 cases were retrieved from the safety database which were reviewed in further detail and according to BC criteria. The O/E were <1 for all analyses. Overall, the review of thrombocytopenia from clinical study data, post-authorisation spontaneous reports, medical literature and O/E analyses. While there are spontaneous post-vaccination reports of de-novo and worsening thrombocytopenia in patients with and without known thrombocytopenia, respectively, it is not outside of the range that would be expected without BNT162b2 vaccination. While it is acknowledged that patients with a diagnostic history of immune thrombocytopenia may be the most vulnerable to thrombocytopenia if precipitated by the vaccine, the undulating nature of the disorder calls into question the vaccine as the clear cause. A hypothesis can be made about an immune response and molecular mimicry as a mechanism for thrombocytopenia, but this would be speculative in nature. Based on the totality of the data, thrombocytopenia is not determined to be a causally associated adverse effect of the vaccine. This signal was closed on 04 August 2021 and the complete evaluation provided in the first PSUR.

No new or significant safety information about this closed signal was received after its signal evaluation and closure date.

Rapporteur assessment comment:

In the first PSUR (DLP 18 June 2021) a thorough review of cases of all available sources (CT and PM data, literature, O/E analysis) reporting ITP following vaccination with Comirnaty was provided. Overall, it was concluded that no new safety information was identified, and the topic will be continuously monitored through routine pharmacovigilance.

Herpes Zoster including Ophthalmic herpes zoster (EMEA/H/C/005735/MEA/002.7)

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in the first PSUR.

During the reporting interval, the signal was re-opened on 2 September 2021 at the request of PRAC in the Assessment Report for 8th SSR, following publication of Bada N et al., *Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting* (N Engl J Med, 25 Aug 2021). The signal evaluation included review of the clinical and post-marketing safety database, literature and O/E analysis.

In the Phase 2/3 safety population of Study C4591001 in participants ≥16 years of age, from dose 1 to 1 month post dose 2 (blinded placebo-controlled follow-up period), there were 12 cases of Herpes zoster and 1 case of Ophthalmic herpes zoster in the BNT group and 10 and 1 cases, respectively, in the placebo group. There was one placebo case of Herpes zoster in the Placebo group of Phase 1/2/3 study (C4591007) to evaluate up to 3 dose levels of BNT162b2 for safety, tolerability, immunogenicity, and efficacy in participants ≥5 to <12 years of age. The safety database was searched for all COVID vaccine (BNT162B2; BNT162B2s01) cases reported cumulatively through 07 September 2021 and MedDRA v 24.0 PTs: Genital herpes zoster; Herpes zoster, Herpes zoster cutaneous disseminated, Herpes zoster infection neurological; Herpes zoster meningitis; Herpes zoster meningoencephalitis; Herpes zoster meningomyelitis; Herpes zoster meningoradiculitis; Herpes zoster necrotising retinopathy; Herpes zoster oticus; Herpes zoster pharyngitis; Herpes zoster reactivation; Ophthalmic herpes zoster. Overall, the profile of the reports of herpes zoster in younger patients in close temporal association with vaccine administration align with the usual presentation of non-complicated herpes zoster and do not support a

difference in severity, treatment or medical care that would suggest particular precautions or changes in standard of care for these patients. The O/E ratios were well below 1 overall and for all ages assuming a 21-day risk window for estimating expected case count, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. Literature articles identified for this analysis were mainly case reports, followed by a few observational studies lacking data from comparison groups and/or background rates of herpes zoster that could provide more insight into a possible causal association between BNT/Pfizer COVID-19 vaccine and HZ. Of the literature that reported on actual studies that provided some measure/assessment of correlation between vaccination and zoster, there was 1 other study reported showing a slightly elevated risk ratio for post-vaccination herpes zoster infection compared to background, but it is not sufficient evidence to conclude a causal association given that there are other conflicting publications. Overall, the reviewed information does not indicate a causal association between the vaccine and herpes zoster. This signal was closed on 30 September 2021 and the complete evaluation provided in 10th SSR.

No new or significant safety information about this closed signal was received after its signal evaluation and closure date.

Rapporteur assessment comment:

After review of data from clinical studies, post-marketing reports, literature, O/E analyses on HZ, provided in the October 2021 SSR (EMEA/H/C/005735/MEA/002.9), it was concluded that no new safety information was identified, and signal was closed.

Appendicitis (EMEA/H/C/005735/MEA/002.9)

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in the first PSUR.

During the reporting interval, the signal was re-opened on 2 September 2021 at the request of PRAC in the Assessment Report for SMSR #8, following publication of Bada N et al., *Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting* (N Engl J Med, 25 Aug 2021). The signal evaluation included review of the clinical and post-marketing safety database, literature and O/E analysis.

In the Phase 2/3 safety population of Study C4591001 in participants ≥16 years of age, from the time of dose 1 to the unblinding date, the number of cases was similar in the two arms. There were 14 cases of appendicitis and 1 case of perforated appendicitis in the BNT162b2 group (15 cases total, N=21,926), and 9 cases of appendicitis, 2 cases of complicated appendicitis, and 1 case of perforated appendicitis in the placebo group (12 cases total, N=21,921). The data-lock date was 13 March 2021. The Pfizer safety database was searched for all BNT162b2 vaccine reports received through 08 September 2021 using MedDRA version 24.0 search criteria: PTs: appendicitis, appendicitis perforated; complicated appendicitis. Of the total 269 cases, 1/2 of the cases were eliminated from further analysis due to implausible latency and lack of causal relationship or insufficient clinical details. Subsequently, 1/4 of the cases either provided a clear alternate aetiology for appendicitis or were confounded by concurrent conditions and/or concomitant medications that may have predisposed to GI inflammation and/or appendicitis. Even without removing any cases, the O/E ratio was below 1 indicating no increased risk of appendicitis. Review of the literature review did not identify a significant safety information for vaccine associated appendicitis. Notably, a recent publication of an analysis of the VSD demonstrated that there was no increased risk of appendicitis. Overall, the reviewed information does not indicate a causal association between the vaccine and appendicitis. This signal was closed on 22 September 2022 and the complete evaluation provided in 10th SSR.

No new or significant safety information about this closed signal was received after its evaluation and closure date.

Rapporteur assessment comment: Following a review of all available data on appendicitis (post-marketing cases, published observational studies not reporting consistent results, no imbalance in the clinical studies, O/E ratios below 1) provided in the October 2021 SSR (EMEA/H/C/005735/MEA/002.9), it was concluded that no new safety information was identified, and closing of the signal was accepted.

2.2.2.2. *Signal Evaluation Plan for Ongoing Signals*

Table 26. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Vasculitis	The signal evaluation of vasculitis includes the review of clinical trial data, post-marketing safety database, literature and epidemiology analyses (O/E analyses)
Cerebral Venous Sinus Thrombosis (CVST)	The signal evaluation of CVST includes the review of clinical trial data, post-marketing safety database, literature and epidemiology analyses (O/E analyses)

Rapporteur assessment comment: Regarding vasculitis, please refer to the assessment of the adverse events of special interest (AESIs), vasculitic events below. Regarding CVST, please refer to the assessment of the adverse events of special interest (AESIs), stroke events below.

2.3. Evaluation of risks and safety topics under monitoring

Follow-up questionnaires

Response to the PRAC request 3 from the first PSUR (procedure EMEA/H/C/PSUSA/00010898/202106):

> *Regarding the follow-up questionnaires anaphylaxis and VAED/VAERD, the MAH should continue to re-assess the need for continuing this routine PhV activity and provide process data (e.g., response rate, need for corrective action).*

MAH's response:

The MAH has processes in place to conduct Data Capture Aid (DCA) usage review and performance metrics on a monthly basis to ensure that DCA questionnaires are utilized for cases meeting DCA follow-up criteria. For cases that meet DCA criteria but for which a DCA was not used (e.g., follow-up has been conducted without receiving additional information, or follow-up cannot be performed), the MAH records the reason the DCA was not used (e.g., DCA not used – consumer/reporter refused consent to contact HCP, reporter refused contact, reporter noncontactable, legal, Health Authority [HA], literature). Cases are not included within the monthly DCA report when a HA has stated that they will not accept follow-up for these cases or that the HA will conduct the follow-up.

A DCA Performance Monthly Report is generated to include a summary and a detailed report by product of the DCA review findings and any actions taken if a specific issue or concern was identified to ensure

DCA follow-up. The response rate and the clinical significance of the information received through the special follow up is not routinely tracked in this process, and thus it cannot be described in this response.

The most recent DCA monthly report includes data through November 2021 (Table 1). To align with the time period of the PSUR, DCA metrics were captured for 6 calendar months, i.e., from June 2021 through November 2021. Two DCAs for BNT162b2 were effective during this period: VAED and Anaphylaxis.

Table 1. Monthly Data Capture Aid – June 2021 through November 2021

Month Year	Cases received potentially meeting DCA criteria	DCA used	Non-HCP Reporter	FU Unfeasible[a]	Reporter refused consent or contact; contact by phone no response; office closed no contact details (pandemic)	Literature source	Contact details withheld/ no contact details, reporter unidentifiable or non-contactable	DCA used previously	License partner	Legal/ EV-web report	Reporter is Health Authority	Case Did not meet reporting criteria	Retrospectively used DCA
Jun-21	12,626	2,325	1,165	196	127	23	330	401	239	9	7544	232	35
Jul-21	12,890	3024	935	172	214	101	420	64	1	6	7721	191	30
Aug-21	11,431	1,949	2,113	226	183	37	577	154	40	50	5885	148	10
Sep-21	13,691	2,793	1078	262	372	24	896	226	60	29	7416	535	
Oct-21	17,521	1778	1099	159	484	55	769	167	131	1	11045	1829	2
Nov-21	6128	537	391	55	94	81	889	63	29	4	3979	6	
Total	74,287	12,406	6,781	1,070	1,474	321	3,881	1,075	500	99	43,590	2,941	77
Percentage of all cases		16.7%	9.1%	1.4%	2.0%	0.4%	5.2%	1.4%	0.7%	0.1%	58.7%	4.0%	0.1%

[a] Refused to provide f/u, f/u not possible, no additional info or no new clinical information or initial information complete

As shown in table 1, during this period, a total of 74,287 cases were received that reported events potentially meeting the VAED or Anaphylaxis DCA follow up criteria. Of them, a DCA was used in 12,406 cases (16.7%). The main reasons DCAs were not sent were:

- initial report was from a regulatory authority source (43,590; 58.7%),
- initial report was from a consumer non-HCP (6,781; 9.1%), and
- initial report was from a non-contactable reporter (3,881; 5.2%).

Of the DCAs sent during this period, 9.4% were in compliance with the internal case follow up timelines, whereas the remaining 0.6% (consisting of 77 reports) were followed up retrospectively as a corrective action following their identification in a monthly compliance evaluation.

The DCA metrics reveal that special follow up is only possible for a minority of cases (<20%) cases potentially meeting follow up criteria. The MAH conducts quality and compliance activities to ensure that corrective actions are implemented promptly for missing follow up. To date, corrective actions were only required for a very small percentage of cases that required a DCA follow up (<1%). The reasons that the remaining 80% of cases potentially requiring DCA follow-up, are not sent a DCA is due to the report source (e.g., regulatory authority, non-HCP consumer, non-contactable reporter). In these situations, corrective actions cannot be taken. Such cases severely impair the MAH ability to improve the quality of information in the safety reports to enable a thorough medical analysis.

As part of the routine PV and safety surveillance and risk management activities, the MAH is continuously monitoring the use and value of the risk management measures, including but not limited to the special follow up activities. The MAH plans to conduct further evaluation of DCA effectiveness in the coming future with the objective of analyzing the response rate and clinical and safety value of the responses

received in the follow up activities and will report results and/or recommended actions in future aggregate reports or Risk Management Plan as appropriate.

Rapporteur assessment comment:

During the 6-month period June through November 2021, there were 74,287 cases that reported events for VAED or Anaphylaxis DCA follow up. A DCA was sent to 12,406 of the 74,287 cases (16.7%). The remaining 61,881 cases (83.3%) were not send a DCA because the report source was a regulatory authority, a non-HCP consumer, or a non-contactable reporter. Corrective actions were required for <1% of the cases which is considered a very low percentage. The MAH stated that no response rates could be presented because this was not routinely tracked and that the MAH will further evaluate the DCAs response rate and clinical/safety value of the responses received in future reports, which is endorsed.

Regarding if the follow-up questionnaires can be discontinued, 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. **Request for next PSUR**

Issue partly solved

Evaluation of Important Identified Risks

Anaphylaxis

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

Clinical trial data

- Number of cases: 2 (0.28% of 721 cases of the total CT dataset), compared to 1 case (0.14%) retrieved in the first PSUR. The investigator and the Sponsor reported that there was not a reasonable possibility that the events anaphylactic reactions in both cases were related to the blinded study vaccine/BNT162b2, or clinical trial procedure. In 1 case the participant had an anaphylaxis secondary to insect bite and the other case reported acute anaphylaxis reaction to walnuts.

Post-marketing data

- Number of relevant cases: 3507 (0.53% of 657,528 cases, the total PM dataset), compared to 3827 cases (1.2%) retrieved in the first PSUR, of which 2705 medically confirmed cases.
- Subjects' gender: female (2655), male (714) and unknown (138).
- Subjects' age in years: n = 3250, range: 8-98, mean: 43.5, median: 43.0.
- Relevant event seriousness: serious (3654), non-serious (3).
- Reported relevant PTs: Anaphylactic reaction (3015), Anaphylactic shock (552), Anaphylactoid reaction (87), Anaphylactoid shock (3).
- Time to event onset (n=3008), range: <24 hours to 151 days, median: 0 days.
- Duration of relevant events (n=1195 out of 1929 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 102 days, median: 0 days.

- Relevant event outcome : fatal (19), resolved/resolving (2573), resolved with sequelae (64), not resolved (273), unknown (734).
- Paediatric (179), Adults (2694), Elderly (401) and Unknown (233). No significant difference observed in the reporting proportion of anaphylaxis relevant PTs between paediatric, adult and elderly populations (0.91.% in paediatric vs 0.55% in adults vs 0.46% in elderly).
- Number of subjects with comorbidities: 733 (21% of the cases reporting anaphylaxis). The reporting proportion of anaphylaxis related events with fatal outcome (0.8%) is comparable in individuals with comorbid conditions when compared to the reporting proportion (0.5%) observed in the individuals without comorbidities.

Literature

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

MAH's conclusion

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

Rapporteur assessment comment:

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

Following discussions by PRAC on the need to have anaphylaxis included as an important identified risk in the EU RMP of Comirnaty and other COVID-19 vaccines, a request was made from EMA to the MAH to consider at the next regulatory opportunity to reclassify anaphylaxis as not "important", discuss it in RMP section SVII.2, and remove it from the RMP list of safety concerns.

Myocarditis and Pericarditis

Myocarditis search criteria - PTs: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis.

Pericarditis search criteria - PTs: Autoimmune pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

There were 10822 potentially relevant cases of Myocarditis and Pericarditis: 6350 cases reported myocarditis and 5312 cases reported pericarditis (in 840 of these 10822 cases, the subjects developed both myocarditis and pericarditis):

- **Myocarditis cases** medically confirmed and having a TTO ≤ 21 days: 2007 cases were individually reviewed and assessed according to BC Myocarditis Case Definition and Level of Certainty Classification (version 1.5.0, 16 July 2021):

Age group	Brighton Collaboration Level (no. of cases)				
	1	2	3	4	5
5-11	0	0	0	6	0
12-15	28	41	6	167	7
16-17	46	22	2	151	3
18-24	82	67	10	336	12
25-29	32	20	2	133	3
30-39	38	21	3	198	11
40+	48	39	11	352	10
Unknown	1	2	0	96	1
Total	*275*	*212*	*34*	*1439*	*47*

Level 1 indicates a definitive case (i.e. it includes criteria for the highest level of diagnostic certainty of myocarditis), level 2 indicates a probable case, and level 3 indicates a possible case.
Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.

- Country of incidence (>5 occurrence): France (123), Spain (33), Japan (18), UK (11), Czech Republic, Germany, Sweden (10 each), Denmark, Italy (9 each), Netherlands (7), and Switzerland (6). The remaining 29 cases were distributed among 16 countries.
- Subjects' gender: female (47) and male (228);
- Subjects' age in years (n =274): range: 12 – 84, mean: 27.7, median 22.0.
- Medical history (n=164): medical conditions (≥10 occurrences) included Tobacco user (34), Myocarditis (16), Asthma (13), Obesity (12), Hypertension and Alcohol use (10).
- Time to event onset: <24 hours: 13 events; 1-5 days: 180 events; 6-13 days: 55 events; 14-21 days: 27 events.
- Duration of relevant events (for those cases where the event resolved); n=39; Up to 3 days: 7 events; 4-6 days: 15 events; 7-31 days: 17 events.
- Most frequently co-reported PTs (≥20 occurrence): Chest pain (107), Pyrexia (69), Dyspnoea (31), Headache (26), Troponin increased (24), Nausea (22).
- Relevant event outcome: fatal (4), resolved/resolving (207), resolved with sequelae (7), not resolved (43) and unknown (14).

- **Pericarditis cases** medically confirmed and having a TTO ≤ 21 days: 1461 cases were individual reviewed and assessed according to the Brighton Collaboration (BC) Pericarditis Case Definition and Level of Certainty Classification (version 1.0.0, 15 July 2021):

Age group	Brighton Collaboration Level (no. of cases)				
	1	2	3	4	5
5-11	0	0	0	1	0
12-15	3	14	1	67	8
16-17	2	10	2	53	5
18-24	1	15	5	175	12
25-29	4	7	5	136	17
30-39	1	10	2	275	24
40+	11	13	9	477	27
Unknown	0	0	0	68	1
Total	*22*	*69*	*24*	*1252*	*94*

Level 1 indicates a definitive case (i.e. it includes criteria for the highest level of diagnostic certainty of pericarditis), level 2 indicates a probable case, and level 3 indicates a possible case.
Level 4 is defined as "reported event of pericarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of pericarditis.

- There were 22 cases assessed as BC level 1. For this cluster of BC level 1 cases, there were 13 males and 9 females between 12 and 93 years of age (mean=40.6, median=38.5). All cases were assessed as serious due to hospitalisation and/or medically significant (15) or due to medically significant (7); none had a serious outcome. In 16 cases pericarditis occurred within 1 week post vaccine administration. The reporting countries in that BC level 1 cluster were France (10), Japan (3), Czech Republic, Italy (2 each), the remaining 5 cases originated from 5 different countries. Insufficient description of cardiovascular and/or non-cardiovascular medical history and diagnostic to rule out other aetiologies in majority of these cases continues to preclude proper medical adjudication of causality assessment between administration of the vaccine and occurrence of Pericarditis.

Literature

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

MAH's conclusion

Evaluation of Myocarditis and Pericarditis did not reveal any significant new safety information for this interval. Based upon review of the available information, no additional change to the RSI is warranted at this time. Activities to further characterise myocarditis and pericarditis following Pfizer/BioNTech COVID-19 vaccination are in progress and new safety information will be communicated as it becomes available.

Rapporteur assessment comment:

Myocarditis and pericarditis are closely monitored through the SSRs for Comirnaty in which the MAH is requested to use a broader search strategy to identify relevant publications and other pieces of information to further characterise the risk of myocarditis and pericarditis, especially in terms of outcomes as well to explore whether risk mitigation strategies would be feasible (procedure EMEA/H/C/005735/MEA 002.12).

Please refer to the separate EU procedures EMEA/H/C/005735/II/0059 and EMEA/H/C/005735/SDA/032 concerning myocarditis and pericarditis. Following the PRAC meeting in July and December 2021, myocarditis and pericarditis were added to sections 4.4. and 4.8 of the Comirnaty SmPC, and the package leaflet accordingly.

No new important safety information concerning myocarditis and pericarditis could be identified.

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: 1490 (0.2% of 657,528 cases, the total PM dataset), compared to 584 (0.2%) retrieved in the first PSUR of which 1164 medically confirmed cases. All cases were serious.
- Gender: female (720), male (743), and unknown (27).
- Age in years (n = 1435), range: 12 – 104, mean: 68.0, median: 73.0.
- Reported relevant PTs by organ system:
    - Respiratory system PTs (1413): COVID-19 pneumonia (684), Dyspnoea (444), Hypoxia, Respiratory failure (67 each), Pulmonary embolism (53), Acute respiratory distress syndrome (51), and Tachypnoea (47).
    - Gastrointestinal/Hepatic system PTs (350): Diarrhoea (208), Vomiting (89), Abdominal pain (52), and Jaundice (1);
    - Cardiovascular system PTs (146): Myocarditis (77), Cardia failure (45), Arrhythmia (18), Acute myocardial infarction (4), and Cardiogenic shock (2);
    - Renal and urinary system PTs (71): Acute kidney injury (44), and Renal failure (27);
    - Nervous system PTs (45): Cerebrovascular accident, Seizure (15 each), Altered state of consciousness (13), and Encephalopathy (2);
    - Vascular system PTs (19): Deep vein thrombosis (9), Peripheral ischaemia (5), Shock (4), and Vasculitis (1);
    - Blood and lymphatic system PTs (16): Thrombocytopenia (16).

- Immune system PTs (7): Vaccine associated enhanced disease (4), and Multisystem inflammatory syndrome in children (3);
- Other PTs (17): Multiple organ dysfunction syndrome (14), Chillblains (2), and Erythema multiforme (1).

- Case outcome: fatal (278), not resolved (417), resolved/resolving (608), resolved with sequelae (15), and unknown (172).
- COVID-19 positivity:
  - Suspected COVID-19 infection: 161 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (156 cases) or to Vaccination failure (5 cases)] ;
  - Confirmed COVID-19 infection: 1329 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (585 cases) or Vaccination failure (744 cases, 4 of these cases also co-reported Vaccine associated enhanced disease)].

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: 35 (blinded therapy [6], BNT162b2 [26] and placebo [3]) (4.9% of 721 cases, the total CT dataset) compared to 33 cases (4.7%) retrieved in the first PSUR.
- Country of incidence: US (31), Argentina (3), Germany (1).
- Subjects' gender: female (8), and male (27).
- Subjects' age in years (n = 35), range: 18-83, mean: 61.6, median: 62.0.

- Medical history (n = 33): the reported relevant medical conditions (>2 occurrence) included Hypertension (13), Blood cholesterol increased, Coronary artery disease, Type 2 diabetes mellitus (3 each).
- COVID-19 medical history: None.
- Co-suspect medications: alendronate, dulaglutide, fexofenadine, fluoxetine, glipizide, losartan, and metformin (1 each).
- Reported relevant PTs: Coronary artery disease (10), Acute myocardial infarction (9), Myocardial infarction (8), Chest pain (5), Cardiac failure, Cardiogenic shock, Postural orthostatic tachycardia syndrome, and tachycardia (1 each).
- BNT162b2 related event coded to the PT: Tachycardia (1). Time to onset of event 7 days and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-authorization data

- Number of cases: 29,486 (4.5% of 657,528 cases, the total PM dataset), compared to 8398 (2.6%) cases retrieved in the first PSUR; medically confirmed cases (11,537).
- Country of incidence (>100 occurrence): Germany (5148), UK (4302), France (3244), Australia (2539), Italy (2350), US (1615), Japan (1498), Netherlands (1456), Canada (624), Spain (475), Taiwan, Province of China (465), Norway (426), Sweden (422), Finland (407), Mexico (361), Austria (313), New Zealand (296), Ireland (267), Greece (266), Czech Republic, Denmark (253 each), Belgium (245), Philippines (234), Brazil (209), Malaysia (167), Lithuania (159), Romania (135), Portugal (132), Croatia (121), and Switzerland (108); the remaining 996 cases were distributed among 56 countries.
- Subjects' gender: female (17,914), male (11,003) and unknown (568).
- Subjects' age in years (n = 27,696), range: 2 – 109, mean: 43.1, median: 41.0.
- Medical history (n = 12,050 cases): the most frequently (>200 occurrence) reported relevant medical conditions included Hypertension (1874), Diabetes mellitus (440), Obesity (373), Tobacco user (371), Atrial fibrillation (343), Type 2 diabetes mellitus (293), Depression (289), Arrhythmia (275), Chest pain (255), Anxiety (242), Myocardial infarction (232), and Dyslipidaemia (213).
- COVID-19 Medical history (n = 1670 cases): the medical conditions reported included COVID-19 (946), Suspected COVID-19 (693), Post-acute COVID-19 syndrome (28), COVID-19 pneumonia (13), Asymptomatic COVID-19 (12), Coronavirus infection, SARS-CoV-2 test positive (11 each), Exposure to SARS-CoV-2 (9), SARS-CoV-2 antibody test positive (3).
- Co-suspects (n = 282 cases): the frequently (>5 occurrences) reported relevant co-suspect medication was adalimumab (8).
- Number of relevant events: 32,034.
- Relevant event seriousness: serious (16,434), non-serious (15,606).
- Relevant PTs: Chest pain (17,526), Tachycardia (8253), Arrhythmia (3294), Myocardial infarction (1211), Cardiac failure (807), Acute myocardial infarction (479), Cardiac failure acute (113), Postural orthostatic tachycardia syndrome (104), Coronary artery disease (101), Cardiogenic shock (92), and Stress cardiomyopathy (54).
- Time to event onset (n = 23,422 occurrences), range: <24 hours to 377 days, median: 1 day.

- Duration of relevant events (n = 4196 out of 8137 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 214 days, median: 1 day.
- Relevant event outcome:47 fatal (803), resolved/resolving (13,481), resolved with sequelae (844), not resolved (9970), unknown (7065).
    - In the 729 cases (reporting 803 relevant events with a fatal outcome), the reported cause of death (>20 occurrences) were coded to PTs Myocardial infarction (248), Cardiac failure (167), Acute myocardial infarction (92), Chest pain (62), Arrhythmia (59), Cardiac arrest (58), Cardio-respiratory arrest (56), Cardiac failure acute (54), Dyspnoea (52), Death (32), Pyrexia (30), Cardiogenic shock (28), Myocarditis (22), and Tachycardia (21). Of the 729 cases, 374 cases involved elderly subjects. Significant medical conditions included hypertension (185), diabetes mellitus (60), cardiac failure (47), atrial fibrillation (43), chronic kidney disease (32), chronic obstructive pulmonary disease, myocardial infarction (31 each), obesity (28), myocardial ischaemia (27), dyslipidaemia (26), type 2 diabetes mellitus (25), coronary artery disease (24), dementia (23), asthma, tobacco user (22 each), arteriosclerosis, cardiac failure chronic, cerebral infarction, and hyperlipidaemia (21 each).

Analysis by age group

- Clinical trials: Adults (18), and Elderly (17).
    - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (1587), Adults (22,658), Elderly (3874) and Unknown (1367).
    - Higher reporting proportion of events coded to the PTs Acute myocardial infarction, Arrhythmia, Cardiac failure, and Myocardial infarction was reported in elderly population when compared to adult and paediatric population (Acute myocardial infarction [1.2% in adults vs 0.2% in paediatrics vs 5.3% in elderly], Arrhythmia [10.7% in adults vs 3.4% in paediatrics vs 18.6% in elderly], Cardiac failure [1.1% in adults vs 0.2% in paediatrics vs 13.4% in elderly], and Myocardial infarction [2.8% in adults vs 0.5% in paediatrics vs 11.6% in elderly]).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 4961 (0.8% of 657,528 cases, the total dataset).
- The reporting proportion of cardiovascular AESIs with fatal outcome (1.1%) is similar in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.3% 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 (PTs: Cardiac failure; Cardiac failure acute); 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:

A relative increase of the number of cases reporting cardiovascular AESIs was received, 29,486 (4.5% of the total PM dataset) cases compared to 8398 (2.6%) cases in the previous 1st PSUR. However, there was substantial increased Comirnaty exposure during the current reporting period compared to the previous reporting period from 635 Mio doses up to 1.4 billion doses.

In the performed O/E analysis all O/E ratios were below 1 and, when available, age stratified O/E ratios were also <1.

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

Haematological AESIs

Search Criteria: *HLTs (All Path) Leukopenias NEC; Neutropenias OR PT Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms).*

Clinical trial data

- Number of cases: 17 (BNT162b2 [9] and blinded therapy [8]) (2.4% of 721 cases, the total CT dataset) compared to 19 cases (2.7%) retrieved in the first PSUR.

Post-authorisation data

- Number of relevant cases: 37,327 (5.7% of 657,528 cases, the total PM dataset), compared to 9430 cases (2.9%) retrieved in the first PSUR.

O/E analysis

- O/E analysis was performed for Haemorrhage: 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:

Haematological AESIs were continuously monitored in the SSRs for Comirnaty during the reporting period.

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

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: 3 (blinded therapy [2] and BNT162b2 [1]) (0.4% of 721 cases, the total CT dataset) compared to 18 cases (2.6%) retrieved in the first PSUR.

Post-authorisation data

- Number of relevant cases: 25,453 (3.9% of 657,528 cases, the total PM dataset), compared to 12,058 cases (3.7%) retrieved in the first PSUR.

O/E analysis

- O/E analysis was performed for Ageusia and Anosmia: 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:
COVID-19 AESIs were continuously monitored in the SSRs 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

- During the reporting period no serious cases from the CT dataset were reported.

Post-authorization data

- Number of cases: 339 (0.05% of 657,528 cases, the total PM dataset), compared to 178 (0.05%) cases retrieved in the first PSUR; medically confirmed cases (235).
- Country of incidence: Japan (70), France (60), UK (43), Italy (31), Australia (30), Germany (21), Netherlands (11), US (9), Ireland, Spain (8 each), Finland (7), Norway (5); the remaining 36 cases were distributed among 19 countries.
- Subjects' gender: female (210), male (120) and No data (9).
- Subjects' age in years (n = 317), range: 12-98, mean: 49.7, median: 49.0
- Medical history (n = 157): the most frequently (≥4 occurrences) reported relevant medical conditions included Erythema multiforme (9), Seasonal allergy (7), Drug hypersensitivity, Food allergy (6 each), Hypothyroidism (5), Allergy to animal, Chillblains (4 each).
- COVID-19 Medical history (n = 13): COVID-19 (8), Suspected COVID-19 (4), and Asymptomatic COVID-19 (1).
- Co-suspects (n = 11): Influenza Vaccine (surface antigen, inactivated, adjuvanted) (1).
- Number of events: 339; serious (249), non-serious (90).
- Reported relevant PTs: Erythema multiforme (231), Chillblains (108)
- Time to event onset (n = 244), range: <24 hours to 77 days, median: 3 days.
- Duration of relevant events (n = 45 out of 95 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 49 days, median: 9 days:
- Relevant event outcome:47 resolved/resolving (178), resolved with sequelae (6), not resolved (112), unknown (44).

Analysis by age group

- Post-marketing: Paediatric (21), Adults (212), Elderly (91) and Unknown (15).

- 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 event chillblains between adult and elderly population.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 72 (21.2% of the cases reporting dermatological AESIs). A higher reporting proportion of dermatological AESIs was reported in subjects without significant comorbidities (78.8%) 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

Erythema multiforme was a safety topic determined to be validated signal, categorised as "no risk". 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 to the signal procedure (EMEA/H/C/005735/SDA/034, EPITT ref. 19721) in which erythema multiforme was included as ADR in the product information of Comirnaty.

No new important safety concern could be identified for dermatological AESIs

Facial paralysis

Search Criteria: *PTs Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis.*

Clinical trial data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the first PSUR.

Post-authorization data

- Number of cases: 4515 (0.7% of 657,528 cases, the total PM dataset), compared to 2392 cases (0.7%) retrieved in the first PSUR; medically confirmed cases (2232).
- Country of incidence: Germany (925), France (669), UK (409), Australia (339), Italy (266), Hong Kong (234), Japan, US (173 each), Netherlands (154), Sweden (113), Spain (112); the remaining 948 cases were distributed among 45 countries.
- Subjects' gender: female (2478), male (1845), and unknown (192).
- Subjects' age in years (n = 4151), range: 12 – 99, mean 54.5, median 47.0
- Medical history (n = 1826): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (392), Diabetes mellitus (101), Obesity (80), Hypothyroidism (76), Facial paralysis, Type 2 diabetes mellitus (65 each), Bell's palsy (56), Migraine (55), Tobacco user (51), Depression (46), Dyslipidaemia (39), Cerebrovascular accident and Hypercholesterolaemia (37 each).
- COVID 19 Medical history (n = 149): reported medical conditions were coded to the PTs COVID 19 (90), Suspected COVID 19 (58), Coronavirus infection (2), Exposure to SARS CoV 2, Post-acute COVID 19 syndrome, and SARS CoV 2 test positive (1 each).

- Co-suspects (n = 47): the relevant co suspect vaccines/medications were botulinum toxin type A and Diphtheria vaccine toxoid, HIB vaccine, Pertussis vaccine, Polio vaccine inact, Tetanus vaccine toxoid (1 each).
- Number of relevant events: 4515; serious (4246) and non-serious (284).
- Reported relevant PTs: Bell's palsy (1539), Facial paralysis (2289), Facial paresis (686), and Oculofacial paralysis (1).
- Time to event onset (n = 3425 events), range: <24 hours to 273 days, median 6 days.
- Duration of relevant events (n = 396 out of 861 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 201 days, median: 5 days.
- Relevant event outcome: fatal (1), resolved/resolving (1630), resolved with sequelae (120), not resolved at the time of reporting (1737), and unknown (1042).
    - In the single fatal case, the cause of death was coded to the PTs Aphasia, Brain oedema, Cerebral haematoma, Cerebrovascular accident, Facial paralysis, Fall, Haematoma, Hemiplegia, and Respiratory distress. The case involved an 82 year old female subject with a medical history of articular calcification, atrial fibrillation, cerebral amyloid angiopathy, and haemorrhagic stroke.

Analysis by age group

- Post-marketing: Paediatric (142), Adults (3241), Elderly (803) and Unknown (329).
- 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: 745 (16.5% of PM cases reporting facial paralysis, no CT cases reported).
- Only 1 case reported a fatal outcome for the relevant event coded to the PT Facial paralysis and hence a meaningful comparison cannot be made.

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. It is anticipated that large epidemiologic surveillance studies will contribute to the assessment of facial paralysis in a meaningful way. Of note, cases of Bell's palsy are being collected in epidemiology studies that are both primary data collection studies (e.g., C4591008, C4591010) and secondary data collection studies (e.g., C4591009, C4591011, C4591012, C4591021).

Rapporteur assessment comment:

No new important safety concern could be identified for facial paralysis.

Hepatic AESIs

Search Criteria: *SMQ Liver related investigations, signs and symptoms (Narrow and Broad) OR PT Liver injury*.

Clinical trial data

- Number of cases: 2 (BNT162b2) (0.28% of 721 cases, the total CT dataset) compared to 1 case (0.14%) retrieved in the first PSUR.
- Country of incidence: US (2).
- Subjects' gender: female (2).
- Subjects' age: 52 and 64 years respectively.
- Medical history (n=2): relevant medical history included Hypothyroidism and Blood cholesterol increased (1 each).
- COVID 19 Medical history: None.
- Relevant Co-suspect medication: Atorvastatin (1).
- Reported relevant PT: Hepatic enzyme increased (2), not related to BNT162b2.

Post-authorization data

- Number of relevant cases: 1393 (0.2% of 657,528 cases, the total PM dataset), compared to 550 cases (0.2%) retrieved in the first PSUR; medically confirmed cases (867).
- Country of incidence: Japan (317), France (239), Germany (165), UK (102), US (92), Italy (85), Spain (48), Netherlands (43), Australia (42), Canada (27), Norway (24), Denmark (19), Finland (18), Austria (17), Sweden (16), New Zealand (13), Greece (12), Belgium, Taiwan, province of China (11 each), Czech Republic (10), Brazil, Portugal (8 each), Switzerland (7), Hungary (6), Ireland, Poland, Romania (5 each); the remaining 38 cases were distributed among 19 countries.
- Subjects' gender: female (797), male (557), and no data (39).
- Subjects' age in years (n = 1306), range: 12 – 109, mean: 52.6, median: 52.0.
- Medical history (n = 823): the most frequently reported relevant medical conditions (≥ 5 occurrences) included Dyslipidaemia (42), Diabetes mellitus (37), Hypothyroidism, Type 2 diabetes mellitus (34 each), Obesity (29), Cholecystectomy, Hypercholesterolaemia (19 each), Alcohol use (16), Hyperlipidaemia (13), Hepatic steatosis (9), Hepatic function abnormal (7), Hepatic cirrhosis, Type 1 diabetes mellitus (6 each), and Liver disorder (5).
- COVID 19 Medical history (n = 61): the medical conditions reported included COVID 19 (36), Suspected COVID 19 (20), COVID 19 pneumonia (2), Asymptomatic COVID 19, COVID-19 immunisation, and Exposure to SARS-CoV-2 (1 each).
- Co-suspects (n = 62): the relevant co suspect medications reported were methotrexate (4), adalimumab (3), amoxicillin, apixaban, paclitaxel (2 each), atorvastatin, amiodarone, cyclophosphamide, etoposide, ibuprofen and palbociclib (1 each).
- Number of relevant events: 1917; serious (933) and nonserious (984).
- Most frequently reported relevant PTs (≥50 occurrences): Alanine aminotransferase increased (241), Aspartate aminotransferase increased (206), Hepatic function abnormal (199), Hepatic enzyme increased (165), Gamma-glutamyltransferase increased (164), Liver function test abnormal (113), Transaminases increased (103), Hepatic pain (102), Blood bilirubin increased

(83), Liver function test increased (73), Ascites, Blood alkaline phosphatase increased (72 each), Hepatomegaly (63).

- Time to event onset (n = 1275 events) , range: □24 hours to 174 days, median: 7 days.
- Duration of relevant events (n = 133 out of 299 occurrences with outcome of resolved/resolved with sequelae), range: 10 minutes to 180 days, median: 25 days.
- Relevant event outcome: fatal (14), resolved/resolving (638), resolved with sequelae (23), not resolved at the time of reporting (330), and unknown (913).
    - In 13 cases (reporting 14 relevant events with a fatal outcome), the cause of death were coded to the PTs Hepatic function abnormal (5), Ascites (4), Congestive hepatopathy (2), Hepatic enzyme increased, Hepatomegaly, and Transaminase increased (1 each). Nine (9) of the 13 cases involved subjects who were ≥60 years of age.
    - When the medical history was provided (11 cases), the subject's medical condition included Type 2 diabetes mellitus (6), Diabetes mellitus (5), Hepatic cirrhosis (2), Hepatic cancer, Hepatic encephalopathy, Hyperlipidaemia, Hypothyroidism, Hepatic neoplasm and Transaminases increased (1 each).

Analysis by age group

- Clinical trial: Adult (2).
- Post-marketing: Paediatric (66), Adults (835), Elderly (418) and No data (74).
    - Among the frequently (≥2%) reported relevant hepatic events, PT Hepatic pain was reported significantly higher in adult population when compared to elderly population (16% in adult vs 6% in elderly). Upon further review, the majority of the events (hepatic pain) was assessed as non-serious in adult population (55 of 76 events).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 419 (30% of the CT and PM cases reporting hepatic AESIs).
- The reporting proportion of hepatic AESIs with fatal outcome (1.5%) is slightly higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (0.6%).

O/E analysis

- O/E analysis was performed for Acute liver injury/Liver injury: all O/E ratios <1.

MAH's conclusion

Hepatic events were a safety topic determined to be validated signal, categorised as "no risk". 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:

Regarding autoimmune hepatitis, please refer to the separate signal procedure EMEA/H/C/005791/SDA/054 (EPITT 19749).

Relevant medical history was reported in 823 (59%) of the 1393 cases reporting hepatic AESIs, and the reporting proportion of hepatic AESIs with fatal outcome was slightly higher in cases with comorbid conditions compared to cases without comorbidities, 1.5% versus 0.6% respectively.

No other new important safety concern could be identified for hepatic AESIs.

Immune-mediated/autoimmune AESIs

Search Criteria: *SMQ Immune-mediated/autoimmune disorders (Broad and Narrow) OR HLGT (All Path) Autoimmune disorders OR PTs Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity; Hypersensitivity myocarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis; Thyroiditis subacute.*

Clinical Trial Data

- Number of cases: 20 (BNT162b2 [13], blinded therapy [7], and placebo [1]) (2.8% of 721 cases, the total CT dataset) compared to 15 cases (2.1%) retrieved in the first PSUR.

Post-authorization data

- Number of cases: 21,994 (3.3% of 657,528 cases of the total PM dataset), compared to 6902 cases (2.1%) retrieved in the first PSUR.

Analysis by age group

- Clinical trial: Paediatric (2), Adults (12), and Elderly (6).
- Post-marketing: Paediatric (1649), Adults (15,537), Elderly (3195) and Unknown (1613).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 4703 (21.4% of the CT and PM cases reporting immune mediated/autoimmune AESIs).

O/E analysis

- O/E analysis was performed for Autoimmune thyroiditis, Encephalitis, Myasthenia gravis, Transverse myelitis, Myocarditis, Pericarditis, Polymyalgia rheumatica, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Type 1 diabetes mellitus, and Urticarial vasculitis: except for myocarditis, and myocarditis/pericarditis, all O/E ratios are below 1.

MAH's conclusion

Primary analysis (global): overall O/E, only myocarditis using the low, mid, and high background rates meet the signal criteria with the upper limit of the O/E 95% CI >1 in at least one risk window.

Age-specific analyses (EEA and US): myocarditis, and myocarditis/pericarditis are noted to have O/E >1 in at least one age-group and risk window.

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:

Regarding myocarditis and pericarditis, please refer to section 'Evaluation of Important Identified Risks' of this assessment report.

Regarding myasthenia gravis, an updated cumulative review up to 11 Oct 2021 was assessed in the 11th SSR (procedure EMEA/H/C/005735/MEA/002.10). It was concluded that there was insufficient evidence to support a causal association between the vaccine and development or worsening of myasthenia gravis.

Regarding exacerbation of autoimmune/inflammatory disorders, please refer to 'Exacerbation (flare-up) of pre-existing AI/Inflammatory Disorders' in section 'Post-approval regulatory requests' of this assessment report. In this section, also a review of subacute thyroiditis is assessed.

Regarding thrombocytopenia thrombosis syndrome (TTS), in the 8th SSR (procedure EMEA/H/C/005735/MEA/002.7) it was concluded that no new safety concern was identified.

Immune-mediated/autoimmune AESIs were continuously monitored in the SSRs 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 Autoinflammatory disease; Cytokine release syndrome; Cytokine storm; Distributive shock; Haemophagocytic lymphohistiocytosis; Hypotensive crisis; Kawasaki's disease; Macrophage activation; Macrophages increased; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Septic shock; Systemic inflammatory response syndrome; Toxic shock syndrome; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease.*

Clinical Trial Data

- Number of cases: 2 (BNT162b2 [2]) (0.3% of 721 cases, the total CT dataset) compared to 3 cases (0.3%) retrieved in the first PSUR.

Post-authorization data

- Number of relevant cases: 438 (0.07% of 657,528 cases of the total PM dataset), compared to 183 (0.1%) retrieved in the first PSUR.

Analysis by age group

- Clinical trial: Adult (1), Elderly (1).
- Post-marketing: Paediatric (53 adolescent), Adults (167), Elderly (201) and Unknown (17).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 189 (43.0% of the cases reporting Multisystem Inflammatory Syndrome AESIs).

O/E analysis

- O/E analysis was performed for Multisystem inflammatory syndrome (includes PTs: Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome): in the age stratified analyses the O/E ratios were only above 1 for persons 18-24 years old using a 21-day (O/E ratio 1.868, 95%CI 0.896; 3.436) or 42 -day risk period (O/E ratio 1.790, 95%CI 0.979; 3.004), cumulatively.

MAH's conclusion

Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C) was evaluated as signal in the reporting interval and closed as "no risk". No new 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 to 'Multisystem Inflammatory Syndrome in Children and Adults' in section 'Post-approval regulatory requests' in this assessment report.

Multisystem inflammatory syndrome in children / adults were continuously monitored in the SSRs for Comirnaty during the reporting period.

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; Polyarthritis; Post viral fatigue syndrome; Rheumatoid arthritis.*

Clinical Trial Data

- Number of cases: 4 (BNT162b2 [2], placebo and blinded therapy [1 each]) (0.6% of 721 cases, the total CT dataset) compared to 2 cases (0.28%) retrieved in the first PSUR.

Post-authorization data

- Number of relevant cases: 58,250 (8.9% of 657,528 cases, the total PM dataset), compared to 36,146 cases (11.0%) retrieved in the first PSUR.

Analysis by age group

- Clinical trial: Adult (2), Elderly (2).
- Post-marketing: Paediatric (616), Adults (43,590), Elderly (6980) and Unknown (3064).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 6044 (10.4% of the cases reporting musculoskeletal AESIs).

O/E analysis

- O/E analysis was performed for Rheumatoid arthritis, Polyarthritis, Chronic fatigue syndrome, and Post viral fatigue 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. Safety surveillance will continue.

Rapporteur assessment comment:

Regarding rhabdomyolysis, a cumulative review up to 12 Oct 2021 was assessed in the 11th SSR (procedure EMEA/H/C/005735/MEA/002.10) with a further causality assessment in the 12th SSR (procedure EMEA/H/C/005735/MEA/002.11). It was concluded that the cases reporting rhabdomyolysis did not support a causal association between Comirnaty and rhabdomyolysis.

Musculoskeletal AESIs were continuously monitored in the SSRs for Comirnaty during the reporting period.

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

Neurological AESIs (including demyelination)

Search Criteria: *SMQ Convulsions (Narrow and Broad) OR SMQ Demyelination (Narrow and Broad) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Neuropathy peripheral; Polyneuropathy.*

Clinical Trial Data

- Number of cases: 7 (BNT162b2 [2], blinded therapy [5] (0.97% of 721 cases, the total CT dataset) compared to 8 cases (1.14%) retrieved in the first PSUR.

Post-authorization data

- Number of relevant cases: 7197 (1.1% of 657,528 cases, the total PM dataset), compared to 3471 cases (1.1%) retrieved in the first PSUR.

Analysis by age group

- Clinical trial: Adult (3), Adolescent (1) and child (3).
- Post-marketing: Paediatric (524), Adults (4978), Elderly (1268) and Unknown (427).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1753 (24.4% of the cases reporting neurological AESIs).

O/E analysis

- O/E analysis was performed for ADEM, Encephalopathy, Fibromyalgia, Guillain-Barre syndrome, Meningitis, Meningitis aseptic, Multiple sclerosis, Multiple sclerosis relapse, Myelitis transverse, Neuropathy peripheral, Optic neuritis, Polyneuropathy and Seizure/Seizure disorders: 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 SSRs for Comirnaty 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; 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.*

Clinical Trial Data

- Number of cases: 2 (blinded therapy [1] and BNT162b2 [1]) (0.28% of 721 cases, the total CT dataset) compared to 3 cases (0.43%) retrieved in the first PSUR.

Post-authorization data

- Number of relevant cases: 118,843 (18.1% of 657,528 cases, the total PM dataset), compared to 70,105 cases (21.4%) retrieved in the first PSUR.

Analysis by age group

- Clinical trial: Paediatric (2).
- Post-marketing: Paediatric (3389), Adult (73,062), Elderly (34382), and Unknown (8010).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 12002 (10.1% of the cases reporting other AESI).

O/E analysis

- O/E analysis was performed on Herpes zoster: all O/E ratios were <1.

MAH's conclusion

Herpes zoster, including Ophthalmic herpes zoster, was a signal evaluated and determined not to be a risk. 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:

Regarding herpes zoster, a cumulative review was assessed in the 8th SSR (procedure EMEA/H/C/005735/MEA/002.9) and it was concluded that there was no new safety concern, and the signal was closed.

Other AESIs including herpes zoster were continuously monitored in the SSRs for Comirnaty during the reporting period.

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

Pregnancy related AESIs

Rapporteur assessment comment:

Please refer to the Section 2.2.1.2. 'Pregnancy and Lactation'.

Renal AESIs

Search Criteria: *PTs Acute kidney injury; Renal failure.*

Clinical Trial Data

- Number of cases: 7 (BNT162b2 [4] and blinded therapy [3]) (0.97% of 721 cases, the total CT dataset) compared to 3 cases (0.43%) retrieved in the first PSUR.
- Country of incidence: US (7).
- Subjects' gender: female (3), male (4).
- Subjects' age in years (n = 7), range: 44 – 78, mean: 63.9, median: 68.

- Medical history (n = 3): the relevant medical histories included Chronic kidney disease and Type 2 diabetes mellitus (2 each), Obesity, Blood cholesterol increased, Hypothyroidism (1 each).
- COVID 19 Medical history: None.
- Co-suspects: None.
- Reported relevant PT (7): Acute kidney injury (7). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

Post-authorization data

- Number of cases: 612 (0.09% of 657,528 cases, the total PM dataset), compared to 387 cases (0.12%) retrieved in the first PSUR; medically confirmed cases (415).
- Country of incidence: France (141), Germany (122), Italy (42), Japan (41), US (40), Spain (31), UK (30), New Zealand (15), Austria (14), Netherlands (13), Australia (12), Malta (11); the remaining 100 cases were distributed among 29 countries.
- Subjects' gender: female (261), male (345), and Unknown (6).
- Subjects' age in years (n = 583), range: 12 – 104, mean: 65, median: 70.0.
- Medical history (n = 462): the most frequently (≥5 occurrences) reported medical conditions included Diabetes mellitus (59), Chronic kidney disease (51), Type 2 diabetes mellitus (49), Obesity (30), Renal failure (18), Renal transplant (14), Acute kidney injury (8), Blood cholesterol increased (6), Renal disorder, Renal impairment (5 each).
- COVID-19 Medical history (n = 20): COVID-19 (14), Suspected COVID-19 (5), Asymptomatic COVID-19 (1).
- Co-suspects (n= 36): the reported relevant co-suspect medications included methotrexate sodium, ibuprofen (2 each), cyclosporin, zoledronic acid (1 each).
- Number of relevant events: 626; serious (624), nonserious (2).
- Most frequently reported relevant PTs: Acute kidney injury (337), Renal failure (289).
- Time to relevant event onset (n = 346) , range: <24 hours to 180 days, median: 9 days.
- Duration of relevant events (n = 18 out of 85 occurrences with outcome of resolved/resolved with sequelae), range: 3 - 68 days; Median 68 days.
- Relevant event outcome: fatal (102), resolved or resolving (152), resolved with sequelae (21), not resolved at the time of reporting (133), and unknown (218).
    - In 102 cases, the reported cause of death was coded to the PTs Renal failure (50), Acute kidney injury (37). Most (87 of 102 cases) of the fatal cases involved elderly subjects. When the medical history was provided (73 cases), significant medical conditions included Diabetes mellitus (20), Chronic kidney disease (14), Type 2 diabetes mellitus (11), Renal failure (10), Obesity (6), Renal impairment (3), Renal cancer, Renal disorder (2 each).

Analysis by age group

- Clinical trial: Adult (3), Elderly (4).
- Post-marketing: Paediatric (18), Adult (215), Elderly (355) and Unknown (24).
    - No significant difference observed in the reporting proportion of frequently reported renal AEs (≥2%) between adult and elderly population. However, a higher reporting proportion

of events coded to the PT Renal failure was observed in elderly population when compared to adult population (Renal failure [29.8% in adults vs 37.1% in elderly].

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 347 (56.7% of the cases reporting renal AESIs).
- The reporting proportion of renal AESIs with fatal outcome (14.3%) is higher in subjects without comorbid conditions when compared to the reporting proportion observed in the subjects with comorbidities (9.8% of events with fatal outcome).

O/E analysis

O/E analysis was performed for Acute kidney injury and Renal failure: 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:

Regarding glomerulonephritis and nephrotic syndrome, please refer to section 2.2.1.6. 'Glomerulonephritis and nephrotic syndrome' of this assessment report.

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

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: 38 (Blinded therapy [22], BNT162b2 [14], Zolpidem and Diazepam [1 each]) (5.3% of 721 cases, the total CT dataset) compared to 28 cases (4.0%) retrieved in the first PSUR.
- Country of incidence: US (30), Argentina (4), China, Poland (2 each).
- Subjects' gender: female (16), male (22).
- Subjects' age in years (n = 29), range: 7 – 84, mean: 59.9, median: 61.
- Medical history (n = 32): the relevant medical conditions included Asthma (6), Chronic obstructive pulmonary disease (4), Seasonal allergy, Respiratory syncytial virus infection (2 each), Interstitial lung disease, Bronchitis and Neonatal respiratory distress (1 each).
- COVID 19 medical history (n = 1): COVID immunization (1).
- Co-suspects: None.
- Reported relevant PTs (39): Pneumonia (16), Respiratory syncytial virus bronchiolitis (6), Cardio-respiratory arrest (4), Acute respiratory failure, Hypoxia, Pneumonia aspiration, Respiratory failure (2 each), Acute respiratory distress syndrome, Atypical pneumonia, Lower respiratory tract infection viral, Lung abscess, Pneumonia respiratory syncytial viral (1 each)

- Of the above SAEs, in 1 case, Acute respiratory distress syndrome was assessed as related to diazepam.

Post-authorisation data

- Number of cases: 3356 (0.51% of 657,528 cases, the total PM dataset), compared to 2263 cases (0.7%) retrieved in the first PSUR; medically confirmed cases (2014).
- Country of incidence: Japan (614), France (515), Germany (375), UK (258), US (188), Italy (187), Netherlands, Belgium (140 each), Spain (119), Australia (98), Finland (53), Sweden (52), Norway (51), Austria (50); the remaining 516 cases were distributed among 45 countries.
- Subjects' gender: female (1738), male (1560), and unknown (58).
- Subjects' age in years (n = 3169), range: 6 – 100, mean: 61.3, median: 65.0.
- Medical history (n = 2190): the most frequently (≥5 occurrences) reported medical conditions included Asthma (195), Chronic obstructive pulmonary disease (147), Pneumonia (80), Seasonal allergy (62), Pulmonary embolism (36), Lower respiratory tract infection (29), Lung neoplasm malignant (23), Pneumonia aspiration (22), Respiratory failure (20), Bronchitis (18), Chronic respiratory failure (17), Bronchitis chronic (15), Lung disorder (14), Pulmonary fibrosis (13),Respiratory tract infection (8), Upper Respiratory infection (5).
- COVID 19 Medical history (n = 208): the most frequently reported medical conditions (≥2 occurrences) included COVID-19 (138), Suspected COVID 19 (48), COVID-19 pneumonia (10), Exposure to SARS-CoV-2 (6), Asymptomatic COVID-19, SARS-CoV-2 test positive (2 each).
- Co-suspects (n = 119): the reported relevant co-suspect medications included adalimumab (12), atorvastatin, methotrexate (5 each), etanercept (2), amiodarone hydrochloride (1).
- Number of relevant events: 3624; serious (3162), nonserious (462).
- Most frequently reported relevant PTs (≥ 100 occurrences): Pneumonia (1249), Respiratory disorder (492), Cardio-respiratory arrest (370), Respiratory failure (335), Bronchitis (309), Hypoxia (240), Lower respiratory tract infection (205), Pneumonia aspiration (109), Acute respiratory failure (106) and Acute respiratory distress syndrome (103).
- Time to relevant event onset (n = 2378), range: <24 hours to 180 days, median: 4 days.
- Duration of relevant events (n = 202 out of 560 occurrences with outcome of resolved/resolved with sequelae), range: from 2 minutes to 150 days, median: 7 days.
- Relevant event outcome:47 fatal (737), resolved or resolving (1076), resolved with sequelae (82), not resolved at the time of reporting (709), and unknown (1024).
    - In 737 cases, the reported cause of death (≥10 occurrences) was coded to the PTs Cardio-respiratory arrest (269), Pneumonia (159), Respiratory failure (100), Pneumonia aspiration (42), Acute respiratory distress syndrome (41), Acute respiratory failure (39), Hypoxia (30), Respiratory disorder (21), Cardiopulmonary failure (16). Most (546 of 737 cases) of the fatal cases involved elderly subjects. When the medical history was provided (600 cases), significant medical conditions included Chronic obstructive pulmonary disease (52), Asthma (28), Pneumonia (23), Tobacco user (20), Lung neoplasm malignant, Pneumonia aspiration (18 each), Interstitial lung disease (15), Pulmonary embolism (13).

Analysis by age group

- Clinical trial: Paediatric (10), Adult (17) and Elderly (11).

- Post-marketing: Paediatric (73), Adult (979), Elderly (2163) and Unknown (141).
    - No significant difference observed in the reporting proportion of frequently reported respiratory AEs (≥2%) between adult and elderly population. However, a higher reporting proportion of events coded to the PTs Acute respiratory distress syndrome and Acute respiratory failure was observed in elderly population when compared to adult population (Acute respiratory distress syndrome [3.8% vs 1.3%], Acute respiratory failure [4.2% vs 1.1%].

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1362 (40.1% of the cases reporting respiratory AESIs). A higher reporting proportion of respiratory AESIs was reported in subjects without significant comorbidities (59.9 %) when compared to subjects with significant comorbidities.
- The reporting proportion of respiratory events with resolved (14.9%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (5.4% of events with resolved).

O/E analysis

O/E analysis was performed for Acute respiratory distress 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. Safety surveillance will continue.

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

Stroke

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

Clinical trial data

- Number of cases: 19 (blinded therapy [10] and BNT162b2 [9]) (2.6% of 721 cases, the total CT dataset) compared to 20 cases (2.8%) retrieved in the first PSUR.
- Reported relevant PTs (20): Cerebrovascular accident (10), Cerebral infarction (3), Cerebral haemorrhage, Ischaemic stroke (2 each), Brain stem infarction, Cerebral venous thrombosis, and Intraventricular haemorrhage (1 each). None of the SAEs were assessed as related to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 4834 (0.7% of 657,528 cases, the total PM dataset), compared to 2930 cases (0.9%) retrieved in the first PSUR; medically confirmed cases (2571).
- Most frequently reported relevant PTs (≥2%): Cerebrovascular accident (1830), Cerebral infarction (984), Ischaemic stroke (609), Cerebral haemorrhage (534), Cerebral venous sinus thrombosis (250), Cerebral thrombosis (173), Cerebral venous thrombosis (138), and Cerebral ischaemia (124).

Analysis by age group

- Clinical trial: Paediatric (1), Adult (8), and Elderly (10).
- Post-marketing: Paediatric (40), Adult (2096), Elderly (2437), Unknown (261).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1365 (28.1% of the CT and PM cases reporting stroke).

O/E analysis

- O/E analysis was performed for Ischemic stroke and Hemorrhagic stroke: 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:

Stroke was continuously monitored in the SSRs for Comirnaty during the reporting period. In the 13th SSR of Comirnaty a review of cases reporting cerebral venous sinus thrombosis through 24 Nov 2021 was assessed which resulted in a request for the next 14th SSR, to provide a cumulative review of cases reporting cerebral venous sinus thrombosis through the end date of the next SSR interval period (with matching exposure data), with detailed information of the cerebral venous sinus thrombosis cases (which are considered the most informative cases) and a causality assessment per case using the WHO-UMC system for standardised case causality assessment (procedure EMEA/H/C/005735/MEA/002.12).

EMA O/E analysis

An observed-to-expected (O-E) analysis was performed to compare (in the pre-defined risk periods: 14- and 30-day period) the number of cases of Cerebral venous sinus thrombosis (CVST), Disseminated intravascular coagulation (DIC), Deep vein thrombosis (DVT) without thrombocytopenia and Pulmonary embolism (PE) received in EudraVigilance (observed) to the estimated number of cases (expected) that would have naturally occurred in the same population without vaccination:

• EU/EEA Coverage was sourced from ECDC website up to Week 9-2022.

• Observed cases: EEA cases in EudraVigilance (exc. UK and NI). Date of extraction: 16 March 2022.

• Data Provider for the background incidence rates (IR): SIDIAP. Rates for the four respective entities (i.e. DVT, PE, CVST, DIC) were ascertained from SIDIAP CMBDH-HA, (System for the development of research in primary care, with hospital linkage). SIDIAP is a primary care records database that covers approximately 80% of the population of Catalonia, Spain (approximately 5.7 million people) and is now linked to the minimum basic set of hospital discharge data (CMBD-HA), which includes diagnosis and procedures registered during hospital admissions. SIDIAP contains anonymised longitudinal patient information including sociodemographic characteristics, morbidity (International Classification of Disease; ICD-10), clinical and lifestyle variables, laboratory tests and treatments (drug prescriptions, drugs purchased at the community pharmacy and hospital discharge information). The rates are based on the average of a four year period prior to the pandemic (i.e. 2017-2019).

While the overall picture of coagulation disorders seems to be reassuring for mRNAs vaccines (i.e. no statistically significant imbalance observed for DVT, PE and DIC), there seems to be an imbalance for

CVST in the younger age groups for Comirnaty in the 20-29 age group: (D14) O/E ratio 7.85 (95%CI 5.72 - 10.5); (D30) O/E ratio 5.04 (95%CI 3.87 - 6.47).

In view of these results and the imbalance in younger age groups for Comirnaty, a cumulative review of CVST cases reported with mRNAs vaccines (below 30 years of age) was performed:

100 cases of CVST + 3 duplicates were reported to EudraVigilance, having the following inclusion criteria: EEA only; serious cases only; Age group under 30 years old; DLP: 9 March 2022; PTs: cerebral venous sinus thrombosis, cerebral venous thrombosis, cerebral thrombosis, cavernous sinus thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis.

The following observations were made:

• 64F, 33M, 3 unknown;

• 61 cases from HCPs, 39 cases from consumers;

• 4 cases reported as fatal;

• 15 cases after D1, 31 cases after D2 (out of which one case in heterologous vaccination), 5 cases after D3. In 49 cases the number of the dose was not reported.

• TTO: 1 case happened before vaccination, 16 cases happened in the first 7 days following the latest vaccination, 23 cases happened between days 8-14 following the latest vaccination, 14 cases happened between days 15-29 following the latest vaccination, 16 cases happened between days 30-158 following the latest vaccination. The TTO was not reported in 30 cases.

• In 49 cases possible alternative explanations could exist (including use of contraceptives in 18 cases). In 51 cases no alternative explanations were reported (this number also includes the cases with very limited information).

• In 10 cases thrombocytopenia was co-reported.

• Causality assessment as per the reporter: 1 case multifactorial, 5 cases unlikely related, 4 cases possible, 1 case probable, 1 case related. In 88 cases the reporter did not assess the causality.

• EMA case assessment: 42 cases not assessable, 12 cases inconclusive, 35 cases confounded, 1 case not related, 10 cases could not be excluded.

Overall, the issue does not represent a signal for Comirnaty at this stage.

In the context of literature review, a paper by *Hviid et al.* was retrieved, concluding that: "*In this exploratory retrospective cohort study among frontline personnel in Denmark, receipt of the AZD1222 vaccine was associated with a small excess risk for deep venous thrombosis. Although the corresponding risks for the more rare and severe thrombotic outcomes (such as cerebral venous sinus thrombosis) were not statistically significantly increased, statistical precision was low, and clinically relevant risks could not be excluded with certainty. There was no statistically significant association of BNT162b2 vaccination with thrombotic or thrombocytopenic events.*" Of note, limitation of the study included difficult to capture very rare events, due to the limited population.

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 assessment report.

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: 15 (BNT162b2 [8], blinded therapy [6] and placebo [1]) (2.1% of 721 cases, the total CT dataset) compared to 23 cases (3.3%) retrieved in the first PSUR.

  Reported relevant PTs (16): Pulmonary embolism (12), Deep vein thrombosis (3), and Peripheral artery thrombosis (1). None of the SAEs were assessed as related to BNT162b2 or blinded therapy or placebo.

Post-authorisation data

- Number of cases: 6507 (1.0% of 657,528 cases, the total PM dataset), compared to 4725 cases (1.4%) retrieved in the first PSUR; medically confirmed cases (4108).

Analysis by age group

- Clinical trial: Adults (7) and Elderly (8).
- Post-marketing: Paediatric (70), Adults (3938), Elderly (2278) and Unknown (221).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1750 (26.8% of the CT and PM cases reporting thromboembolic events).

O/E analysis

- O/E analysis was performed for Deep vein thrombosis, Disseminated intravascular coagulation, and Pulmonary embolism: 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 SSRs for Comirnaty 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 first PSUR.

Post-authorisation data

- Number of cases: 854 (0.13% of 657,528 cases, the total PM dataset), compared to 360 cases (0.1%) retrieved in the first PSUR; medically confirmed cases (546).
- Most frequently reported relevant PTs (≥20 occurrences): Vasculitis (330), Giant cell arteritis (119), Cutaneous vasculitis (114), Peripheral ischaemia (77), Henoch-Schonlein purpura (70), Vasculitic rash (27), Behcet's syndrome (24), Hypersensitivity vasculitis (23), Anti-neutrophil cytoplasmic antibody positive vasculitis (22).

Analysis by age group

- Post-marketing: Paediatric (44), Adults (437), Elderly (328) and Unknown (45).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 302 (35.4% of the PM cases reporting vasculitic events).

O/E analysis

- O/E analysis was performed for Behcet's syndrome, Cutaneous vasculitis, Giant cell arteritis, Limb ischaemia, Vasculitic rash, and Vasculitis: all O/E ratios were below 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:

Regarding vasculitis, in the 13th SSR of Comirnaty a cumulative review with cases reporting vasculitis retrieved through 15 Nov 2021 (N=504 cases) was assessed. The signal was not closed because a detailed causality assessment of the 207 cases considered without a known confounding factor was lacking, which resulted in a request for the next 14th SSR of Comirnaty, to perform a cumulative review of cases of interest reporting vasculitis through the end date of the safety summary report interval period, with detailed information of the cases which are considered the most informative cases and a causality assessment per case using the WHO-UMC system for standardised case causality assessment (procedure EMEA/H/C/005735/MEA/002.12).

Vasculitic events were continuously monitored in the SSRs for Comirnaty during the reporting period.

No other new important safety concern could be identified for vasculitic events.

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: 7 (blinded therapy [5], BNT162b2 [2]) (1.0% of 721 cases, the total CT dataset, compared to 3 cases (0.4%) retrieved in the first PSUR).
- Country of incidence: US (5), South Africa (2).
- Subjects' gender: female (4), and male (3).
- Subjects' age in years (n = 7), range: 21 – 64, mean: 43.9, median: 44.
- Medical history (n = 7): HIV infection (5), Prophylaxis against HIV infection, Malnutrition (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported PTs (13): Acute kidney injury, Acute myocardial infarction, Anaemia, Cephalo-pelvic disproportion, Chest pain, COVID-19 pneumonia, Death, Foetal death, Hypertension, Maternal exposure during pregnancy, Postpartum haemorrhage, Premature separation of placenta, and Sepsis (1 each). None of the events were related to BNT162b2 or blinded therapy.

Post-authorisation data

- Number of cases: 393 (0.06% of 657,528 cases, the total PM dataset), compared to 294 cases (0.09%) retrieved in the first PSUR:

Patients with pre-existing HIV Infection:

  - 201 cases (0.03% of 657,528 cases, the total PM dataset); medically confirmed cases (98).
  - Country of incidence: France (80), US (39), UK (18), Italy (10), Germany (8), Netherlands (6), South Africa, Switzerland (5 each), Belgium, Canada (4 each), Sweden (3), Austria, Brazil, Panama, Portugal, Spain, Taiwan (2 each). The remaining 7 cases were distributed among 7 countries.
  - Subjects' gender: female (43), male (148) and unknown (10).
  - Subjects' age in years (n = 190), range: 18 – 89, mean: 48.3, median: 50.
  - COVID-19 Medical history (n = 17): COVID-19 (12), Suspected COVID-19 (5).
  - Co suspect vaccines/medications (7): Bictegravir/emtricitabine/tenofovir (2), Anakinra, caffeine/papaver somniferum tincture/paracetamol, celecoxib, COVID-19 vaccine (unspecified), cyproterone/ethinylestradiol, dexamethasone, emtricitabine, fluconazole, paracetamol, sulfamethoxazole/trimethoprim, tenofovir, tramadol (1 each).
  - Of the 201 cases reporting a pre-existing HIV condition, 13 subjects reported cardiac disorders. The events in these cases were coded to PTs Myocarditis (5), Palpitations (3), Angina pectoris (2), Atrial fibrillation, Bundle branch block right, Myocardial infarction, Myocarditis post infection, Pericardial haemorrhage, Pericarditis, Tachycardia (1 each). Of the 17 events 16 were assessed as serious and 1 event were non-serious. Outcome of the events was reported as fatal (1), resolved with sequelae (2), resolved/resolving (6), not resolved (3), and unknown (5).

- Of the 201 cases, 78 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (32), Dizziness (14), Paraesthesia (9), Facial paralysis (8), Somnolence (5), Hypoaesthesia (4), Balance disorder, Cerebrovascular accident, Paralysis, Parosmia, Partial seizures, Seizure (2 each), Ageusia, Anaesthesia, Axonal and demyelinating polyneuropathy, Bell's palsy, Burning sensation, Cerebral venous thrombosis, Disturbance in attention, Epilepsy, Guillain-Barre syndrome, Hemiparesis, Hemiplegia, Hyperaesthesia, Hypersomnia, Ischaemic cerebral infarction, Loss of consciousness, Migraine, Nervous system disorder, Paraparesis, Polyneuropathy, Postictal paralysis, Sensory disturbance, and Tremor (1 each). Forty-nine (49) were assessed as serious and 57 were non-serious. Outcome of the events was reported as fatal (1), resolved/resolving (47), resolving with sequelae (1), not resolved (32), and unknown (26).
- Of the 201 cases, 24 subjects reported infectious events. The events in these cases were coded to PTs COVID-19 (8), Herpes zoster (3), Cellulitis, COVID-19 pneumonia, Eye infection, Herpes simplex, Herpes simplex reactivation, Infection, Influenza, Labyrinthitis, Nasopharyngitis, Rhinitis, Secondary syphilis, Suspected COVID-19, Syphilis, Syphilis genital, Tonsilitis, Vestibular neuronitis (1 each). Of the 27 events, 18 were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (1), resolved/resolving (11), not resolved (7), and unknown (8).
- Time to event onset (n = 515), range: <24 hours to 185 days, median: 1 day.
- Duration of events (n = 69), range: <1 day to 60 days, median 2 days.
- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing HIV infection when compared to the subjects without the disease.
- Of the 201 cases, 166 cases involved adults, 25 cases involved elderly and in 10 cases age group was not reported. Due to the low volume of cases reported in elderly, it was not possible to make a meaningful comparison between the adults and elderly patient population.

Patients with pre-existing tuberculosis:

- 139 cases (0.02% of 657,528 cases, the total PM dataset); medically confirmed cases (75).
- Country of incidence : France (64), US (17), UK (11), Germany, Japan (9 each), Spain (6), Iceland, Italy, South Africa (3 each), Croatia and Sweden (2 each). The remaining 10 cases were distributed among 10 countries.
- Subjects' gender: female (90), male (48), Unknown (1).
- Subjects' age in years (n = 138), range: 22 – 98, mean: 64, median: 67.
- COVID-19 Medical history (n = 7): COVID 19 (5), and Suspected COVID-19 (2).
- Co suspect vaccines/medications (3): COVID-19 AstraZeneca vaccine, influenza vaccine, levofloxacin (1 each).
- Of the 139 cases reporting a pre-existing tuberculosis, 30 subjects reported cardiac disorders. The events in these cases were coded to PTs Tachycardia (8), Palpitations (5), Arrhythmia (4), Atrial fibrillation, Cardiac failure, Myocarditis, Pericarditis (3 each), Angina pectoris, Cardiomegaly (2 each), Atrioventricular block complete, Cardiac arrest, Cardiac failure congestive, Cardiac fibrillation, Cardiomyopathy, Cardiovascular disorder,

Extrasystoles, Myocardial infarction, Pericarditis constrictive, Supraventricular tachycardia, and Ventricular fibrillation (1 each). Of the 44 events, 35 were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (28), not resolved (4), and unknown (8).

- Of the 139 cases, 42 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (15), Dizziness (14), Paraesthesia (6), Tremor (4), Hypoaesthesia, Loss of consciousness (3 each), Hypotonia, Migraine, Sinus headache, Speech disorder (2 each), Ageusia, Altered state of consciousness, Anaesthesia, Anosmia, Aphasia, Axonal and demyelinating polyneuropathy, Axonal neuropathy, Burning sensation, Carotid artery stenosis, Cerebral atrophy, Cerebral ventricle dilatation, Cluster headache, Depressed level of consciousness, Disturbance in attention, Dysstasia, Hemiparesis, Ischaemic stroke, Lacunar stroke, Movement disorder, Myasthenia gravis, Polyneuropathy, Quadriparesis, Sciatic nerve palsy, Syncope, Tension headache, and Transient global amnesia (1 each). Of the 79 events, 38 were assessed as serious and 41 events were non-serious. Outcome of the events was reported as fatal (5), resolved/resolving (36), not resolved (9), resolved with sequelae (2), and unknown (27).
- Of the 139 cases, 25 subjects reported infectious events. The events in these cases were coded to PTs COVID-19 (9), COVID-19 pneumonia (7), Pneumonia (5), Asymptomatic COVID-19 (2), Candida infection, Herpes zoster, Influenza, Oropharyngeal candidiasis, Pericarditis tuberculous, Rhinitis, Sepsis, Septic shock, Sialoadenitis, Superinfection bacterial, and Vulvovaginal candidiasis (1 each). Of the 34 events, 30 were assessed as serious and 4 events were non-serious. Outcome of the events was reported as fatal (5), resolved/resolving (6), not resolved (7), and unknown (16).
- Time to event onset (n = 507), range: <24 hours to 254 days, median: 4 days.
- Duration of events (n = 77),95 range: 1 day to 87 days, median 2 days.
- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing tuberculosis when compared to the subjects without the disease.
- Of the 139 cases, 63 cases involved adults, and 75 cases involved elderly, and the age group was not reported in 1 case. The reporting proportion of infectious events was higher in elderly (15.8%) compared to the adult population (2.2%); and more adult subjects reported nervous system disorders as compared to the elderly (20.1% in adults vs 9.4% in elderly). No significant difference was observed in the reporting proportion of cardiac events (12.2% in elderly vs 9.4% in adults) between the elderly and adult population.

Patients with pre-existing malnutrition:

- 52 cases (<0.01% of 657,528 cases, the total PM dataset); medically confirmed cases (48).
- Country of incidence: France (31), Japan (4), Czech Republic, Germany (3 each), Norway (2); the remaining cases were reported from 9 countries.
- Subjects' gender: female (29), male (23).
- Subjects' age in years (n = 50), range: 22 – 95, mean: 74, median: 79.
- COVID-19 Medical history (n = 2): COVID-19 (1), and Suspected COVID-19 (1).

- Co suspect medications (3): amiodarone, atorvastatin/ezetimibe, bisoprolol, buspirone, fentanyl, furosemide, levofloxacin, macrogol, metformin, metoclopramide/pancreatin, morphine, paracetamol, phloroglucinol/trimethyl phloroglucinol, potassium chloride, quetiapine, risedronate (1 each).
- In these 52 cases, the most frequently reported events (≥5 occurrences) were COVID19 (13), Dyspnoea (10), Drug ineffective, Vaccination failure (9 each), Asthenia, Inappropriate schedule of product administration (6 each), Cough, General physical health deterioration, and Pyrexia (5 each).
- Of the 52 cases reporting pre-existing malnutrition, 15 subjects reported PTs Asthenia (6), General physical health deterioration (5), Condition aggravated, Decreased appetite (4 each), and Adult failure to thrive, Malnutrition (1 each). Of the total 21 events, 12 events were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (3), resolved/resolving (5), not resolved (2), and unknown (11).
- Time to event onset (n = 244), range: <24 hours to 265 days, median: 12 days.
- Duration of events (n = 17),95 range: <1 day to 62 days, median 1 week.
- Of the 52 cases, 39 were reported in elderly and 13 cases involved adults. Due to the low volume of cases reported in adults, it was not possible to make a meaningful comparison between the adults and elderly patient population.

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

As of 13 March 2021, in the C4591001 Phase 2/3 reactogenicity subset of participants with e-diary data, there were 177 BNT162b2 and 187 placebo participants with baseline positive SARS CoV 2 status, and 4701 BNT162b2 and 4690 placebo participants with baseline negative SARS-CoV-2 status.

For local reactions, the frequency of redness, swelling, and pain at the injection site after any dose of BNT162b2 was 8.5%, 10.2%, and 80.2% compared with 9.9%, 11.1%, and 84.5% for participants positive and negative at baseline, respectively. The frequency of local reactions was numerically higher in those negative at baseline, but these differences are not clinically meaningful.

Some systemic events appear to be more common after the first dose in subjects with baseline positive status than in negative participants, but this reverses after the second dose with the groups being similar after any dose. For example, any fever was seen in 12.4% of with baseline positive status and 2.6% of negative participants after the first dose, but after the second dose it was observed in 7.8% of baseline positive and 14.8% of baseline seronegative participants. Overall, any fever after either dose was reported for 31 participants (17.5%) positive at baseline compared to 714 participants (15.1%) negative at baseline. Severe fever (>38.9 °C to 40.0 °C) was reported in 1 participant (0.6%) and 49 participants (1.0%) in those positive and negative at baseline, respectively. The frequency for other systemic events after any dose of BNT162b2 was numerically lower for those positive at baseline: fatigue, headache and chills the frequency was 54.2%, 49.7% and 32.8% compared with 65%, 57.4%, 34.7% for those positive

and negative for SARS-CoV-2 at baseline. Joint pain was reported by 27.1% compared to 25.0% of those positive and negative for SARS CoV-2 at baseline. The baseline SARS-CoV-2 positive subgroup included far fewer participants than the baseline negative subgroup, so these results should be interpreted with caution.

Rapporteur assessment comment:

Here the MAH presented exactly the same data as in the previous 1st PSUR without an update on clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2 in current reporting period. Therefore, the MAH is requested to confirm that there is no additional information during the current reporting period of the 2nd PSUR concerning clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2. If not, the new data should be submitted. **Request for supplementary information**

Local adverse reactions

Search criteria: *PTs Erythema; Injection site erythema; Injection site pain; Injection site swelling; Swelling.*

Clinical trial data

- There were no serious clinical trial cases of local reactions reported during the reporting interval.

Post-authorisation data

- Number of cases: 21,240 (3.2% of 657,528 cases, the total PM dataset), compared to 21,806 cases (6.7%) retrieved in the first PSUR; medically confirmed cases (11,594).
- Country of incidence (>2%): Japan (6678), UK (3589), Italy (1924), US (1905), Germany (1056), France (992), Netherlands (712), Malaysia (543).
- Subjects' gender: female (16,189), male (4444) and unknown (607).
- Subjects' age in years (n = 19,403), range: 0.06 - 120, mean: 45.2, median: 44.
- Medical history (n = 18,696): the most frequently (≥2%) reported medical conditions included Suppressed lactation (872), Hypertension (869), Seasonal allergy (722), Drug hypersensitivity (707), Asthma (699), Food allergy (656), Hypersensitivity (501), Diabetes mellitus (269), Hypothyroidism (250), Depression (212), Mite allergy (172), Migraine (170).
- COVID-19 Medical history (n = 846): COVID-19 (439), Suspected COVID-19 (382), Coronavirus infection (6), Exposure to SARS-CoV-2 (4), Post-acute COVID-19 syndrome (4), SARS-CoV-2 test positive (4), COVID-19 pneumonia (3), Asymptomatic COVID-19 (2), Coronavirus test positive (1), COVID-19 treatment (1).
- Co suspect vaccines/medications (n = 252): those reported in ≥ 2 cases included Influenza vaccine (41), Adalimumab (12), COVID-19 AstraZeneca vaccine (10), Hepatitis A vaccine (8), Influenza vaccine (surface antigen, inactivated, adjuvanted) (6), BCG vaccine, Macrogol (5 each), COVID-19 Moderna vaccine, Influenza vaccine INACT SPLIT 4V (4 each), Alemtuzumab, Amlodipine besilate, Amoxicillin, Atorvastatin calcium, Diclofenac sodium, Infliximab, Mepolizumab, Methotrexate sodium, Ocrelizumab (3 each), Beclometasone, Cetirizine, Etanercept, Hyaluronic Acid, Influenza vaccine INACT SAG 3V, Lercanidipine Hydrochloride, Levothyroxine, Metamizole sodium, Methylprednisolone, Prednisone, Rituximab, Rosuvastatin, Sulfasalazine (2 each).

- Number of relevant events: 23,092.
- Relevant event seriousness: serious (3341), non-serious (19,756).
- Most frequently reported relevant PTs (≥2%): Erythema (9951), Swelling (9293), Injection site pain (2872), Injection site erythema (560), Injection site swelling (416).
- Most frequently co-reported PTs (> 5%): Pain (4828). Headache (4522), Pyrexia (3787), Pruritus (3579), Fatigue (3195), Malaise (2872), Myalgia (2714), Arthralgia (2169), Vaccination site pain (1996), Pain in extremity (1922), Rash (1751), Lymphadenopathy (1570), Chills (1514), Nausea (1419), Immunisation (1365), Peripheral swelling (1278), Off label use (1169), Axillary pain (1104), and Urticaria (1065).
- Time to event onset (n = 23,163) range: < 24 hours – 175 days, median: 2 days
- Duration of relevant events (n = 3454 out of 7777 occurrences with outcome of resolved/resolved with sequelae), range: < 24 hours to 536 days median 3.8 days.
- Relevant event outcome: fatal (7), resolved/resolving (11,781), resolved with sequelae (153), not resolved (4435), unknown (6781).
- Time to onset of fatal events were 1 day (2 events), 5 days (2 events), 7 days (1 event), 11 days (1 event), and 60 days (1 event). There were 7 cases reporting fatal events of interest (Erythema [3 cases] and Swelling [4 case]) in elderly (5 cases) and adult (2 cases) patients. Review of these cases identified additional fatal adverse events reported in these cases. The local adverse reactions were not the primary cause of death in these cases.

Analysis by age group

- Post-marketing - Paediatric (377), Adults (16,375), Elderly (3030) and Unknown (1458). In general, the events of interest were similar by percentage across age group, with Erythema, Injection site pain, and Swelling more frequently reported.

Analysis by presence of comorbidities

- Post-marketing - Number of subjects with comorbidities: 2676 (0.4% of 657,528 cases, the total PM dataset). Subjects with comorbidities were reported in 12.6% of the Local adverse Reactions dataset. Given the nature of the adverse events of interest reported (Erythema, Injection site erythema, Injection site pain, Injection site swelling, Swelling) and the percentage of patients with comorbidities in the 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 7311 cases, Dose 2 in 7044 cases, Dose 3 in 1575 cases, Dose 4 in 1 case, and the dose number was not specified in 5319 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 21,240 cases representing 3.2% of the cases in the reporting period. The majority of events (85.6%) were non-serious events with 51.5% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 7 fatal cases describing local adverse reactions; two were adult and 5 were elderly subjects. 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. 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: 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.

Systemic adverse reactions

Search criteria: *PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia*.

Clinical trial data

- Number of cases: 4 (BNT162b2 [2], and blinded therapy [2]) (0.6% of 721 cases, the total CT dataset) compared to 3 cases (0.4%) retrieved in the first PSUR.
- Country of incidence: US (2), China, and Finland (1 each).
- Subjects' gender: female (2), and male (2).
- Subjects' age (n = 4), 4, 5, 18, and 68 years, respectively.
- Medical history (n = 3): Anorexia nervosa, Atrial septal defect, Constipation, Croup infectious, Depression, Depression suicidal, Ehler-Danlos syndrome, Febrile convulsion, Gastrooesophageal reflux disease, Generalised anxiety disorder, Lymphadenopathy, Postural orthostatic Tachycardia syndrome, Seasonal allergy, and Wheezing, (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of relevant events: 4.
- Relevant PTs: Arthralgia, and Pyrexia (2 each). Of these SAEs, one event of pyrexia (outcome resolved) was assessed as related to BNT162b2 by the investigator and Sponsor.
- Time to event onset (n = 4): 2, 43, 70, and 112 days, respectively.
- Duration of event (n = 3): 4, 12, and 106 days.
- Relevant event outcome: resolved/resolving (4).

Post-authorisation data

- Number of cases: 279,184 (42.5% of 657,528 cases in the total PM dataset), compared to 157,857 cases (48.3%) retrieved in the first PSUR; medically confirmed cases (112,997).
- Country of incidence (top 10 countries): Japan (64,971), Netherlands (49,585), Germany (30,386), UK (26,056), US (15,908), Italy (12,801), France (10,541), Spain (8,392), Australia (6,407), and Denmark (5,242).
- Subjects' gender: female (199,808), male (71,443) and unknown (7933).
- Subjects' age in years (n = 254,831), range: 2 – 109, mean: 43.1; median: 41.0.

- Medical history (n = 83310): the most frequently (>1000 cases) reported medical conditions included Hypertension (8372), Asthma (6040), Suppressed lactation (5873), Seasonal allergy (5455), Drug hypersensitivity (5297), Disease risk factor (4463), Food allergy (3905), Hypersensitivity (3624), Hypothyroidism (2595), Migraine (2191), Depression (2163), Diabetes mellitus (2139), Anxiety (1504), Mite allergy (1253), Pain (1226), Fibromyalgia (1224), Gastro-oesophageal reflux disease (1139), Type 2 diabetes mellitus (1137), Allergy to animal (1119), Obesity (1118), Autoimmune thyroiditis (1086), Headache (1037), Immunodeficiency (1033), and Rheumatoid arthritis (1020).
- COVID-19 Medical history (n = 19,908): COVID-19 (11753), Suspected COVID-19 (7727), Post-acute COVID-19 syndrome (108), SARS-CoV-2 test positive (105), COVID-19 pneumonia (59), Coronavirus infection (55), Exposure to SARS-CoV-2 (45), Asymptomatic COVID-19 (37), Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (8 each), and Coronavirus test positive (3).
- Co-suspects (n = 2084): the most frequently (≥20 occurrences) reported co-suspect medications included influenza vaccine (324), COVID-19 vaccine (239 [non-MAH or unspecified]), adalimumab (140), hepatitis A vaccine (56), methotrexate (37), paracetamol (31), ocrelizumab (28), ibuprofen (23), nitrofurantoin, tofacitinib (21 each), etanercept, upadacitinib (20 each).
- Number of relevant events: 545,486; serious (62,906), non-serious (482,720).
- Relevant PTs: Headache (135,032), Fatigue (109,454), Pyrexia (105,981), Myalgia (84,890), Arthralgia (56,609), and Chills (53,520).
- Time to event onset (n = 437,197) range < 24 hours to 365 days, median: 0 days.
- Duration of event (n = 170,217), range: <24 hours to 365 days, median: <24 hours.
- Relevant event outcome: fatal (462), not resolved (124,790), resolved/resolving (327,321), resolved with sequelae (3685), and unknown (90779).
    - In 357 cases, the relevant events (462) were reported as fatal: Pyrexia (223), Fatigue, Headache (81 each), Chills (29), Myalgia (28), and Arthralgia (20). In these cases, the most frequently reported other fatal events (>20 occurrences) included Dyspnoea (84), Malaise (56), Asthenia (39), Vomiting (38), Cough (35), COVID-19 (34), Nausea (32), Pneumonia (29), Decreased appetite (27), Cardiac arrest, Immunisation (25 each), Death, and Dizziness (22 each). Most (241 of 357 cases) of the cases with a fatal outcome involved elderly subjects.

Analysis by age group

- Clinical trial: Paediatric (2, PT Pyrexia), Adults (1, PT Arthralgia), Elderly (1 PT Arthralgia). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Per the RSI, the most frequent systemic adverse reactions in subjects 16 years of age and older (in order from highest to lowest frequencies) were fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), and pyrexia (>10%); the most frequent systemic adverse reactions in adolescents 12 through 15 years of age were fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%). 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: 25409 (3.9% of 658,249 cases in the total dataset and 9.1% of 279188 [4 CT and 278184 PM] cases reporting systemic adverse reactions).
- Clinical trial - One of the CT cases reported selected comorbidities: the case involved a paediatric participant (5 years) with a history of croup infectious, febrile convulsion, lymphadenopathy and wheezing, who experienced a serious event coded to PT Pyrexia; the participant was recovering from the event.
- 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 62919 cases, 2 doses in 100,838 cases; 3 doses in 10576 cases, 4 doses in 20 cases, and in 104836 cases the dose was either not specified or reported as others.
- Clinical trial - Vaccination dose number: 2 doses (3) 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 whose vaccine doses were not reported or unclear; 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 279,188 (4 CT and 279,184 PM) cases representing 42.5% of the cases in the total dataset for the reporting period. The majority of events (88.5%) were non-serious events with 60.7% of the events resolved, resolved with sequelae or resolving at the time of reporting. Evaluation of systemic adverse reaction cases did not reveal any significant new safety information based on analysis by age group, 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:

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.

Severe reactogenicity

Search criteria: *PT Extensive swelling of vaccinated limb*.

Post-authorisation data

- Number of cases: 1558 (0.24% of 657,528 cases, the total PM dataset), compared to 427 cases (0.13%) retrieved in the first PSUR; medically confirmed cases (126).

- Country of incidence: Netherlands (1126), Belgium (333), Australia (33), France (25), Croatia (10), UK (8), Italy (5); the remaining 18 cases were distributed among 10 countries.
- Subjects' gender: female (1296), male (260), unknown (2).
- Subjects' age in years (n = 1505), range: 12.0 - 91.0, mean: 42.7, median: 41.0.
- Medical history (n = 625): the relevant reported medical conditions included Drug hypersensitivity (34), Hypersensitivity (30).
- COVID-19 Medical history (n = 322): medical conditions reported included COVID-19 (192), Suspected COVID-19 (129) and Asymptomatic COVID-19 (1).
- Relevant Co-suspects: Influenza vaccine (3), BCG vaccine (1)
- Number of relevant events: 1558; serious (226), non-serious (1332).
- The reported relevant PT included Extensive swelling of vaccinated limb. Majority of the cases did not describe the type or extent of swelling and reported (verbatim) terms such as, "reaction at or around the injection site: extensive swelling of vaccinated limb"; many also reported additional events related to warmth, pain or redness at the injection site, with no additional relevant details; some 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. Majority of cases reporting swelling associated with the injection site, no treatment was required, and no case reported long lasting or permanent sequelae following the event.
- Time to event onset (n = 1441) , range: <24 hours to 164 days, median: 0 day.
- Duration of relevant events was reported in 324 occurrences with outcome of resolved; it ranged from 30 min to 30 days, median: 4 days.
- Relevant event outcome:47 resolved/resolving (859), resolved with sequelae (8), not resolved (641), unknown (51).

Analysis by age group

- Post-marketing: Paediatric (27), Adult (1340), Elderly (176), Unknown (15). A higher reporting proportion of events coded to the PT Extensive swelling of vaccinated limb was observed in elderly versus adult population (Extensive swelling of vaccinated limb [20.3% in elderly vs 18.3% in adults]

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 80 (5.1% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (94.9%) when compared to patients with significant comorbidities. The reporting proportion of event severe reactogenicity with events resolved/resolving (63%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (54.7% of events with resolved/resolving).

MAH's conclusion

There was a total of 1558 cases, in the safety database reporting the PT Extensive swelling of vaccinated limb with the use of BNT162b2, and were mostly reported from the Netherlands (1126, 72%) and Belgium (333, 21.3%). Majority of cases involved females (1296, 83.2%) and were reported in subjects

aged 31-64 years (958, 61.5%). Two-hundred and twenty-six (226; 14.5%) of the events were assessed as serious due to meeting medically significant criteria (there were no hospitalisations due to reported events). There was no case reporting a fatal outcome. One thousand two hundred and one (1201) cases reported time to onset of the event as the same day or the day following vaccination. For all the cases reporting swelling associated with the injection site, no 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.

Age-related adverse reactions

Clinical trial data

- Number of cases: 721.
- Time to event onset (n = 816), range <24 hours to 364 days, median: 105 days.
- Relevant event outcome: fatal (59), resolved/resolving (745), resolved with sequelae (34), not resolved (155), unknown (9).

Post-authorisation data

- Number of cases: 657,528.
- Time to event onset (n = 1,628,114), range <24 hours to 365 days, median: 1 day.
- Relevant event outcome: fatal (12,608), resolved/resolving (1,030,580), resolved with sequelae (23,677), not resolved (546,986), unknown (566,691).

Analysis by age group

- Clinical trial: Paediatric (68), Adults (353), Elderly (233) and Unknown (7).
    - The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 48, Table 49 and Table 50 (not reproduced here).The Infections and infestations and Injury, poisoning and procedural complications SOCs were included in the top 5 SOCs for all 3 age groups.
    - There were 39 cases reporting 44 events in the Pregnancy, puerperium and perinatal conditions SOC for the adult age group. It is not unexpected for events of Pregnancy, puerperium and perinatal conditions to be reported more frequently in adult subjects compared to elderly and paediatric subjects.
    - There were 60 cases reporting 65 events in the Cardiac disorders SOC for the adult and elderly age group. Forty-six (46) cases reported relevant medical history (e.g., hypertension, coronary artery disease, atrial fibrillation, congestive cardiac failure) which may have contributed to the relevant events. The most frequently reported events (≥5 occurrences) in the Cardiac disorders SOC for the adult and elderly age group were

Coronary artery disease (10), Acute myocardial infarction (9), Myocardial infarction (8), Atrial fibrillation (6), and Cardiac failure congestive (5).

- There were 108 cases reporting 116 events in the Neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC for the adult and elderly age group. Thirty-three (33) cases reported pre-existing medical history of cancer (e.g., breast cancer, basal cell carcinoma, prostate cancer, renal cell carcinoma). The most frequently reported events ≥5 occurrences) in the Neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC for the adult and elderly age group were Prostate cancer (14), Breast cancer, and Invasive ductal breast carcinoma (5 each). When reported, latency ranged from 7 days to 451 days with a median of 148 days.
- There were 6 cases reporting 6 events in the Psychiatric disorders SOC for the paediatric age group. The 6 events reported were Suicidal ideation (3), Anorexia nervosa, Psychotic disorder and Suicide attempt (1 each). The events were assessed as unrelated to BNT162b2 by the investigator and the Sponsor.
- The distribution of the most frequently reported serious PTs (≥ 2%) by age group in the 661 CT cases where the participants were directly exposed to BNT162b2, is shown in figure 13 (not reproduced here). Events of maternal exposure to be reported more frequently in adult patients compared to elderly and paediatric subjects is expected.

- Post-marketing: Paediatric (19,637), Adults (492,065), Elderly (87,443) and Unknown (57,128).
  - The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 51, Table 52, and Table 53 (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, Injury, poisoning and procedural complications in the paediatric age group and Skin and subcutaneous tissue disorders in the elderly age group.
  - In the Reproductive system and breast disorders SOC for adult age group, event seriousness was assessed as serious (16,551) and non-serious (68,336). Event outcome was reported as resolved/resolving (29,006), not resolved (37,691), resolved with sequel (819), and unknown (17,892). The most commonly reported PTs (>1000 occurrences) in Reproductive system and breast disorders for the adult and elderly age group were Heavy menstrual bleeding (15,021), Menstrual disorder (10,459), Menstruation delayed (8342), Menstruation irregular (7656), Dysmenorrhoea (7477), Intermenstrual bleeding (6993), Amenorrhoea (5922), Polymenorrhoea (5310), Vaginal haemorrhage (2529), Breast pain (2254), Oligomenorrhoea (1654), Hypomenorrhoea (1468), and Postmenopausal haemorrhage (1321). 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.
  - There were 2860 cases reporting 4376 events in the in Injury, poisoning and procedural complications SOC for the paediatric age group. Of note, some cases more reported more than 1 PT. Event seriousness was assessed as serious (265) and non-serious (4111). Event outcome was reported as resolved/resolving (265), not resolved (63), resolved with sequel (7), unknown (4036) and fatal (6). The fatal cases are reviewed in Section Death. The majority of cases (2481 cases) reported events indicative of medication error and/or off label use. The most commonly reported PTs (>100 occurrences) in Injury, poisoning and procedural complications for the paediatric age group were Poor quality product administered (816), Off label use (401), Inappropriate schedule of product administration

(400), Product administered to patient of inappropriate age (354), Expired product administered (324), Product preparation issue (251), Overdose (244), Product use issue (238), Underdose (173), Fall (160), Product preparation error (151), Incorrect dose administered (142), and Product storage error (105). Of the 160 events of Fall, 82 were assesses as non-serious and 78 were serious. The outcome was reported as resolved/resolving (92), not resolved (7), resolved with sequel (4), unknown (57). The co-reported PTs (> 20 occurrences) in these 160 cases reporting Fall were Loss of consciousness (67), Presyncope (50), Syncope (49), Malaise (28), Pyrexia (27), Dizziness (26), Headache (24), Seizure (24), and Pallor (23). Off label use, Product administered to patient of inappropriate age and Product use issue cases are reviewed in Section Off-Label Use. Poor quality product administered, Inappropriate schedule of product administration, Expired product administered, Product preparation issue, Product preparation error, Incorrect dose administered, Product storage error and Underdose are reviewed in Section Medication Errors. Overdose is reviewed in Section Overdose.

- In the Skin and subcutaneous tissue disorders SOC for elderly age group, event seriousness was assessed as serious (3919) and non-serious (11,935). Event outcome was reported as resolved/resolving (7414), not resolved (4727), resolved with sequel (149), unknown (3561) and fatal (68). The fatal cases are reviewed in Section Death. The most commonly reported PTs (>250 occurrences) in Skin and subcutaneous tissue disorders for the adult and elderly age group were Rash (2902), Pruritus (2665), Erythema (1922), Urticaria (1539), Hyperhidrosis (771), Rash pruritic (611), Eczema (340), Rash erythematous (337), and Blister (273). Most of these events are listed or consistent with listed events as per the current RSI.
- The distribution of the most frequently reported overall PTs (≥ 2%) by age group is shown in figure 14 (not reproduced here). Most of these events are listed or consistent with listed events as per the current RSI.

MAH's conclusion

A review of 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 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).*

Clinical trial data

- Number of cases: 15 (blinded therapy [2], BNT162b2 [13]) (2.1% of 721 cases in the total CT dataset) compared to 16 cases (2.3%) retrieved in the first PSUR.
- Country of incidence: US (12), Argentina (2), Brazil (1).
- Subjects' gender: female (8), male (7).

- Subjects' age in years (n = 15), range: 18 – 84, mean: 53.7, median: 56.0.
- Medical history (n = 14): the relevant medical conditions reported more than were coded to PTs Hypertension, Myocardial infarction (3 each), Depression (2).
- COVID-19 Medical history: None.
- Co-suspects: The reported co-suspects included fexofenadine, fluoxetine (1 each).
- Reported relevant PTs (15): Syncope (8), Anxiety (2), Dizziness, Dyspnoea, Loss of consciousness, Palpitations, Tachycardia (1 each). The event tachycardia was assessed as related to BNT162b2 by the investigators.
- Time to event onset (n = 15; no events reported a fatal outcome) range 7 days to 271 days.
- Duration of event (n = 11 of 15 relevant events with outcome of resolved/resolved with sequelae): ranges from <24 hours to 30 days.

Post-authorisation data

- Number of relevant cases: 104,405 (15.9% of 657,528 cases, the total PM dataset), compared to 57,806 cases (17.7%) retrieved in the first PSUR; medically confirmed cases (38,436).
- Country of incidence (≥2%): Germany (16,624), UK (15,168), Netherlands (9240), France (8378), Japan (8126), US (7575), Italy (6119), Australia (5014), Philippines (2695), Spain (2248), Sweden (2114).
- Subjects' gender: female (73,772), male (28,408) and unknown (2225).
- Subjects' age in years (n = 97,495), range: 2 - 121, mean: 43.9, median: 42.0.
- Medical history (n = 40,679): the most frequently (≥2%) reported relevant medical conditions included Hypertension (4847), Asthma (3930), Depression (1196), and Anxiety (1104).
- COVID-19 Medical history (n = 6145): COVID-19 (3381), Suspected COVID-19 (2551), Post-acute COVID-19 syndrome (73), SARS-CoV-2 test positive (42), COVID-19 pneumonia (27), Coronavirus infection (23), Asymptomatic COVID-19 (21), Exposure to SARS-CoV-2(18), SARS-CoV-2 antibody test positive (6), Occupational exposure to SARS-CoV-2 (2), Coronavirus test positive (1).
- Co-suspects (n = 924): the most frequently (≥ 10 occurrences) reported co-suspect vaccines/medications included influenza vaccine (125), COVID 19 vaccine NRVV AD (83), adalimumab, (33), COVID-19 Moderna vaccine, hepatitis A vaccine (26 each), ocrelizumab, ibuprofen (12 each), and treprostinil (11).
- Number of relevant events: 133,499; serious (47,556), non-serious (86,005).
- Most frequently reported relevant PTs (≥2%): Dizziness (37,982), Dyspnoea (23,756), Paraesthesia (19,809), Palpitations (12822), Tachycardia (8253), Hyperhidrosis (7234), Syncope (6408), Blood pressure increased (6337), Loss of consciousness (3542), Anxiety (3084), and Paraesthesia oral (2284).
- Time to event onset (n = 101,754), range < 24 hours to 365 days, median: 1 day.
- Duration of event (n = 17,486 of 133,499 relevant events with outcome of resolved/resolved with sequelae) ranged from <24 hours to 365 days.
- Relevant event outcome: fatal (552), resolved/resolving (65,522), resolved with sequelae (2163), not resolved (39,343), unknown (26,894).

- The reported cause of death was (≥30 occurrences) coded to the PTs Dyspnoea (241), Loss of consciousness (73), Pyrexia (62), Cardiac arrest (48), Cough and Covid 19 (36 each), Syncope (33), Dizziness (32), Vomiting (31) and Cardio-respiratory arrest (30). When the medical history was provided (n = 296), significant medical conditions included (≥ 25 occurrences) Hypertension (114), Diabetes mellitus (38), and Chronic obstructive pulmonary disease (29).

Analysis by age group

- Clinical data: Adults (9) and Elderly (6).
    - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (3916), Adults (80,942), Elderly (13,000) and Unknown (6547).
    - No significant difference was observed in the reporting proportion of frequently (≥2%) reported relevant events between the adult and elderly population. A higher reporting proportion of relevant PT, Syncope was observed in the paediatric population when compared to the adult or elderly population (23.4% in paediatric vs 10.2% in adults vs 6.6% in elderly). This is consistent with expectations based on age-related event reports from other vaccines.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 14,406 (13.8% of the cases reporting stress/anxiety ADRs). The reporting proportion of cases with fatal outcome is higher in subjects with comorbid conditions (1.4%) when compared to the reporting proportion observed in subjects without comorbidities (0.3%). In these cases, underlying comorbidities or events not related to stress/anxiety, are likely to be contributory to subject's death.

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.

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: 44 (blinded therapy [19], BNT162b2 [24] and placebo [1]) (6.1% of 721 cases, the total CT dataset) compared to 46 cases (6.6%) retrieved in the first PSUR.
- Country of incidence: the US (35), Argentina (5), Brazil, Dominican Republic, Germany, Turkey (1 each).

- Subjects' gender: female (13) and male (31).
- Subjects' age in years (n = 44), range: 20.0 – 89.0 years, mean: 62.2 years, median: 63.0 years
- Medical history (n = 40): the most frequently (>5 occurrences) reported medical conditions included Hypertension (24), Depression, Obesity (10 each), Hypercholesterolaemia, Hyperlipidaemia (8 each), Anxiety, Gastro-oesophageal reflux disease (7 each), Benign prostatic hyperplasia, Insomnia, and Type 2 diabetes mellitus (6 each).
- COVID 19 Medical history: None.
- Causes of death most frequently reported (>2 occurrences): Death (7), Disease progression, Pulmonary embolism (4 each), Cardiac arrest, Cardio-respiratory arrest, Completed suicide, and Sepsis (3 each).
- Autopsy results were provided in 4 cases. Angiosarcoma, Arteriosclerosis, Cardio-respiratory arrest, Pulmonary embolism, Shock haemorrhagic, and Vascular neoplasm were singularly reported.
- Events with a fatal outcome (n = 54): The most frequently reported PTs (>2 occurrences): Death (7), Cardio-respiratory arrest, Pulmonary embolism (4 each), Completed suicide, and Sepsis (3 each). None of these events are considered related to blinded therapy/BNT162b2.
- Co-suspects were reported in 2 cases and they were cocaine and fentanyl (1 each).
- Time to event onset (n = 39), range: 14 – 363 days, median: 230 days.

Post-authorisation data

- Number of cases: 5215 (0.8% of 657,528 cases, the total PM dataset) compared to 5042 (1.5% of 327,125 cases, the total PM dataset) analysed in the first PSUR; medically confirmed cases (3482).
- Country of incidence (≥2%): Japan (961), Germany (797), France (643), the US (380), Italy (254), the UK (243), Austria (182), Netherlands (128), Philippines (126), Australia (123), and New Zealand (115).
- Subjects' gender: female (2089), male (2775), unknown (351).
- Subjects' age in years (n = 4608), range: 5.0 months – 106.0 years, mean: 71.4 years, median: 75.0 years.
- Medical history (n = 3132) : The most frequently reported (≥100 occurrences) medical conditions included cardiac and vascular disorders (e.g., Hypertension [1181], Atrial fibrillation [340], Cardiac failure [215], Dyslipidaemia [150], Myocardial ischaemia [145], Cerebrovascular accident [119], Hypercholesterolaemia [112], Myocardial infarction [107], Coronary artery disease [100]). Other most frequently reported (>100 occurrences) medical conditions included Diabetes mellitus (379), Type 2 diabetes mellitus (227), Chronic obstructive pulmonary disease (213), Chronic kidney disease (186), Dementia (174), Obesity (173), Depression (113), Asthma (105), Hypothyroidism (103), and Tobacco user (102).
- COVID 19 Medical history (n = 161): COVID-19 (117), Suspected COVID-19 (19), COVID-19 pneumonia (10), Asymptomatic COVID-19 (9), Exposure to SARS-CoV-2 (5), Coronavirus infection, SARS-CoV-2 test positive (3 each), and SARS-CoV-2 antibody test positive (1).
- Causes of death most frequently reported (>100 occurrences): Death (1229), COVID-19 (503), Cardiac arrest (323), Vaccination failure (310), Cardio-respiratory arrest (255), Myocardial infarction (251), Dyspnoea (242), Pulmonary embolism (217), Sudden death (202), Drug

ineffective (199), Pyrexia (193), Cardiac failure (172), COVID-19 pneumonia (169), Pneumonia (155), Cerebral haemorrhage (127), and Cerebrovascular accident (124).

- Autopsy results were provided in 281 cases and the most commonly reported (≥10 occurrences) were: Pulmonary embolism (26), Acute myocardial infarction, Myocardial infarction (20 each), Arteriosclerosis coronary artery, Pulmonary oedema (17 each), Arteriosclerosis (16), Cardiomegaly (15), Myocarditis (14), Cardiac failure acute (13), Pulmonary congestion (12), Cardiac failure, and Cerebral haemorrhage (10 each).
- Co-suspect vaccines/medications (n = 145): the most frequently reported (>2 occurrences) were COVID-19 AstraZeneca vaccine (14), influenza vaccine (9), influenza vaccine INACT SAG 4V, influenza vaccine INACT SPLIT 4V (8 each), apixaban, methotrexate (7 each), levofloxacin (5), acetylsalicylate lysine, adalimumab, influenza vaccine INACT SAG 3V, paracetamol, and rivaroxaban (3 each).
- Events with a fatal outcome (n = 12,250): The most frequently reported (≥2%) events coded to the PTs: Death (1192), COVID-19 (542), Vaccination failure (379), Cardiac arrest (338), Dyspnoea (277), Drug ineffective (270), Cardio-respiratory arrest (269), Myocardial infarction (258), Immunisation (257), Sudden death (245), Pulmonary embolism (224), Pyrexia (223), Cardiac failure (174), COVID-19 pneumonia (170), Pneumonia (159), Cerebrovascular accident (132), Cerebral haemorrhage (126), and Malaise (102).
- Time to fatal event onset (n = 8523), range: <24 hours to 306 days, median: 6 days.

Analysis by age group

- Clinical trial: Adults (18-64) (25), and Elderly (65 years and older) (19).
    - 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) (77), Adults (18-64 years) (1220), Elderly (65 years and older) (3390) and Unknown (528).
    - There is a significant difference observed in the reporting proportion for majority of the frequently reported fatal events (≥2% events listed above) in elderly population when compared to adult population due to higher proportion of fatal cases reported in subjects over 64 years of age (65.1% vs 23.4%, respectively). There is no meaningful comparison between elderly vs paediatric population possible due to the low number of paediatric fatal cases reported (1.5% vs 65.1%, respectively).
    - Most of the cases reporting a fatal outcome (45.8%) were in subjects over 75 years of age. This reflects one of the priority groups targeted for vaccination by many regions and countries, including Europe and the US, that is, elderly (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: 2090 (0.3% of 658,249, the total dataset) when compared to 2760 (0.8% of 327,827 cases) in the first PSUR.
- 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 except COVID-19 pneumonia. In most of the cases reporting this event, the subject experienced vaccination failure or drug ineffective and majority of these cases reported

cardiac disorders, vascular disorders, diabetes mellitus, respiratory disorders as comorbid conditions.

Analysis by dose

- Number of vaccine doses administered at the time of the subjects' death:
    - First dose (1259)
    - Second dose (2379). Of the 2379 cases, 660 cases (27.7%) reported a latency of same day to 3 days after vaccination. There were 5882 fatal events. The most frequently reported (>100 occurrences) fatal events were coded to PTs COVID-19 (432), Death (376), Vaccination failure (362), Drug ineffective (177), Cardio-respiratory arrest (158), COVID-19 pneumonia (142), Cardiac arrest (136), Pulmonary embolism (126), Dyspnoea (125), Myocardial infarction (103), and Pyrexia (102).
    - Third dose (407). Majority of these cases (>10 occurrences) originated from France (77), Germany (70), UK (59), Italy (24), Austria, the US (23 each), Sweden (19), Spain (14), Belgium, Israel (13 each), Hungary, Netherlands, Norway (11 each). There were 1272 fatal events. The most frequently reported (>20 occurrences) fatal events were coded to PTs Immunisation23 (250), Death (111), Off label use (64), Sudden death (43), Interchange of vaccine products (38), Cardiac arrest (36), COVID-19, Pyrexia (24 each), and Pulmonary embolism (21).
    - In the remaining cases (1170), it was not specified if the subjects received the first, second or the third vaccine dose at the time of the subject's death.

Analysis by dose interval

- Among the 4595 cases involving subjects, who received 3 doses of BNT162b2 with different time intervals than the recommended intervals, there were 101 cases (360 fatal AEs) that reported death in 97 elderly and 4 adult subjects.
- The most frequently (≥ 2%) reported AEs leading to death the subjects, who received 3 doses of BNT162b2 administered with time intervals different from recommended posology [Immunisation23 (65), Death (21), Sudden death (15), Off label use (11), Cardiac failure (10), Pyrexia (9) and Cardiac arrest (8)], are consistent with the most commonly reported fatal events in the overall PM dataset, except for the PT Immunisation that is selected per case processing conventions to collect cases reporting third/booster doses and the PT Off label use that is reported in this dataset due to the administration of dosages in unapproved time intervals.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

MAH's conclusion

No new risks were identified following review of fatal cases, particularly in the comorbid elderly population.

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

- There were no serious clinical trial cases of overdose of the vaccine reported during the current interval period, compared to 2 cases (0.3%) retrieved in the first PSUR.

Post-authorisation data

- Number of cases: 1985 (0.3% of 657,528 cases, the total PM dataset), compared to 1498 cases (0.5%) retrieved in the first PSUR; medically confirmed cases (1430).
- Country of incidence (≥2%): US (1060), Italy (231), Portugal (148), UK (97), Japan (89), Canada (75), France (58) and Germany (38).
- Subjects' gender: female (823), male (559) and unknown (603).
- Subjects' age in years (n = 1339), range: 0.17 – 98, mean: 39.6, median: 38.0.
- Medical history (n = 277): the most frequently (≥2%) reported medical conditions included: Hypertension (38), Drug hypersensitivity (27), Asthma (21), COVID-19 (18), Obesity (16), Diabetes mellitus (15), Depression, Food allergy (12 each), Hypersensitivity (8), Attention deficit hyperactivity disorder, Hypothyroidism, Rheumatoid arthritis (7 each), Allergy to metals, Dementia, Hypercholesterolaemia, Suppressed lactation,19 Tobacco user (6 each), Fibromyalgia, Migraine, Overweight, Pain and Seasonal allergy (5 each).
- Co-suspect vaccines/medications: influenza vaccine (8), COVID-19 Moderna vaccine (4), COVID-19 AstraZeneca vaccine, sodium chloride (2 each), furosemide, vildagliptin, glatiramer acetate, influenza vaccine RHA 3V (baculovirus), letrozole, amoxicillin, simvastatin, meningococcal group B RLP2086, meningococcal vaccine A/C/Y/W conj (dip tox), prednisone, methotrexate sodium and water for injection (1 each).
- Number of relevant events: 1985; serious (57), non-serious (1928).
- Relevant PTs: Overdose (1881) and Accidental overdose (104).
- Relevant event outcome: resolved/resolving (46), not resolved (11), fatal (2), resolved with sequelae (2), unknown (1924).
- Most frequently co-reported PTs (≥2%): Product preparation error (413), Product preparation issue (369), Vaccination site pain (152), Pyrexia (147), Headache (140), Poor quality product administered (96), Fatigue (84), Incorrect dose administered (83), Immunisation23 (82), Pain in extremity (81), and Off label use (79).

Analysis by age group

- Paediatric (267), Adults (917), Elderly (211) and Unknown (590). 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: 109 (5.5% 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 2 ml for the paediatric subjects aged 5 through 11 years (728; 36.7% of the total cases reporting overdose);
- administration of undiluted vaccine (464; 23.4% 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 (270; 13.6% of the total cases reporting overdose);
- administration of a double dose of vaccine (156; 7.9% of the total cases reporting overdose);
- full adult dose of vaccine administered to paediatric subjects aged 5 through 11 years instead of the recommended 10 mcg dosage (69; 3.5% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 281 cases, the reason for overdose was not reported or unclear. No new significant safety information was identified based on the review of these cases. 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.

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; Substance abuse; Substance abuser; Substance dependence; Substance use; Substance use disorder; Toxicity to various agents; Withdrawal syndrome.*

Misuse Search criteria: *PTs 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.*

Post-authorisation data

- Number of cases: 45 (0.01% of 657,528 cases, the total PM dataset), compared to 65 cases (0.01%) retrieved in the first PSUR; medically confirmed cases (13).

- Country of incidence (≥2%): US (15), UK (7), Canada, France (5 each), Germany (4), Japan (3), Italy (2), Australia, Finland, Peru and Spain (1 each).
- Subjects' gender: female (28), male (14) and unknown (3).
- Subjects' age in years (n = 36), range: 11 - 90, mean: 52.2, median: 52.5.
- Medical history (n = 20): the most frequently (≥2 occurrences) reported medical conditions included Drug hypersensitivity, Hypertension and Suppressed lactation19 (2 each).
- COVID-19 Medical history (n = 2): COVID-19 and Exposure to SARS-CoV-2 (1 each).
- Co suspect vaccines/medications (n = 17): adalimumab (3), COVID-19 Moderna vaccine (2), abatacept, apixaban, clozapine, COVID-19 AstraZeneca vaccine, ebastine, fenofibrate, linagliptin, metformin, pantoprazole, pirfenidone, teriflunomide and valproate (1 each).
- Number of events: 233 (of which 46 were events of interest); serious (10), non-serious (36).
- Relevant PTs: Intentional product misuse (11), Intentional dose omission (10), Needle track marks (8), Toxicity to various agents and Intentional product use issue (7 each), Disturbance in social behaviour, Drug level increased and Drug tolerance decreased (1 each).
- Co-reported AEs (≥2 %): Off label use (7), Interchange of vaccine products (5), Drug ineffective, Asthenia and Pruritus (4 each).
- Time to event onset (n = 13), range: 0 - 7 days, median: 0 days.
- Relevant event outcome: resolved/resolving (8), not resolved (11), unknown (27).

Analysis by age group

- Post-marketing: Paediatric (3), Adults (24), Elderly (11) and Unknown (9). 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: 1 dose in 15 cases, 2 doses in 8 cases, 3 doses in 3 cases and number of doses was not specified in 19 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 45 cases representing 0.01% of the overall post-marketing dataset, that reported events indicative of misuse. Most of the cases involved subjects who intentionally omitted their second BNT162b2 dose or received the second dose after the recommended time frame per the RSI. In general, the most frequently co-reported events observed in these cases was 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.

Occupational exposure

Search criteria: *PTs Exposure to contaminated device; Occupational exposure to product; Occupational exposure to radiation; Occupational exposure to toxic agent*.

Post-authorisation data

- Number of cases: 41 (0.01% of 657,528 cases, the total PM dataset), compared to 32 cases (0.01%) retrieved in the first PSUR; medically confirmed cases (27), NMC cases (14).
- Country of incidence: Japan (17), US (12), Germany (3), Canada, Denmark, Spain (2 each), Italy, Netherlands and UK (1 each).
- Subjects' gender: female (26), male (4) and unknown (11).
- Subjects' age in years (n = 16), range: 14 - 60, mean 38, median 35.0.
- Medical history (n = 10): Chorioretinopathy (7), Allergy to animal, Depression, Disease risk factor, Dust allergy, Food allergy, Milk allergy, Mite allergy, Seasonal allergy and Thyroid hormones decreased (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspects (n = 3): COVID-19 AstraZeneca vaccine, influenza vaccine, COVID-19 J&J vaccine and sodium chloride (1 each).
- Number of events: 94 (of which 40 were events of interest); serious (1), non-serious (39).
- Reported relevant PT: Occupational exposure to product (40).
- Co-reported AEs (≥2 occurrences): Ocular hyperaemia (3), Burning sensation, Erythema, Exposure via eye contact, Eye irritation, Interchange of vaccine products, Off label use, Product use issue and Underdose (2 each).
- Time to event onset (n = 6): < 24 hours.
- Relevant event outcome: resolving (1), unknown (39).

Analysis by age group

- Post-marketing: Paediatric (1), Adults (15), Unknown (25). 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 41 cases representing 0.01% 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.

Lack of therapeutic efficacy

Search Criteria: PTs Drug ineffective, Vaccination failure.

Post-authorization data

- Number of cases: 21,457 (3.3% of 657,528 cases, the total PM dataset), compared to 6376 cases (1.9%) retrieved in the first PSUR; medically confirmed cases (16,473).
- Relevant lack of efficacy events: 21,457 (Vaccination failure [11,934] and Drug ineffective [9523]).
- Country of incidence (≥2%): Austria (9009), US (2016), France (1865), Germany (1484), Portugal (1479), Italy (891), UK (806), Spain (480), and Japan (450). Please note, there is an increased number of cases from Austria as compared to the PSUR #1 (204 cases in PSUR #1). This is due to active solicitation of LOE cases, including retrospective cases, by Austrian Board of Health starting from August 2021.
- Subjects' gender: female (11,504), male (8744) and unknown (1209).
- Subjects' age in years (n = 19,261), range: 6 – 106, mean: 52.8, median: 50.0.
- Relevant event seriousness: all serious.

Confirmed vaccination failure (10,877 cases)

- Vaccination failure was reported in 10,877 cases, indicative of appropriately and fully vaccinated subjects (appropriate series of 2 doses at the appropriate interval), who developed clinical, and laboratory confirmed (e.g., COVID-19 PCR positive test, antigen test) COVID 19 infection, on or after day 7 post second dose. In 175 of these 10,877 cases, a third dose was also administered (including 1 case with administration of a fourth dose).
- Age groups: Adolescent (182), Adults (7099), Elderly (3479) and Unknown (117).
- Time to event onset was known for 10,609 cases; in the remaining 268 cases, it was implied that vaccination failure was reported on or after day 7 post second dose, however detailed information was not provided:
    - Time to onset reported after the second dose ranged from 7 to 309 days.
    - Time to onset reported after the third dose ranged from 1 day to 186 days.
    - Time to onset reported after the fourth dose; 13 days in 1 subject.
- Reported COVID-19 infection related events: COVID-19 (10,517), COVID-19 pneumonia (387), SARS-CoV-2 test positive (173), Suspected COVID-19 (33), Coronavirus pneumonia (4), Coronavirus infection (3), Post-acute COVID-19 syndrome (2), Multisystem inflammatory syndrome in children, Pneumonia viral, and SARS-CoV-2 sepsis (1 each).
- Outcome of COVID-19 infection related events:47 resolved/resolving (2406), resolved with sequelae (20), not resolved (553), unknown (7738), and fatal (409).
- Of the 10,877 subjects with confirmed vaccination failure, in 1184 cases, the COVID 19 events were severe, resulting in: Hospitalisation (non-fatal/non-life threatening) (N=730), Disability (N=5), Life threatening (N=78), Death (N=371).

Suspected vaccination failure (1777 cases)

- Lack of efficacy (PTs Drug ineffective or Vaccination failure) was reported in 1777 cases, wherein the subjects received 2 doses of vaccine at appropriate interval and reported to develop COVID-

19 infection on or after day 7 post second dose, but laboratory confirmation of the infection (e.g., COVID-19 PCR positive test, antigen test) was not reported or clinical disease was unconfirmed (i.e., asymptomatic COVID-19). In 26 of these 1777 cases, a third dose was also administered.

- Age groups: Adolescent (25), Adults (1136), Elderly (559) and Unknown (57).
- Time to event onset was known for 1623 cases; in the remaining 154 cases, it was implied that vaccination failure was reported on or after day 7 post second dose, however detailed information was not provided:
    - Time to onset reported after the second dose ranged from 7 to 300 days.
    - Time to onset reported after the third dose ranged from 1 day to 56 days.
- Reported COVID-19 infection related events:122 COVID-19 (825), Asymptomatic COVID 19 (507), Suspected COVID-19 (414), COVID-19 pneumonia (42), SARS CoV 2 test positive (27), and Coronavirus pneumonia (1).
- Outcome of COVID-19 infection related events: resolved/resolving (611), resolved with sequelae (4), not resolved (109), unknown (1057), and fatal (35).

Not a vaccination failure case (8803 cases)

- There were 8803 cases reporting Drug ineffective that were indicative of occurrence of the disease:
    - in subjects who experienced a vaccine preventable illness from day 14 after receiving the first dose to day 6 after receipt of the second dose;
    - in subjects for whom it was not possible to determine whether they received the appropriate series of 2 doses at the appropriate interval;
    - in subjects for whom it was not possible to determine how many days have passed since the first or second dose administration.
- Age groups: Children (13), Adolescent (137), Adults (5046), Elderly (1832) and Unknown (1775).
- Reported COVID-19 infection related events:122 COVID-19 (7117), Suspected COVID-19 (1167), Asymptomatic COVID-19 (261), COVID-19 pneumonia (255), SARS-CoV-2 test positive (97), Post-acute COVID-19 syndrome (7), Coronavirus infection (6), Pneumonia viral (3), Coronavirus pneumonia, Multisystem inflammatory syndrome in children (2 each), Multisystem inflammatory syndrome, and SARS-CoV-2 test false negative (1 each).
- Outcome of COVID-19 infection related events:47 resolved/resolving (2090), resolved with sequelae (56), not resolved (630), unknown (5872), and fatal (277).
- According to the RSI, subjects may not be protected until at least 7 days after their second dose of the vaccine, therefore for the above 8803 cases where lack of efficacy was reported, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness.

SARS-CoV-2 Variants (6526 cases)

In 6526 of the 21,457 cases, information on SARS-CoV-2 variants was provided.

- Delta (India) variant (5833 cases)

    - Country of incidence (>2 occurrences): Austria (5362), France (324), US (52), Germany (27), Italy (17), Norway (16), Turkey (7), and Hong Kong (4).
    - Lack of efficacy events: Vaccination failure (4345) and Drug ineffective (1488).
    - Outcome of COVID-19 infection related events: 47 resolved/resolving (186), resolved with sequelae (3), not resolved (81), unknown (5465), and fatal (124).
- Alpha (UK) variant124 (620 cases)
    - Country of incidence: Austria (401), France (150), Germany (24), Greece (23), Italy (17), Spain (2), Czech Republic, Norway, and Saudi Arabia (1 each).
    - Lack of efficacy events: Vaccination failure (558) and Drug ineffective (62).
    - Outcome of COVID-19 infection related events: 47 resolved/resolving (90), resolved with sequelae (4), not resolved (26), unknown (465), and fatal (55).
- C1 variant [as reported] (36 cases)
    - Country of incidence: France (36).
    - Lack of efficacy events: Vaccination failure (29) and Drug ineffective (7).
    - Outcome of COVID-19 infection related events: resolving (3), not resolved (3), unknown (27), and fatal (3).
- Beta (South Africa) variant124 (11 cases)
    - Country of incidence: France (7), Germany (2), Austria, and Israel (1 each).
    - Lack of efficacy events: Vaccination failure (8) and Drug ineffective (3).
    - Outcome of COVID-19 infection related events: resolved/resolving (4), unknown (6), and fatal (1).
- South African or Brazilian variant [as reported] (9 cases)
    - Country of incidence: France (9).
    - Lack of efficacy events: Vaccination failure (9).
    - Outcome of COVID-19 infection related events: resolved/resolving (4), not resolved (2), and unknown (3).
- Lambda (Peru) variant (5 cases)
    - Country of incidence: Israel (5).
    - Lack of efficacy events: Vaccination failure (5).
    - Outcome of COVID-19 infection related events: unknown (5).
- Omicron variant (4 cases)
    - Country of incidence: Hong Kong (2), Denmark, and US (1 each).
    - Lack of efficacy events: Vaccination failure (2) and Drug ineffective (2).
    - Outcome of COVID-19 infection related events: resolved (1) and unknown (3).
- V3 variant [as reported] (4 cases)
    - Country of incidence: France (4).

- Lack of efficacy events: Vaccination failure (3) and Drug ineffective (1).
- Outcome of COVID-19 infection related events: unknown (3) and fatal (1).

- Others (4 cases)
  - In 4 other cases, variant was reported as Eta (Nigeria), Gamma (Brazil), Kappa (India), and B.1.1.29, respectively.

Literature

- Review of the literature did not identify any 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:

No new important safety concern could be identified for lack of therapeutic efficacy. Nevertheless, with the emergence of new SARS-CoV-2 variants lack of efficacy should remain under close scrutiny and the Rapporteur should be notified immediately in case of new findings or unexpected trends.

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: 22,533 (3.4% of 657,528 cases, the total PM dataset), compared to 4672 cases (1.4%) retrieved in the first PSUR; medically confirmed cases (5439).
- Country of incidence (≥2%): UK (13,188), Germany (1892), US (1629), the Netherlands (1137), and Canada (533).
- Subjects' gender: female (16,301), male (5050) and unknown (1182).
- Subjects' age in years (n = 18,844), range: 0.04 - 103 years, mean: 49.6, median: 50.0.
- Medical history (n = 10,789): the most frequently (≥2%) reported medical conditions included Breast feeding (1503), Suspected COVID-19 (1243), Hypertension (1050), Asthma (857), Immunodeficiency (748), COVID-19 (591), Disease risk factor (585), Clinical trial participant (570), Steroid therapy (407), Hypothyroidism (380), Rheumatoid arthritis (349), Diabetes mellitus (325), Depression (293), Drug hypersensitivity (285), Hypersensitivity (257), and Anxiety (219).
- COVID-19 Medical history (n = 1799): the most frequently (≥2%) reported medical conditions included Suspected COVID-19 (1243), and COVID-19 (591).
- Co-suspects (n = 1206): the most frequently (≥2%) reported co-suspect vaccines/medications included influenza vaccine (310), COVID-19 AstraZeneca vaccine (301), COVID-19 Moderna

vaccine (169), hepatitis A vaccine (99), influenza vaccine (surface antigen, inactivated, adjuvanted) (43), influenza vaccine inact split 4v (27), influenza vaccine inact sag 3v (23), and adalimumab (20).

- Number of events: 130,024 (of which 26,044 were events of interest).; 20 serious (6058), non-serious (20,003).
- Most frequently reported relevant PTs (≥2%): Off label use (22,002) and Product use issue (4001). Of note, of the 22,533 cases, 916 did not report additional events. The majority of cases described off-label use as
    - intentionally used in an unapproved population:
        - 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.
        - Those receiving anticoagulant therapy or with a bleeding disorder that would contraindicate an intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.
    - alternative dosing or scheduling regimens (i.e., Full primary series not received, longer/shorter amount 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.

<u>Analysis by dose interval</u>

- Among these cases, 1114 (468 serious and 646 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 (1069), Product use issue (120) and Product administered to patient of inappropriate age (3).
- Upon review, no significant differences in the occurrence of the most frequently relevant PTs and co-reported AEs and clinical outcome in subjects, who received the 3 doses of vaccine with not recommend time intervals compared to the population receiving BNT162b2 in unapproved conditions was identified.

<u>Literature</u>

- 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: Please also refer to the assessment of MAH's response to PRAC request 4a and 4b above from the first PSUR (section 'Post-approval regulatory requests' of this report). No new important safety concern could be identified for off-label use.

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*.

Post-authorisation data

- Number of cases: 844 (0.1% of 657,528 cases, the total PM dataset), compared to 472 cases (0.1%) retrieved in the first PSUR; medically confirmed cases (101).
- Country of incidence (≥2%): US (183), Germany (168), Netherlands (126), UK (74), Turkey (34), Japan (28), Canada, France (25 each), Brazil (19) and Sweden (17).
- Subjects' gender: female (483), male (297) and unknown (64).
- Subjects' age in years (n = 526), range: 11 - 99, mean: 53.7, median: 54.0.
- Medical history (n = 654): the most frequently (≥2%) reported medical conditions included Hypertension (33), Asthma (30), Seasonal allergy (27), Arthritis, Migraine (24 each), Arthralgia (23), Multiple sclerosis (20), Fibromyalgia, Rheumatoid arthritis (19), Chronic obstructive pulmonary disease, Diabetes mellitus, Drug hypersensitivity, Hypersensitivity (17 each), Hypothyroidism, Suppressed lactation (16 each), Fatigue, Psoriasis (15 each), Food allergy, Pain (14 each) and Headache (13).
- COVID-19 Medical history (n = 160): COVID-19 (65), Suspected COVID-19 (16), Post-acute COVID-19 syndrome (6).
- Co-suspects (n = 10): amoxicillin, certolizumab pegol, digoxin, etonogestrel, glimepiride, hydrocortisone acetate/neomycin sulfate/polymyxin B sulfate, influenza vaccine, insulin aspart, levothyroxine, mepolizumab, metformin, metoprolol tartrate, pioglitazone, prednisolone, risankizumab, tofacitinib citrate (1 each).
- Number of events: 1992 (of which 845 were events of interest); serious (22), non-serious (823).
- Relevant PTs: Therapeutic response unexpected (841) and Drug effective for unapproved indication (4).
- 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.
- Time to event onset (n = 270), range: 0 - 266 days, median: 2 days.
- Relevant event outcome: resolved/resolving (131), resolved with sequelae (5), not resolved (132), unknown (580).

Analysis by age group

- Post-marketing: Paediatric (9), Adults (377), Elderly (174) and Unknown (285). 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.

Update on special populations

Use in elderly

Clinical trial data

- Number of cases: 233 (blinded therapy [73], BNT162b2 [149], placebo [8], BNT162b2S01 [2] and BNT162b3 [1]) (32.3% of 721 cases, the total CT dataset), compared to 255 cases (36.0%) retrieved in the first PSUR.
- Country of incidence (≥2%): US (201), Argentina (17), Germany (6) and China (5).
- Subjects' gender: female (99), male (134).
- Subjects' age in years (n = 233), range: 65 - 91, mean: 72.8, median: 72.0.
- Medical history (n = 214): the most frequently HLGT (≥20 occurrences) reported medical conditions included vascular hypertensive disorders (124), lipid metabolism disorders (79), joint disorders (58), gastrointestinal motility and defaecation conditions (54), glucose metabolism disorders (incl. diabetes mellitus) (52), allergic conditions (39), appetite and general nutritional disorders (37), cardiac arrhythmias (33), prostatic disorders (excl. infections and inflammations) (32), lifestyle issues (30), thyroid gland disorders (27), coronary artery disorders, bronchial disorders (excl. neoplasms) (26 each), depressed mood disorders and disturbances, gastrointestinal therapeutic procedures (23 each), infections - pathogen unspecified, anxiety disorders and symptoms (21 each), bone disorders (excl. congenital and fractures), sleep disorders and disturbances (20 each).
- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspects (n = 5): ibuprofen (2), dabigatran etexilate mesilate, loratadine and pravastatin sodium (1 each).
- Number of relevant events: 295.

- Most frequently reported PTs (≥2%): Prostate cancer (11), Cerebrovascular accident, Coronary artery disease, Osteoarthritis, Syncope and Urinary tract infection (6 each).
- BNT162b2 related event coded to the PT Transient ischaemic attack (1).
- Time to event onset: n = 278, range: from 1 day to 418 days, median: 140 days.
- Event outcome: fatal (24), resolved/resolving (196), resolved with sequelae (8), not resolved (66), unknown (1).

Post-authorisation data

- Number of cases: 87,982 (13.4% of 657,528 cases, the total PM dataset), compared to 61,833 cases (18.9%) retrieved in the first PSUR; medically confirmed cases (40,971).
- Country of incidence (≥2%): Japan (13,413), Netherlands (13,029), France (12,770), Germany (10,954), US (7058), UK (6448), Italy (4158), Austria (3244), Spain (1982) and Sweden (1697).
- Subjects' gender: female (53,863), male (32,819) and unknown (1300).
- Subjects' age in years (n = 85,323), range: 65 – 121, mean: 74.7, median: 73.0.
- Medical history (n = 38,252): the most frequently (≥2200 occurrences) reported HLGT medical conditions included vascular hypertensive disorders (12,299), glucose metabolism disorders (incl. diabetes mellitus) (5318), allergic conditions (4817), viral infectious disorders (4505), lipid metabolism disorders (3380), cardiac arrhythmias (3376), bronchial disorders (excl. neoplasms) (3146), joint disorders (3038), thyroid gland disorders (2684), central nervous system vascular disorders (2360), coronary artery disorders (2302) and lifestyle issues (2208).
- COVID-19 Medical history (n = 3723): the most frequently (≥27 occurrences) reported medical conditions included COVID-19 (2482), Suspected COVID-19 (1083), COVID 19 pneumonia (52), Exposure to SARS-CoV-2 (28) and SARS CoV-2 test positive (27).
- Co-suspects (n = 1535) the most frequently (≥26 occurrences) reported co-suspect vaccines/medications included influenza vaccine (165), adalimumab (105), COVID-19 AstraZeneca vaccine (66), COVID-19 Moderna vaccine (57), influenza vaccine (surface antigen, inactivated, adjuvanted) (45), apixaban (42), influenza vaccine inact SAG 3V (30), mepolizumab, methotrexate (26 each).
- Number of events: 278,931; the most frequently (≥2%) reported PTs: Headache (10,954), Fatigue (10,818), Pyrexia (9794), Vaccination site pain (8396), Malaise (8286), Myalgia (7980), Arthralgia (6642), Nausea (5773), Immunisation (5693), Chills (5410), COVID-19 (5101), Pain in extremity (5022), Dizziness (4375), Off label use (4213), Vaccination failure (3754), Asthenia (3691), Dyspnoea (3600), Pain (3513), Herpes zoster (3114), Rash (2913), Diarrhoea (2826), Interchange of vaccine products (2817), Inappropriate schedule of product administration (2767), Pruritus (2694), Vomiting (2152), Drug ineffective (2137), Erythema (1938), Vaccination site swelling (1886).
- Event seriousness: serious (105,076), non-serious (173,938).
- Time to event onset: n = 211,483, range: from <1 to 525 days, median: 1 day.
- Event outcome: fatal (8557), resolved/resolving (121,566), resolved with sequelae (4333), not resolved (63,715), unknown (81,488).

Analysis by presence of comorbidities

- Number of elderly subjects with comorbidities: 19,599 (22.2% of 88,215 cases, the total elderly dataset). Upon review, no significant differences in the occurrence of the most frequently reported AEs and in the fatalities in the elderly subjects with comorbidities compared to the elderly population without underlying diseases was identified.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 in elderly patients.

MAH's conclusion

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: 25 (blinded therapy [23], BNT162b2 [1] and placebo [1]), originated from Protocol C4591007 (3.5% of 721 cases, the total CT dataset), compared to no cases retrieved in the first PSUR.

Post-authorisation data

- Number of cases: 83 (0.01% of 657,528 cases, the total PM dataset), compared to 64 cases (0.02%) retrieved in the first PSUR.

Rapporteur assessment comment:
The use of Comirnaty in children <5 years old is 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: 18 (blinded therapy [14] and BNT162b2 [4]), originated from Protocols C4591007, C4591007-OPEN LABEL and C4591024 (2.5% of 721 cases, the total CT dataset), compared to no cases retrieved in the first PSUR.
- Country of incidence: US (9), Poland (6) and Finland (3).
- Subjects' gender: female, male (9 each).
- Subjects' age in years (n = 18), range: 5 – 11, mean: 7.4, median: 7.0
- Medical history (n = 8): the most frequently (≥2) reported medical conditions included Asthma (3), Nasopharyngitis and Hemiparesis (2 each).

- COVID-19 Medical history: None.
- Co suspect vaccines/medications (n = 2): bamlanivimab, etesevimab and HPV vaccine (1 each).
- PTs (20): Abdominal pain, Abscess limb, Appendicitis, Arthritis bacterial, Asthma, Dehydration, Disease recurrence, Epilepsy, Epiphyseal fracture, Foreign body ingestion, Infusion related reaction, Pancreatitis, Pharyngitis streptococcal, Pneumonia respiratory syncytial viral, Pyelonephritis, Pyrexia, Testicular appendage torsion, Transient ischaemic attack, Upper limb fracture and Urinary tract infection (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy, but the AE Transient ischaemic attack, occurred in an 11-year-old female subject on day 113 after the second dose of BNT162b2. The investigator considered the SAE related to BNT162b2 and to the concomitant Human papillomavirus vaccine, received 4 days prior to the onset of the event. The MAH considered there was not a reasonable possibility that the event was related to vaccine administration, based on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause this event and time course. A potential contributory role of concurrent viral herpangina is an alternative explanation, as neurologic complications rarely occur with enteroviruses.
- Time to event onset: n = 20, range: 3 - 153 days, median: 31.5 days.
- Duration of event: n = 14, range: <1 day to 44 days, median: 6 days.
- Event outcome: resolved/resolving (20).

Post-authorisation data

- Number of cases: 1227 (0.2% of 657,528 cases, the total PM dataset), compared to 68 cases (0.02%) retrieved in the first PSUR; medically confirmed 692 cases.
- Country of incidence (≥2%): US (941), Canada (57), Germany, Puerto Rico (46 each) and France (27).
- Subjects' gender: female (435), male (451) and unknown (341).
- Subjects' age in years (n = 1049), range: 5 – 11, mean: 8.6, median: 9.0.
- Medical history (n = 167): the most frequently (>2) reported medical conditions included Asthma (30), Food allergy (21), Attention deficit hyperactivity disorder, Hypersensitivity (17 each), Seasonal allergy (10), Drug hypersensitivity (9), Anxiety, Autism spectrum disorder (8 each), Epilepsy (6), Eczema, Nasopharyngitis (5 each), Cardiac murmur, Coeliac disease, Constipation, Seizure (4 each), Obesity, Pyrexia (3 each).
- COVID-19 Medical history: COVID-19 (14), Suspected COVID-19 (5).
- Co-suspects (n = 28): influenza vaccine (22), COVID-19 vaccine mRNA (mRNA-1273), influenza vaccine inact split 3V (3 each), diphtheria vaccine toxoid/pertussis vaccine acellular/tetanus vaccine toxoid, HPV vaccine VLP RL 4V (yeast), influenza vaccine inact SAG 3V, influenza vaccine inact whole 3V and meningococcal vaccine (1 each).
- Number of events: 3101.
- Event seriousness: serious (255), non-serious (2847).
- Most frequently reported PTs (≥2%): Product administered to patient of inappropriate age (252), Poor quality product administered (244), Off label use (216), Expired product administered136

(183), Product preparation issue136 (180), Product use issue (145), Overdose (102), Pyrexia (95), Headache (73), Vomiting (72), Incorrect dose administered (66) and Pain in extremity (64).

- Time to event onset (n = 2047), range: <1 to 34 days, median: <1 day.
- Duration of event (n = 143), range: <1 to 28 days, median: 1 day.
- Relevant event outcome: resolved/resolving (679), resolved with sequelae (10), not resolved (251), fatal (2), unknown (2160).
- Fatal cases (both reporting the fatal PT Death): the limited information reported in these cases does not allow any meaningful assessment:
    - The first NMC case involved a 6-year-old male subject received BNT162b2 (dose unknown) and experienced a fatal outcome. An additional event reported in this case coded to PT Drug ineffective. Date of vaccination and onset date of the AEs are not provided. It was not reported if an autopsy was performed.
    - The second MC case reported a 5-year-old subject (gender unknown) died four days after the BNT162b2 first dose. No information on autopsy was available.

Rapporteur assessment comment:

During the current reporting interval the Comirnaty indication was extended to 5-11 years old children (procedure EMEA/H/C/005735/X/0077).

No new important safety information could be identified regarding the use of Comirnaty in paediatric persons ≥5 years and ≤ 11 years of age.

Paediatric subjects ≥12 years of age

Clinical trial data

- Number of cases: 24 (BNT162b2 [18] and blinded therapy [6]) originated from Protocol C4591001 (7), C4591001-OPEN LABEL (15) and C4591031 (2) (3.3% of 721 cases, the total CT dataset), compared to 27 cases (3.8%) retrieved in the first PSUR.
- Country of incidence: US (24).
- Subjects' gender: female (11) and male (13).
- Subjects' age in years (n = 24), range: 12 – 17, mean: 14.8, median: 15.0.
- Medical history (n = 17): the most frequently (≥2) reported medical conditions included Depression (4), Anxiety (3), Acne, Cerebral palsy, Generalised anxiety disorder, Major depression, Oppositional defiant disorder, Seasonal allergy and Seizure (2 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 2): escitalopram oxalate, sertraline hydrochloride (1 each).
- PTs (26): Appendicitis (4), Suicidal ideation (3), Upper limb fracture (2), Acute lymphocytic leukaemia, Anaphylactic reaction, Anorexia nervosa, Arthropod bite, Cerebral haemorrhage, Dyskinesia, Epilepsy, Kidney infection, Mucoepidermoid carcinoma of salivary gland, Myocarditis, Psychotic disorder, Radius fracture, Somnolence, Suicide attempt, Syringomyelia, Traumatic renal injury and Ulna fracture (1 each).

- All events were assessed as unrelated to BNT162b2 or blinded therapy, but the AEs Appendicitis and Myocarditis (1 each) that were assessed related to BNT162b2:
  - A 13-year-old female subject, enrolled in study C4591001-OPEN LABEL, received the BNT162b2 third dose on 17 May 2021 and fourth dose on 07 June 2021. Previously, the subject had received doses of the blinded study vaccine (first dose on 07 January 2021 and second dose on 27 January 2021). The subject presented to hospital 3 days after the fourth dose with abdominal pain and vomiting, acute appendicitis was diagnosed and appendectomy was performed as an outpatient procedure. The subject recovered from the event. The investigator considered there was a reasonable possibility that the event was related to the study vaccine BNT162b2 (dose 3 and 4), while the MAH assessed the AE unrelated to the vaccine administration, based on the short latency of 3 days after dose 2 and on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause this event.
  - A 17-year-old male subject, enrolled in study C4591001-OPEN LABEL, developed myocarditis 3 days after received the booster dose of BNT162b2 (Lot No. P220395-00911). Medical history included seasonal allergy, kidney stone, patella dislocation and anxiety. The subject received sertraline hydrochloride and isotretinoin as concomitant medications. The subject was admitted to hospital due to intense pain; ECG indicated ST elevation, troponin and creatine kinase were elevated, cardiac MRI showed abnormal cardiac MRI, left ventricular free wall subepicardial delayed gadolinium enhancement, consistent with myocarditis. The subject received treatment and was recovering at the time of the report. Both the investigator and the MAH assessed the AE as possibly related to the vaccine administration, based on the plausible temporal relationship.
  - Time to event onset (n = 25), range: from 3 days to 258 days, median: 109 days.
  - Duration of event (n = 16), range: from < 1 to 89 days, median: 5 days.
  - Event outcome: resolved/resolving (20), not resolved (6).

<u>Post-authorisation data</u>

- Number of cases: 18,451 (2.8% of 657,528 cases, the total PM dataset), compared to 1445 cases (0.4%) retrieved in the first PSUR; medically confirmed cases (8344).
- Country of incidence (≥2%): US (2340), Netherlands (2057), UK (1901), Germany (1774), France (1711), Japan (1323), Italy (922), Australia (872), Taiwan (581), Austria (580), Denmark (567) and Spain (566).
- Subjects' gender: female (9900), male (8075) and unknown (476).
- Subjects' age in years (n = 18,024), range: 12 - 17, mean: 14.8, median: 15.0.
- Medical history (n = 3786): the most frequently (≥2%) reported medical conditions included Asthma (554), Seasonal allergy (335), Food allergy (304), Hypersensitivity (195), Drug hypersensitivity (182), Suppressed lactation (160), Attention deficit hyperactivity disorder (133), Epilepsy (112), Mite allergy (110), Rhinitis allergic (103), Anxiety (96), Migraine (93), Depression (88), Allergy to animal (90) and Autism spectrum disorder (82).
- COVID-19 Medical history (n = 966): COVID-19 (622), Suspected COVID-19 (319), COVID-19 immunisation (14), SARS-CoV-2 test positive (10), Asymptomatic COVID-19, Exposure to SARS-CoV-2, Post-acute COVID-19 syndrome (7 each), and SARS-CoV-2-antibody test positive (1).
- Co-suspects (n = 160): the most frequently (≥2%) reported co-suspect vaccines/medications included adalimumab (16), COVID-19 vaccine mRNA (mRNA-1273) (14),

ethinylestradiol/levonorgestrel (11), influenza vaccine (9), sodium chloride (8), dupilumab, COVID-19 J&J vaccine (4 each), HPV vaccine, medroxyprogesterone acetate, mestranol/norethisterone (3 each).

- Number of events: 56,667; serious (20,772), non-serious (35,915).
- Most frequently reported PTs (≥2%): Headache (3501), Pyrexia (3014), Fatigue (2154), Nausea (1933), Malaise (1757), Dizziness (1410), Chest pain (1332), Vaccination site pain (1319) and Myalgia (1237).
- Time to event onset: n = 45,137, range: from <1 to 366 days, median: 1 day.
- Duration of event: n = 10,059, range: from <1 to 406 days, median: 1 day.
- Relevant event outcome fatal (196), resolved/resolving (27,010), not resolved (14,034), resolved with sequelae (458), unknown (15,126).

Fatal cases (73)

- Age: 12 years (11), 13 years (12), 14 years (6), 15 years (11), 16 years (19), 17 years (11), unknown (3).
- MC cases (40), NMC cases (33).
- Gender: females (26), males (44), unknown (3).
- Country (≥ 2): US (12), Germany, Philippines (9 each), Vietnam (5), France, Italy, Japan, Malaysia, New Zealand (3 each), Brazil, Mexico, Romania, Spain, Thailand and UK (2 each).
- Fatal PTs (196): the most frequently (≥ 2) reported AEs included Death (24), Cardiac arrest (9), Dyspnoea, Myocarditis, Pyrexia, Sudden death (6 each), Vomiting (5), Dizziness, Headache, Respiratory failure (4 each), Cardio-respiratory arrest, Pulmonary embolism, Pulmonary oedema, Seizure, Septic shock (3 each), Abdominal pain, Acute myocardial infarction, Anaemia, Anaphylactic reaction, Anaphylactic shock, Arrhythmia, Asthenia, Cardiac disorder, Cardiomegaly, Circulatory collapse, Coagulopathy, Cyanosis, Decreased appetite, Drowning, Fatigue, Lung disorder, Respiratory arrest, Syncope, Thrombotic thrombocytopenic purpura, Unresponsive to stimuli (2 each).
- Relevant medical history (n = 23): Epilepsy (3), Asthma, Hospitalisation (2), Allergy to vaccine, Asymptomatic COVID-19, Bronchopulmonary dysplasia, Cardiac disorder, Cardiomyopathy, Cardiovascular disorder, Cerebral palsy, Congenital multiplex arthrogryposis, COVID-19, Drug hypersensitivity, Dyspnoea, Dyspnoea exertional, Familial risk factor, Glucose-6-phosphate dehydrogenase deficiency, Haemorrhage intracranial, Head injury, Hypoxic-ischaemic encephalopathy, Mitral valve prolapse, Obesity, Pleural effusion, Pneumonia bacterial, Polycythaemia, Post haemorrhagic hydrocephalus, Pulmonary artery atresia, Raynaud's phenomenon, Respiratory failure, Respiratory tract infection, SARS-CoV-2 antibody test positive, Sinus bradycardia, Superficial vein thrombosis, Thalassaemia minor, Tobacco user and Ventricular extrasystoles (1 each).
- The 73 fatal cases are summarised below:
- In 21 cases (7 MC and 14 NMC) reporting only Death (17) or Sudden death (4) as fatal AEs and in one additional MC case reporting Death and Unresponsive to stimuli as AEs causing fatal outcome, neither cause of death nor information on autopsy was provided. The time to fatal event onset is available in 4 cases: 2 days (1), 3 days (2) and 4 days (1). The limited information provided prevented any meaningful causality assessment.

- In one case, the subject did not die due to illness, but due to an unfortunate accident: NMC case; age: 12 years; gender: unknown; fatal PT: Accident occurred 3 days after the vaccination; autopsy: no data.
- In 2 cases, the co-suspect contraceptives could have contributed to the occurrence of the events:
    - MC case; age: 17 years; gender: female; fatal PT: Pulmonary embolism 11 days after the first dose of BNT162b2 (lot No. FF2834); co-suspect: ethinylestradiol/levonorgestrel; autopsy: performed, but results were not provided.
    - NMC case; age: 17 years; gender: female; fatal PT: Cardiac arrest, occurred 9 days after the first dose of BNT162b2; co-suspect: unspecified combined oral contraceptives; autopsy: no data.
- In 7 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:
    - MC case; age: 16 years; gender: male; fatal PT: Pulmonary embolism, occurred 24 days after 2nd dose of BNT162b2; medical history: pleuropneumonia on the left with slight pleural effusion and thrombotic superficial arm vein occlusion; autopsy: unknown if performed.
    - MC case; age: 16 years; gender: male; fatal PTs: Pulmonary oedema, Ventricular extrasystoles, Infarction, Cardiopulmonary failure, all occurred 16 days after the first dose of vaccine (lot No FD0168); medical history: ventricular extrasystoles; autopsy: revealed pulmonary oedema with foci of infarction suggesting an arterial or venous thromboembolic mechanism, thromboembolic cause.
    - MC case; age: 15 years; gender: female; fatal PTs: Cardiac arrest (developed 2 days after 1st dose of BNT162b2) and Brain hypoxia (unknown onset date); medical history: asthma, Marfan's syndrome and mitral valve prolapse; autopsy: not performed.
    - MC case; age: 13 years; gender: male; fatal PTs Disseminated intravascular coagulation, Pulmonary haemorrhage, Pyrexia, Multiple organ dysfunction syndrome, Septic shock (all occurred 2 days after 2nd dose of vaccine, lot No 10020A) and Thoracic haemorrhage (unspecified onset date); medical history: bronchopulmonary dysplasia, intracranial haemorrhage, hypoxic-ischaemic encephalopathy, post-haemorrhagic hydrocephalus, symptomatic epilepsy and respiratory insufficiency; autopsy: not performed.
    - MC case; age: 13 years; gender: female subject; fatal PTs: Respiratory failure, Cardiac arrest, occurred the day after dose 2 of BNT162b2 (lot No FF2382); medical history: severe cardiopathy with congenital pulmonary atresia and left-right shunt prevailing the interventricular septal defect and failure, restrictive respiratory associated with secondary DLCO reduction; autopsy: not performed.
    - MC case; age: 12 years; gender: male; fatal PTs Headache, Pyrexia, Decreased appetite (all developed the day after the 2nd dose of vaccine), Death, Myocarditis (both occurred 2 days after vaccination); medical history: cardiomyopathy and congenital multiplex arthrogryposis. Autopsy results: cardiac death in cardiomyopathy; mechanism of death was multi-factorial and the vaccine dose administered was not the sole trigger of the fatal event. In appreciation of the overall circumstances, the cardiac insufficiency with severe myocardial damage was aggravated by the vaccination, which led to decompensation of the cardiac function. The time of death was thus probably triggered by the physiological vaccination reaction with fever.

- NMC case; age: 17 years; gender: female; fatal PTs Rash, Dizziness, Anaphylactic shock (all occurred on the same date of vaccination, dose unknown), Coagulopathy (unspecified onset date); medical history: allergy to vaccine (unspecified); autopsy: not performed.

- In one case, the results of autopsy did not reveal any evidence of connection between the subject's death and administration of BNT162b2: MC case; age 15 years; gender: male; fatal PTs: Pulmonary oedema, Arrhythmia, Cardiac failure acute (all occurred 20 days after the 1st dose of BNT162b2), Lung disorder, Cardiac disorder, Brain oedema (unknown onset date for these 3 events); medical history: epilepsy. Autopsy results: there was no evidence of an inflammation of the myocardium (myocarditis), therefore, based on the findings, no indications of a connection between the acute heart pump failure causing death and the vaccination against SARS-CoV-2 that was carried out almost three weeks before death. A morphologically detectable cause of the acute pump failure could not be found in any of the investigations carried out; therefore, it was likely to have been a functional cause, most likely a cardiac arrhythmia.

- In the remaining 40 cases (24 MC and 16 NMC) reporting the following fatal PTs Cardiac arrest, Dyspnoea (6 each), Death, Myocarditis, Vomiting (5 each), Pyrexia (4), Seizure, Respiratory failure, Headache, Cardio-respiratory arrest, Dizziness (3 each), Sudden death, Respiratory arrest, Cyanosis, Acute myocardial infarction, Anaemia, Circulatory collapse, Thrombotic thrombocytopenic purpura, Anaphylactic reaction, Cardiomegaly, Abdominal pain, Septic shock, Syncope, Asthenia, Drowning, Fatigue (2 each), Arrhythmia, Cardiac disorder, Coagulopathy, Anaphylactic shock, Postictal state, Completed suicide, Chest discomfort, COVID-19, Oxygen saturation immeasurable, Crepitations, Lung disorder, Pupils unequal, Critical illness, Subarachnoid haemorrhage, Anal sphincter atony, Vaccination site pain, Bladder sphincter atony, Off label use, Decreased appetite, Pericardial effusion, Defaecation disorder, Adverse event following immunisation, Diabetes mellitus, Cardiogenic shock, Diabetic ketoacidosis, Cerebellar haemorrhage, Diarrhoea, Sudden cardiac death, Bone marrow failure, Chest pain, Bradycardia, Ventricular fibrillation, Drug ineffective, Neurological decompensation, Dyskinesia, Ovarian enlargement, Palpitations, Pneumonia, Feeling abnormal, Pulmonary embolism, Breath sounds, Pulmonary sepsis, Hemiparesis, Interchange of vaccine products, Respiratory distress, Intestinal ischaemia, Aneurysm, Leukaemia, Shock, Loss of consciousness, Subdural haematoma, Bronchospasm, Cerebral venous sinus thrombosis, Malaise, Thrombocytopenia, Myocardial infarction, Unresponsive to stimuli, Abnormal faeces, Venous injury, Nausea, ADAMTS-13 activity decreased, Nerve injury, Pulmonary oedema, Nervous system disorder (1 each). No confounding factors have been identified; in most cases (27) the limited information available does not allow a medically meaningful causality assessment, in the remaining cases (13) 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 proved any causal relationship.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1181 (6.0% of 19,828 cases, the total paediatric dataset). Upon review, 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.

Literature

- Review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric subjects.

MAH's conclusion

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 events 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.

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.

Rapporteur assessment comment:

Myocarditis and pericarditis are closely monitored through the SSRs for Comirnaty in which the MAH is requested to use a broader search strategy to identify relevant publications and other pieces of information to further characterise the risk of myocarditis and pericarditis, especially in terms of outcomes as well to explore whether risk mitigation strategies would be feasible (procedure EMEA/H/C/005735/MEA 002.12).

No new important safety information could be identified regarding the use of Comirnaty in paediatric persons ≥12 years of age.

Use in pregnant/lactating women

Rapporteur assessment comment:

Please refer to the assessment of MAH's response to PRAC request 7 regarding pregnancy and lactation above from the first PSUR (section 'Post-approval regulatory requests' of this report).

Use in immunocompromised patients

Search criteria: *PTs included in Malignancy related conditions (SMQ Narrow and Broad Scope); Malignancy related therapeutic and diagnostic procedures (SMQ Narrow and Broad Scope); Malignant or unspecified tumours (SMQ Narrow and Broad Scope); 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 [68], blinded therapy [39], and placebo [3]) (15.3% of 721 cases, the total CT dataset), compared to 105 cases (15.0%) retrieved in the first PSUR.
- Country of incidence: US (88), Argentina (15), Germany (4), South Africa (2), and Brazil (1).
- Subjects' gender: female (70), and male (40).
- Subjects' age in years (n = 109), range: 13 – 86, mean: 62.8, median: 65.
- Medical history (n = 110): the most frequently (≥5 occurrences) reported relevant medical conditions included Hysterectomy (35), Breast cancer (9), Basal cell carcinoma, Cholecystectomy, Prostate cancer (8 each), Radiotherapy (7), Benign prostatic hyperplasia, Breast conserving

surgery, Chemotherapy, Diverticulitis, Tonsillectomy (6 each), Gastrectomy, HIV infection, Nephrectomy (5 each).

- COVID-19 Medical history: COVID-19 (3).
- Co-suspects (n = 3): The reported co-suspect agents included ibuprofen, levothyroxine, and oxycodone (1 each).
- Number of events: 134.
- Most frequently reported clinical PTs (>2%): Diverticulitis (5, 4.5%), Prostate cancer (5, 4.5%), Cerebrovascular accident (3, 2.7%), Condition aggravated (3, 2.7%), Invasive ductal breast carcinoma (3, 2.7%), Small intestinal obstruction (3, 2.7%), Urinary tract infection (3, 2.7%).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.
- Time to event onset: (n = 79 events), range: <24 hours to 181 days, median: 96 days.
- Duration of event: (n = 64 of 68 events with outcome of resolved/resolved with sequelae) ranged from <24 hours to 181 days.
- Reported event outcome: fatal (6), resolved/resolving (85), resolved with sequelae (3), not resolved (38), and unknown (2).

Post-authorisation data

- Number of cases: 14,657 (2.2% of 657,528 cases, the total PM dataset), compared to 11,995 cases (3.7%) retrieved in the first PSUR; medically confirmed cases (6417).
- Country of incidence: France (3429), UK (3178), US (1898), Japan (1106), Germany (937), Italy (707), Czech Republic (499), Sweden (318), Denmark (280), Spain (273), Netherlands (272); the remaining 1760 cases were distributed among 59 countries.
- Subjects' gender: female (9970), male (4381) and unknown (306).
- Subjects' age in years (n = 13,752), range: 7 – 121, mean: 59.0, median: 60.0.
- Medical history (n = 14,657). The most frequently (≥200 occurrences) reported relevant medical conditions included Immunodeficiency (2435), Breast cancer (1964), Thyroidectomy (858), Neoplasm malignant (729), Hysterectomy (688), Prostate cancer (663), Chemotherapy (477), Renal transplant (415), Neoplasm (409), Radiotherapy (405), Surgery (334), Colon cancer (313), Chronic lymphocytic leukaemia (310), Thyroid cancer (306), Lung neoplasm malignant (273), Malignant melanoma (272), Cholecystectomy (270), Appendicectomy (228), Splenectomy (221), Lymphoma (217), Mastectomy (201).
- COVID-19 Medical history (n = 1133): COVID-19 (662), Suspected COVID-19 (416), COVID-19 pneumonia (23), Post-acute COVID-19 syndrome (11), SARS-CoV-2 test positive (8), Exposure to SARS-CoV-2 (5), Asymptomatic COVID-19 (4), Coronavirus infection (3), SARS-CoV-2 antibody test positive (1).
- Co-suspects (n = 453): The most frequently (≥10 cases) reported co-suspect vaccines/medications included Influenza vaccine (44), COVID-19 Vaccine NRVV AD (22), Hepatitis A vaccine (15), pembrolizumab (14), Influenza vaccine (surface antigen, inactivated, adjuvanted) (13), adalimumab (12), nivolumab (11) and rituximab (10).
- Number of events: 62,595.; serious (31,483), non-serious (31,142).

- Most frequently reported clinical PTs (≥3%): Headache (2273, 15.5%), Fatigue (1996, 13.6%), Pyrexia (1990, 13.6%), Immunisation (1771, 12.1%), Pain in extremity (1353, 9.2%), Nausea (1160, 7.9%), Arthralgia (1142, 7.8%), Myalgia (1045, 7.1%), Vaccination site pain (1039, 7.1%), Pain (966, 6.6%), Interchange of vaccine products (955, 6.5%), Asthenia (939, 6.4%), Chills (911, 6.2%), Dyspnoea (906, 6.2%), Malaise (900, 6.1%), Dizziness (835, 5.7%), Lymphadenopathy (738, 5.0%), COVID-19 (638, 4.4%), Diarrhoea (600, 4.1%), Chest pain (538, 3.7%), Vomiting (501, 3.4%), Rash (491, 3.3%), Pruritus (480, 3.3%), Influenza like illness (460, 3.1%), Paraesthesia (433), 3.0%).
- Time to event onset (n = 44,061 events), range: <24 hours to 181 days, median: 1 day.
- Duration of event (n = 6361 of 6370 events with outcome of resolved/resolved with sequelae) ranged from < 24 hours to 181 days.
- Event outcome: fatal (1709), resolved/resolving (23,823), resolved with sequelae (1133), not resolved (15,030), unknown (21,245).

Analysis by age group

- Clinical trial data: Paediatric (2), Adults (50), Elderly (57), and Unknown (1). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing data: Paediatric (119), Adults (7937), Elderly (5754) and Unknown (847).
    - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to PTs COVID-19, Lymphadenopathy and Paraesthesia. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (2.3% [179 cases] in adults vs 7.6% [435 cases] in elderly). In majority of the elderly cases (424 of 435 cases) that reported the event coded to PT COVID-19, the co-reported events was coded to the PTs Drug ineffective (161 cases) and Vaccination failure (263 cases). These cases are also summarized in Section Lack of Therapeutic Efficacy.
    - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (7.1% [566 cases] in adults vs 2.0% [113 cases] in elderly) compared to the elderly population. And a higher reporting proportion of events coded to PT Paraesthesia was observed in the adult population (4.3% [339 cases] in adults vs 1.4% [80 cases] in elderly) compared to the elderly population.
    - No comparison was made to the paediatric population considering limited number of cases.

MAH's conclusion

No new significant safety information was identified based on a review of these cases.

Rapporteur assessment comment:

During the current reporting period the posology for Comirnaty was extended and a third dose may be given at least 28 days after the second dose to individuals aged 12 years and older who are severely immunocompromised (EMEA/H/C/005735/II/0062). Please refer regarding the 3rd (booster) dose of Comirnaty to the separate procedure EMEA/H/C/005735/II/0067.

No new important safety information could be identified in immunocompromised patients exposed to Comirnaty.

Use in patients with autoimmune or inflammatory disorders

Search criteria: *PTs included in HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction*.

Clinical trial data

- Number of cases: 101 (BNT162b2 [60], blinded therapy [33], placebo [7] and BNT162b2s01 [1]) (14.0% of 721 cases, the total CT dataset), compared to 123 cases (17.5%) retrieved in the first PSUR.
- Of the 101 cases, the most frequently reported PTs (≥3%) included: Osteoarthritis (4, 4.0%), Pneumonia (4, 4.0%), Acute myocardial infarction (3, 3.0%), Appendicitis (3, 3.0%), Appendicitis perforated (3, 3.0%), and Atrial fibrillation (3, 3.0%).
- Event outcome: fatal (6), resolved/resolving (103), resolved with sequelae (3), and not resolved (18).
- BNT162b2 related events coded to the PT: Hepatic enzyme increased (1). Time to onset of event is 4 days and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-authorisation data

- Number of cases: 35,514 (5.4% of 657,528, the total PM dataset), compared to 26,352 cases (8.1%) retrieved in the first PSUR; medically confirmed cases (13,435).
- Of the 35,514 cases, the most frequently reported clinical PTs (>3%) included: Headache (6193, 17.4%), Fatigue (5492, 15.5%), Pyrexia (4926, 13.9%), Pain in extremity (3343, 9.4%), Arthralgia (3184, 9.0%), Nausea (3114, 8.8%), Myalgia (2979, 8.4%), Vaccination site pain (2895, 8.2%), Pain (2662, 7.5%), Immunisation (2548, 7.2%), Chills (2543, 7.2%), Dizziness (2487, 7.0%), Malaise (2397, 6.7%), Dyspnoea (2176, 6.1%), Asthenia (2066, 5.8%), Lymphadenopathy (1597, 4.5%), Diarrhoea (1546, 4.4%), Paraesthesia (1527, 4.3%), Chest pain (1390, 3.9%), Interchange of vaccine products (1360, 3.8%), Pruritus (1323, 3.7%), Rash (1299, 3.7%), Vomiting (1169, 3.3%), Hypoaesthesia (1161, 3.3%).
- Event seriousness: serious (63,726), non-serious (86,866).
- Event outcome: fatal (2243), resolved/resolving (62,062), resolved with sequelae (3197), not resolved (41,644), unknown (42,062).
- 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

- During the reporting interval, the focus of the analysis has been narrowed to include exacerbation or flare of PTs of interest (i.e., condition aggravated, disease progression), rather than all events.
- Of the 1452 cases that reported PTs indicative of exacerbation or flare, 711 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., abdominal distension, acute coronary syndrome, arrhythmia, deep vein thrombosis, kidney disease, migraine, trigeminal neuralgia). Of note, 12 of these 711 cases also reported events indicative of exacerbation or flare and are included in the relevant 751 cases below.

- Therefore, 751 cases are included in the analysis:
- Clinical trial data
    - Number of cases: 1 (BNT162b2) (0.1% of 721 cases, the total CT dataset), compared to 1 (0.1%) retrieved in the first PSUR. A [redacted] case, involving a 77-year-old male subject with a history of interstitial lung disease, experienced an exacerbation of interstitial lung disease (PT Condition aggravated) approximately 107 days after receiving the third dose of the BNT162b2. The event resolved after 1 day and was considered unrelated to BNT162b2.
- Post-authorisation data
    - Number of cases: 750 (0.1% of 657,528 cases, the total PM dataset), compared to 371 (0.1%) retrieved in the first PSUR; medically confirmed cases (355).
    - Country of incidence (≥30 occurrences): France (227), UK (96), Germany, US (80 each), Netherlands (40), Japan (38), and Italy (31).
    - Subjects' gender: female (505), male (228) and unknown (17).
    - Subjects' age in years (n = 704), range: 12 - 99, mean: 50.4, median: 50.0.
    - Relevant medical history: the most frequently (≥20 occurrences) reported medical conditions included: Pericarditis (73), Hypothyroidism (50), Myocarditis, Rheumatoid arthritis (46 each), Immune thrombocytopenia (41), Colitis ulcerative (39), Autoimmune thyroiditis, Diabetes mellitus (36 each), Ankylosing spondylitis, Psoriasis (34 each), Basedow's disease (32), Multiple sclerosis (31), Autoimmune disorder 27), Sjogren's syndrome (24), Arthritis, Systemic lupus erythematosus (23 each).
    - COVID-19 Medical history (n = 48): COVID-19 (38), Suspected COVID-19 (8), Asymptomatic COVID-19, SARS CoV-2 test positive (1 each).
    - Co-suspect vaccines/medications: tofacitinib (3), COVID-19 Vaccine NRVV AD (2), acetylsalicylic acid, adalimumab, amitriptyline, apixaban, baclofen, colchicine, COVID-19 vaccine, dupilumab, eltrombopag, ibuprofen, influenza vaccine, insulin, COVID-19 J&J vaccine, melatonin, methotrexate, methylprednisolone, lidocaine, mycophenolate, ocrelizumab, pneumococcal vaccine, prednisolone, prednisone, ruxolitnib, tacrolimus, teriflunomide, and varicella zoster vaccine (1 each).
    - Number of events: 3967 (of which 756 were events of interest i.e., exacerbation/flare AEs); serious (617), non-serious (145).
    - Most frequently reported relevant PTs (≥2%): Condition aggravated (416), Disease recurrence (327).
    - Time to event onset (n = 2536 events), range: 0 - 158 days, median: 3 days.
    - Duration of event (n = 285 events with outcome resolved/resolved with sequelae), range: 0 - 126 days.
    - Relevant event outcome: fatal (4), resolved/resolving (310), resolved with sequelae (14), not resolved (281), unknown (153).
- Analysis by age group
    - Clinical trial: Elderly (1).

- Post-marketing: Paediatric (15), Adults (534), Elderly (158) and Unknown (43). Exacerbation and/or flare of underlying autoimmune 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 adverse events are in this age group. Also, the autoimmune or inflammatory disorders often occur during adulthood.

- Analysis by dose
  - Number of vaccine doses administered at the time of the event onset: 1 dose in 336 cases, 2 doses in 337 cases, 3 doses in 30 cases; in 108 cases the dose was either not specified or reported as other.
  - There are no differences between the AEs reported after the 1st and 2nd dose. Due to the low number of cases who received 3 doses, a comparison of AEs was not made.

MAH's conclusion

Overall, there were 751 cases (1 CT case and 750 PM cases [0.1% 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:

Please refer to the assessment of MAH's response to PRAC request 5 regarding a cumulative review of exacerbation (flare-up) of pre-existing AI/Inflammatory disorders and request 9 regarding a cumulative review of polymyalgia rheumatica and exacerbation or flare-up hereof, above from the first PSUR (section 'Post-approval regulatory requests' of this report).

No other 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: *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: 176 (BNT162b2 [109], blinded therapy [57], and placebo [10]) (24.4% of 721 cases, the total CT dataset), compared to 193 cases (27.5%) retrieved in the first PSUR.
- Country of incidence: US (144), Argentina (22), Germany (4), China (2), Brazil, Dominican Republic, Poland, and Turkey (1 each).

- Subjects' gender: female (81), and male (95).
- Subjects' age in years (n = 174), range: 5 – 88, mean: 60.8, median: 62.5.
- Medical history (n = 176): the most frequently (≥15 occurrences) reported relevant medical conditions included Hypertension (104), Type 2 diabetes mellitus (76), Asthma (49), Obesity (38), Gastrooesophageal reflux disease (31), Osteoarthritis (29), Hypercholesterolaemia, Seasonal allergy (28 each), Hyperlipidaemia (26), Depression (24), Anxiety, Chronic obstructive pulmonary disease (22 each), Hypothyroidism (21), Insomnia (20), Hysterectomy (16), and Benign prostatic hyperplasia (15).
- COVID-19 Medical history: COVID-19 (3).
- Co-suspects (n = 73): The reported co-suspect agents included ibuprofen (2), bamlanivimab, cocaine, diazepam, dulaglutide, etesevimab, fluoxetine, glipizide, ibuprofen, losartan, metformin, and oxycodone (1 each).
- Number of events: 225.
- Most frequently reported clinical PTs (>2%): Urinary tract infection (6, 3.4%), Pulmonary embolism (5, 2.8%), Chronic obstructive pulmonary disease (4, 2.3%), Condition aggravated (4, 2.3%), and Coronary artery disease (4, 2.3%).
- 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.
- Time to event onset: (n = 144 events), range: <24 hours to 181 days, median: 97 days.
- Duration of event: (n = 117 of 119 events with outcome of resolved/resolved with sequelae) ranged from < 24 hours to 365 days.
- Reported event outcome: fatal (19), resolved/resolving (153), resolved with sequelae (11), not resolved (41), and unknown (1).

Post-authorisation data

- Number of cases: 33,889 (5.2% of 657,528, the total PM dataset), compared to 28,023 cases (8.6%) retrieved in the PSUR; medically confirmed cases (15,806).
- Country of incidence: France (5,753), Japan (4,905), US (4,648), UK (4,517), Germany (2,563), Italy (1,433), Sweden (1,102), Czech Republic (1,058), Denmark (955), Netherlands (821), Spain (774), Canada (636), Austria (532), Norway (496), Finland (391), Ireland (389), Belgium (357), Portugal (279), Estonia (222), Switzerland (218), Brazil (215), Croatia (134), South Africa (124), Mexico (119), Greece (116), Hungary (110), Panama (107); the remaining 915 cases were distributed among 61 countries
- Subject's gender: female (21,955), male (11,471), and unknown (463).
- Subject's age in years (n = 32,484), range: 5 - 109 years, mean: 55.2, median: 55.0.
- Medical history (n = 33,889): the most frequently reported (≥500 cases) included: Asthma (14450), Hypertension (7862), Diabetes mellitus (6178), Type 2 diabetes mellitus (3565), Drug hypersensitivity (2149), Seasonal allergy (2118), Chronic obstructive pulmonary disease (2050), Food allergy (1756), Hypersensitivity (1667), Chronic kidney disease (1352), Hypothyroidism (1306), Obesity (1280), Atrial fibrillation (1231), Depression (1131), Type 1 diabetes mellitus (1108), Cardiac failure (1018), Pulmonary embolism (928), Dyslipidaemia (878), Suppressed lactation (785), Gastrooesophageal reflux disease (774), Dementia (697), Mite allergy (672), Hypercholesterolaemia (669), Allergy to animal (661), Migraine (637), Pain (622), Osteoarthritis

(577), Steroid therapy (569), Anxiety, Hyperlipidaemia, Immunodeficiency , Renal failure (562 each), Cerebrovascular accident (535), Sleep apnoea syndrome (525), Osteoporosis (515).

- COVID 19 Medical history (n = 2382): COVID-19 (1617), Suspected COVID-19 (619), COVID-19 pneumonia (47), Post-acute COVID-19 syndrome (28), Exposure to SARS-CoV-2 (21), Asymptomatic COVID-19 (20), SARS-CoV-2 test positive (15), Coronavirus infection (12), SARS-CoV-2 antibody test positive (2), Occupational exposure to SARS-CoV-2 (1).
- Co-suspects (n = 636): The most frequently (>10 occurrences) reported co-suspect vaccines/medications included Influenza vaccine (88), COVID-19 Vaccine NRVV AD (45), Influenza vaccine (surface antigen, inactivated, adjuvanted) (26), adalimumab (23), COVID-19 Vaccine MRNA (MRNA 1273) (18), Hepatitis A vaccine (16), apixaban (12), Influenza vaccine INACT SPLIT 4V (11).
- Number of events: 140,825; serious (77,221), non-serious (63,658).
- Most frequently reported (≥3%) clinical PTs: Headache (5392, 15.9%), Pyrexia (5031, 14.8%), Fatigue (4655, 13.7%), Dyspnoea (3062, 9.0%), Pain in extremity (2871, 8.5%), Nausea (2861, 8.4%), Vaccination site pain (2855, 8.4%), Myalgia (2548, 7.5%), Arthralgia (2431, 7.2%), Malaise (2395, 7.1%), Pain (2369, 7.0%), Dizziness (2272, 6.7%), Chills (2237, 6.6%), Immunisation (2225, 6.6%), Asthenia (1900, 5.6%), Pruritus (1376, 4.1%), Chest pain (1358, 4.0%), Diarrhoea (1352, 4.0%), COVID-19 (1319, 3.9%), Cough (1275, 3.8%), Lymphadenopathy (1274, 3.8%), Vomiting (1241, 3.7%), Interchange of vaccine products (1119, 3.3%), Rash (1106, 3.3%), and Paraesthesia (1074, 3.2%). All the clinical events are listed events per the current COVID-19 mRNA vaccine RSI and were consistent with the most frequent events observed in the overall population.
- Time to event onset (n = 105,814 events), range: <24 hours to 181 days, median: 1 day.
- Duration of event (n = 15,728 of 15,745 events with outcome of resolved/resolved with sequelae) ranged from < 24 hours to 181 days.
- Relevant event outcome: fatal (4398), resolved/resolving (59,616), resolved with sequelae (3037), not resolved (34,030), unknown (40,290).

<u>Analysis by age group</u>

- Clinical trial: Paediatric (7), Adults (88), Elderly (80), and Unknown (1). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (804), Adults (20,163), Elderly (11,677) and Unknown (1245).
    - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to PTs COVID-19, Lymphadenopathy, and paraesthesia. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (1.7% [341 cases] in adults vs 8.1% [942 cases] in elderly). In majority of the elderly cases (906 of 942 cases) that reported the event coded to PT COVID-19, the co-reported events was coded to the PTs Drug ineffective (333 cases) and Vaccination failure (573 cases). These cases are also summarised in Section Lack of Therapeutic Efficacy).
    - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (5.4% [1082 cases] in adults vs 1.1% [126 cases] in elderly) compared to the elderly population. And a higher reporting proportion of events coded to

PT Paraesthesia was observed in the adult population (4.4% [881 cases] in adults vs 1.4% [158 cases] in elderly) compared to the elderly population.

- No comparison was made to the paediatric population considering limited number of cases.

MAH's conclusion

The reporting proportion of not resolved cases (33.5%) and cases resolved with sequelae (2.4%) in frail subjects is similar to the reporting proportion observed in the overall population (32.4% for outcome of not resolved, 1.1% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (4.8%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (0.8%). This is expected, considering that most of the cases reporting a fatal outcome (86%) 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), however it has not been studied in frail individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population. 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.

Interactions with other vaccines

Search criteria: *HLT Interactions.*

Post-authorisation data

- Number of cases: 18 (0.003% of 657,528 cases, the total PM dataset), compared to 2 (0.001%) retrieved in the first PSUR; medically confirmed cases (11).
- Country of incidence: Norway, US (5 each), Denmark, Germany (2 each), Iceland, Spain, Sweden and UK (1 each).
- Subjects' gender: female (9), male (7), unknown (2).
- Subjects' age in years (n = 15): range: 16 - 75, mean: 48.5, median: 52.0.
- Medical history (n = 8): Asthma (3), Headache, Joint injury (2 each), Chronic obstructive pulmonary disease, Dizziness, Drug hypersensitivity, Gastro-oesophageal reflux disease, Glaucoma, Herpes zoster, Hypersensitivity, Hypertension, Hypotension, Myalgia, Pain, Prophylaxis against gastrointestinal ulcer, Tension headache and Urticaria chronic (1 each).
- COVID-19 Medical history: COVID-19 (1).
- Co-suspect vaccines (n = 16): COVID-19 AstraZeneca vaccine (7), influenza vaccine (4), COVID-19 Moderna vaccine (2), BCG vaccine, diphtheria vaccine toxoid, tetanus vaccine toxoid and varicella zoster vaccine RGE (CHO) (1 each). In additional 2 cases interacting vaccines were reported as concomitant drugs: RSV vaccine and diphtheria vaccine toxoid/tetanus vaccine toxoid (1 each).

- Other co-suspects (n = 2): azelastine hydrochloride/fluticasone propionate, desloratadine, levonorgestrel and omalizumab (1 each).
- Number of events: 116 (of which 19 were events of interest).
- Relevant event seriousness: serious (7), non-serious (12).
- Relevant PT: Drug interaction (17), Drug-disease interaction and Potentiating drug interaction (1 each).
- Co-reported AEs (≥ 2%): Headache (8), Off label use (5), Hypertension, Interchange of vaccine products, Product use issue (4 each), Pain, Pyrexia (3 each), COVID-19 immunisation, Crying, Diarrhoea, Discomfort, Dizziness, Fatigue, Herpes zoster, Hypoaesthesia, Immunisation, Loss of personal independence in daily activities, Malaise, Muscle spasms, Muscular weakness, Nausea and Tinnitus (2 each).
- Time to event onset: n = 10, range: <1 - 94 days, median: <1 day.
- Relevant event outcome: resolving/resolved (3), not resolved (6) and unknown (10).

MAH's conclusion

Among the overall 227 cases, 209 were considered not relevant, as a drug interaction did not occur in 7 cases, the interacting agents was not specified in 22 cases, BNT162b2 was not involved in 1 case and in the remaining 179 cases, the interaction occurred with alcohol, food, herbal or concurrent medications rather than another vaccine.

There were 18 cases in the overall post-marketing dataset that involve a vaccine interaction. The most frequently co-reported events other than off label use and interchange of vaccines PTs were events or consequences of events consistent with the known reactogenicity of the vaccine and listed in Section 4.4. Special warnings and precautions for use and Section 4.8 Undesirable effects of the CDS or possibly attributable to the co-suspect vaccine (in one of the 2 cases reporting Herpes zoster, the subject received the varicella zoster vaccine, that is known to possibly caused this). Of note, one case also reported an interaction with the previous COVID-19 infection (PT Drug-disease interaction).

There is no indication of a safety signal of interference of immune response of vaccines noted based on the review of these cases.

Rapporteur assessment comment:

No important new safety information could be identified regarding interactions with other vaccines.

2.4. Characterisation of risks

During the reporting period, the MAH submitted to EMA the updated EU RMP version 2.3 in support of the EU submission for the inclusion of the new important identified risk of myocarditis and pericarditis in the list of safety concerns.

Rapporteur assessment comment:

Please refer regarding the inclusion of myocarditis and pericarditis as an important identified risk in the list of safety concerns to the separate procedure EMEA/H/C/005735/II/0059.

There are no further changes proposed with regards to the list of safety concerns in the Comirnaty RMP.

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 safety topics under monitoring', section 'Evaluation of important identified risks' of this AR. Please note that a request from EMA was made to the MAH to consider at the next regulatory opportunity to reclassify anaphylaxis as not "important", discuss it in RMP section SVII.2, and remove it from the RMP list of safety concerns following discussions by PRAC.

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 safety topics under monitoring', 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 section 2.2.1.2 of this AR.

- Use in immunocompromised patients

Rapporteur assessment comment:

Please refer regarding Use in immunocompromised patients to 'Update on special populations' in section 2.3. 'Evaluation of risks and safety topics under monitoring' of this AR.

- 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 Use in frail patients with co-morbidities to 'Update on special populations' in section 2.3. 'Evaluation of risks and safety topics under monitoring' of this AR.

- Use in patients with autoimmune or inflammatory disorders

Rapporteur assessment comment:

Please refer regarding Use in patients with autoimmune or inflammatory disorders to 'Update on special

populations' in section 2.3. 'Evaluation of risks and safety topics under monitoring' of this AR.

- Interaction with other vaccines

Rapporteur assessment comment:

Please refer regarding Interaction with other vaccines to 'Update on special populations' in section 2.3. 'Evaluation of risks and safety topics under monitoring' of this AR.

- 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. Follow-up of ICSRs is conducted as per MAH's procedures and additional pharmacovigilance activities including the following studies C4591010, C4591011, C4591012, and C4591021 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.

4. Benefit-risk balance

During the current reporting period, the existing indication was extended from "individuals 12 years of age and older" to "individuals 5 years of age and older" (EMEA/H/C/005735/X/0077). A booster dose of Comirnaty (at least 6 months after the second dose) for individuals 18 years of age and older was approved (EMEA/H/C/005735/II/0067). Also, a third dose of Comirnaty (at least 28 days after the second dose) for individuals 12 years of age and older who are severely immunocompromised was approved (EMEA/H/C/005735/II/0062). After the covering period of the PSUR, the posology recommendations for the booster use were further amended from "individuals 18 years of age and older" to "individuals 12 years of age and older", to provide 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).

The following safety issues were identified and included as ADRs in the Comirnaty product information: myocarditis and pericarditis.

The risks have been evaluated in the context of the benefits of the vaccine. No additional changes to the Comirnaty product information or additional risk minimisation activities 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 information from other clinical trials and sources:
    a. From the non-MAH sponsored study "Immunological responses after vaccination for COVID-19 with the messenger ribonucleic acid (mRNA) vaccine Comirnaty in immunosuppressed and immunocompetent individuals" 3 SEAs including liver transplant rejection were considered related to Comirnaty exposure. The MAH is requested to provide more detailed information regarding the methods of the study (including study size) and the SEAs considered related to Comirnaty exposure. Furthermore, it is noted that during the interval period of the current PSUR there were 2 post-marketing cases reporting liver transplant rejection. The MAH is requested to provide more detailed information regarding these 2 cases reporting liver transplant rejection including a causality assessment concerning Comirnaty exposure.
    b. From the non-MAH sponsored study "Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Allo)" there were 2 cases reporting 3 SAEs (cytomegalovirus infection, myelitis and thrombotic microangiopathy) which the MAH considered unrelated to Comirnaty exposure while the investigator considered all SEAs related to Comirnaty exposure. The MAH is requested to provide a detailed explanation regarding the discrepancy between the assessment of the MAH and the assessment of the investigators concerning the causality assessment of the SEAs to Comirnaty exposure.
2. The MAH is requested to perform a cumulative review on the association between Comirnaty and chronic urticaria. 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.
3. Regarding glomerulonephritis and nephrotic syndrome the MAH is requested:
    a. To provide an updated literature review (DLP: 9 May 2022) concerning glomerulonephritis and nephrotic syndrome and for the identified case reports the MAH should include a WHO-UMC causality assessment per case regarding Comirnaty exposure.
    b. To provide an updated review (DLP: 9 May 2022) of cases reporting glomerulonephritis / nephrotic syndrome from their safety database and, when applicable, provide the WHO-UMC causality assessment per case regarding Comirnaty exposure.
4. The MAH is requested to confirm that there is no additional information during the current reporting period of the 2nd PSUR concerning clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2. If not, the new data should be submitted.

6. MAH responses to request for supplementary information

Question 1

Regarding information from other clinical trials and sources:

a. From the non-MAH sponsored study "Immunological responses after vaccination for COVID-19 with the messenger ribonucleic acid (mRNA) vaccine Comirnaty in immunosuppressed and immunocompetent individuals" 3 SEAs including liver transplant rejection were considered related to Comirnaty exposure. The MAH is requested to provide more detailed information regarding the methods of the study (including study size) and the SEAs considered related to Comirnaty exposure. Furthermore, it is noted that during the interval period of the current PSUR there were 2 post-marketing cases reporting liver transplant rejection. The MAH is requested to provide more detailed information regarding these 2 cases reporting liver transplant rejection including a causality assessment concerning Comirnaty exposure.

MAH's response

Non-MAH Sponsored Study SAEs (4 cases)

Among the 11 relevant cases reported from non-MAH sponsored clinical trial sources during the PSUR interval period 19 June 2021 through 18 December 2021, 4 cases (including 1 serious adverse event [SAE] each) originated from the literature article *Bergman P, Blennow O, Hansson L et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine, 2021;Dec;74:103705*, and includes all the information available to the Marketing Authorisation Holder (MAH) on the methods of the study (including study size) and the adverse events (AEs) reported.

Of the 5 severe AEs mentioned in the article that were assessed as "possibly linked" to the vaccination by the investigator:

- the MAH assessed the vasovagal reaction in a HIV patient (moderate) as a non-serious event and, consequently, no case was created for this event, because non-serious events are not reportable into the Adverse Event Monitoring System for an interventional study,
- the MAH assessed the remaining 4 AEs (febrile neutropenia, liver transplant rejection, syncope and respiratory failure) as serious and unrelated to BNT162b2, based on the known safety profile of the vaccine and on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause these events. The 3 cases reporting febrile neutropenia, liver transplant rejection and syncope were unlocked and were in the Primary Review workflow at the data lock point (DLP) of the PSUR, therefore the Company causality was conservatively reported as related. Upon completion of the cases, the causality was updated to unrelated for all the 3 events by the MAH Medical reviewer.

Spontaneous liver transplant rejection reports (2 cases)

During the PSUR reporting interval, 2 spontaneous cases of liver transplant rejection originating from [redacted] were received via the [redacted]

The first case involved a 48-year-old female subject, who received BNT162b2 (dose number was not provided) on an unspecified date, and experienced liver transplant rejection, renal failure and increased liver function tests on an unspecified date. The outcome of the events was unknown. No medical history, concomitant medication or details on vaccine schedule were provided.

In the second case, a 24-year-old female subject received a dose of BNT162b2 (dose number was not provided) on an unspecified date, and developed liver transplant rejection on 27 August 2021. The outcome of the event was not provided. No additional details were available.

The scant information included in both these spontaneous cases does not allow a meaningful causality assessment between the reported events and the vaccine administration.

Rapporteur assessment comment:

The MAH provided a reference (Bergman et al. 2021) that presents detailed information regarding the methods of the study and includes all information regarding the study methods available to the MAH, which is accepted in order to be able to perform a proper assessment. The 3 SAEs which included rejection in a liver transplanted patient were assessed by the MAH and concluded for all 3 SAEs no causal relation to Comirnaty exposure. The MAH explained that the 3 cases reporting febrile neutropenia, liver transplant rejection and syncope were unlocked and were in the Primary Review workflow at the DLP of the PSUR, therefore the MAH's causality was conservatively reported as related. Upon completion of the cases, the causality was updated to unrelated. However, detailed information of the case(s) reporting 3 SAEs including liver transplant rejection was not presented in MAH's response (and not in the publication of Bergman et al.) and therefore MAH's causality assessment could not be confirmed.

The 2 spontaneous cases of liver transplant rejection originating from [redacted] and the limited information provided did not allow a meaningful causality assessment, which is accepted.

Overall regarding liver transplant rejection after Comirnaty exposure, no new safety concern could be identified and the MAH should continue to monitor cases reporting liver transplant rejection as part of their routine pharmacovigilance activities.

Issue solved

b. From the non-MAH sponsored study "Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Allo)" there were 2 cases reporting 3 SAEs (cytomegalovirus infection, myelitis and thrombotic microangiopathy) which the MAH considered unrelated to Comirnaty exposure while the investigator considered all SEAs related to Comirnaty exposure. The MAH is requested to provide a detailed explanation regarding the discrepancy between the assessment of the MAH and the assessment of the investigators concerning the causality assessment of the SAEs to Comirnaty exposure.

MAH's response

During the interval period 19 June 2021 through 18 December 2021, 2 cases from the non-MAH sponsored study *Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Allo)* were received.

The first case involved a [redacted]-year-old [redacted] participant with a relevant medical history of stroke, Acute Myeloid Leukemia (AML), haematopoietic stem cell allograft, acute graft versus host disease (GvHD) and high blood pressure, corticosteroid-induced diabetes, recurrent cytomegalovirus (CMV) infection and enterocolitis due to *E. Coli* treated with quinolones. The participant experienced signs of transplant-associated thrombotic microangiopathy (TA-TMA) with increased lactate dehydrogenase levels, worsening of her chronic renal failure and presence of schizocytes on [redacted], 9 days after receiving the first dose of BNT162b2. On [redacted] the participant presented with a new CMV infection with a high viral load, and on the same date received the second dose of BNT162b2. On [redacted] worsening of TA-TMA occurred and, despite treatment with plasmapheresis, corticosteroids and eculizumab, the subject died on [redacted]

The investigator stated that the most probable cause of the worsening of TA-TMA was the recurrent CMV infection, but a role for the Comirnaty vaccination cannot be ruled out.

The MAH physician medical reviewer considered that there is not a reasonable possibility that the events Thrombotic microangiopathy and CMV infection are related to vaccine administration, based on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause these events. Additionally, the participant 's underlying condition, recurrent CMV infection, and concurrent tacrolimus administration provide a more plausible explanation for the events.

In the second case, a [redacted]-year-old [redacted] participant received 3 doses of BNT162b2 (on [redacted] and [redacted] and, on [redacted] was diagnosed with cervico-dorsal myelitis. High-dose steroids were started with progressive improvement of the neurological situation. The participant had a medical history of AML with 2 haematopoietic stem cell transplantations and received post-grafting immunosuppression until [redacted]

The investigator assessed that the myelitis occurring just after tacrolimus discontinuation might suggest a graft-versus host immune reaction. However, a role of the Comirnaty vaccination cannot be excluded, as myelitis is a very infrequent complication of GvHD and the patient has no other signs of GvHD.

The MAH physician medical reviewer considered that there is not enough evidence to suggest the myelitis was related to vaccine administration based on the known safety profile of the vaccine and on the latency of more than 6 months since the first dose administration. The participant's underlying conditions, including a possible GvHD upon tacrolimus discontinuation, are more plausible alternative explanations.

Rapporteur assessment comment:

As requested, the MAH provided a detailed explanation regarding the discrepancy between the assessment of the MAH and the assessment of the investigators concerning the causality assessment of the SAEs after Comirnaty exposure. The MAH concluded that for both cases reporting the SAEs the participant's underlying conditions provided more plausible explanations for the occurrence of the events, which is endorsed.

Issue solved

Question 2

The MAH is requested to perform a cumulative review on the association between Comirnaty and chronic urticaria. This should include, but not be limited to, information from post-marketing cases, clinical trials, mechanistic studies and literature. The MAH should consider the need for an update of the product information and/or RMP.

MAH's response

1.1.1. Introduction

Urticaria, also known as hives, is a very common condition thought to affect up to 20% of the population in their lifetime. This skin condition is characterised by the appearance of pruritic, erythematous papules or plaques with superficial swelling of the dermis. Urticaria can be classified by both time course of symptoms and the underlying aetiology. Acute urticaria is defined as having skin-symptom duration of less than 6 weeks, whereas chronic urticaria (CU) is generally defined by the presence of urticaria on most days of the week for a period of 6 weeks or longer. CU is further classified by additional criteria. Approximately one-fifth of CU patients have a clear-cut physical trigger for their skin eruptions, and therefore are termed physical urticaria. Examples of physical urticaria include dermographism, delayed-pressure urticaria, cold- and heat-contact urticaria, solar urticaria, aquagenic urticaria, exercise-induced

urticaria, and vibratory urticaria. In the remaining 80% of CU, no external allergen or contributing disease process is identified and, thus, the condition is termed chronic idiopathic urticaria (CIU), which has also more recently been labelled as chronic spontaneous urticaria (CSU). Approximately 40% of patients with CIU/CSU will also report accompanying episodes of angioedema or deeper swelling of dermal or mucosal tissues, whereas 10% have angioedema as their main manifestation.[1]

CIU patients can experience urticaria independent of any exogenous stimulus even if 1 can define circumstances that may worsen symptoms. A search for such an external "cause" is thought to be of little value since the underlying abnormality is considered to be "intrinsic" although the mechanism is not fully understood.[1]

Urticarial lesions or hives are typically raised erythematous plaques that are circumscribed. These lesions can assume a variety of sizes and may be flattened in appearance if a patient is using antihistamines. Any area of the body can be affected, including areas where clothing may compress the skin (waistband). Most lesions have a life span of less than 24 hours.[2]

Urticaria is a predominantly mast cell-driven disease. Histamine and other mediators, such as platelet-activating factor and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation and plasma extravasation as well as cell recruitment to urticarial lesions. The mast cell-activating signals in urticaria are heterogeneous, diverse, and include T cell-driven cytokines and autoantibodies. Histologically, wheals are characterised by oedema of the upper and mid dermis, with dilatation and augmented permeability of the postcapillary venules as well as lymphatic vessels of the upper dermis. In angioedema, similar changes occur primarily in the lower dermis and the subcutis. Skin affected by wheals shows a mixed inflammatory perivascular infiltrate of variable intensity, consisting of T cells, eosinophils, basophils, and other cells. Vessel-wall necrosis, a hallmark of urticarial vasculitis, does not occur in urticaria. The non-lesional skin of CSU patients shows upregulation of adhesion molecules, infiltrating eosinophils, altered cytokine expression and sometimes a mild-to-moderate increase of mast cell numbers.[2]

At any time, up to 1% of the North American population can be affected by CU. The overall prevalence is similar in other regions. Both children and adults can develop CU, but it appears to be more common in adults, with women affected nearly twice as often as men. The average age of patients suggests that the condition typically begins in the third to fifth decades of life. The co-expression of allergic disease in patients with CU appears to be slightly higher than that observed in the general population.[1]

CU is a self-limited disorder in most cases, with an average duration of 2 to 5 years. In patients in whom no trigger is identified, there is a rate of spontaneous remission at 1 year in approximately 30% to 50%. However, symptoms persist beyond 5 years in nearly one-fifth of patients.[1]

Various autoimmune diseases are noted to be more prevalent in subjects with CU. In a study involving a 13,000-patient database relative to 10,000 control subjects, the following diseases were noted to be increased among CU patients: thyroid disorders, coeliac disease, Sjogren syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and type 1 diabetes. The diagnosis of autoimmune disease most often appears in the decade after CU occurrence.

Infections and chronic inflammatory processes have been identified as potentially triggering CSU.[2] In addition, urticaria may be associated with some diseases and conditions characterised by hormonal changes, including endocrinopathy, menstrual cycle, pregnancy, menopause and hormonal contraceptives or hormone replacement therapy. Other mechanisms that have been proposed to contribute to the occurrence of CSU include autoimmunity, coagulation cascade, vitamin D deficiency, and genetic factors.[3]

In all CSU patients, the diagnostic workup includes a thorough history, physical examination (including review of pictures of wheals and/ or angioedema), basic labs, and the assessment of disease activity, impact, and control. The basic labs include a differential blood count and C-reactive protein (CRP) and/or

erythrocyte sedimentation rate, in all patients, and total IgE and IG-anti-TPO.[2] For the treatment of CSU, second-generation H1-antihistamines and omalizumab still rank the first and second on the choice list, respectively.[3]

1.1.1.1. Chronic urticaria and COVID-19

Interestingly, Akca and Kara[4] investigated the effect of the COVID-19 pandemic on the incidence of acute and CU in dermatology patients before and after the onset of the pandemic. They concluded that during the pandemic, the acute urticaria rate was significantly higher than before the pandemic.

Pitlick et al[5] performed a study to describe the clinical presentation, vaccine excipient skin testing results, and outcomes of subsequent COVID-19 vaccination in patients who experienced delayed systemic urticarial reactions after mRNA COVID-19 vaccination. They concluded that systemic urticarial reactions after mRNA COVID-19 vaccination were not life-threatening, could be treated with antihistamines, and were not predicted with vaccine excipient skin testing. They were not a contraindication to subsequent vaccination, although patients should be counselled with regard to the possibility of recurrence.

Urticaria and chronic urticaria cases have been reported after vaccination with all COVID-19 vaccines available in the market.[6,7,8]

1.1.2. Methodology

MAH's safety database contains cases of AE reported spontaneously to MAH, cases reported by the Health Authorities, cases published in the medical literature, cases from MAH-sponsored marketing programs, non-interventional studies, and cases SAE reported from clinical studies regardless of causality.

The MAH safety database was searched for all BNT162b2 vaccine cases received through 09 May 2022 using the MedDRA version 25.0 search criteria: Preferred Term (PT) urticaria chronic.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

In some reports, clinical information (such as MH, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

1.1.3. Results

A total of 244 cases were retrieved using the above-mentioned criteria. There were 183 (75.0%) females, 58 (23.8%) males and for 3 (1.2%), the subject's sex was not reported.

Age ranged between 12 and 87 years (mean 41.2, N:226). Age range stratification is presented in Table 1.

Table 2. Urticaria Age Stratification

Age Stratification	Number of Cases	%
Less than or equal to 17 years	8	3.3 %
18 - 30 years	52	21.3 %
31 - 50 years	108	44.3 %
51 - 64 years	36	14.8 %
65 - 74 years	18	7.4 %
Greater than or equal to 75 years	5	2.0 %
Unknown	17	7.0 %

Most cases were reported from France and the UK. Table 2 presents the top 10 reporting countries.

Table 3. Urticaria Top 10 Reporting Countries

Country	Number of Cases	%
FRANCE	48	19.7 %
UNITED KINGDOM	46	18.9 %
GERMANY	25	10.2 %
UNITED STATES	18	7.4 %
ITALY	13	5.3 %
NORWAY	11	4.5 %
SWEDEN	10	4.1 %
IRELAND	8	3.3 %
JAPAN	8	3.3 %
NETHERLANDS	7	2.9 %
SPAIN	7	2.9 %

A total of 144 (59.0%) cases were assessed as serious and 100 (41%) were not serious.

Patient medical history was reported for 118 patients and 126 patients did not report any MH.

Among the subjects that reported MH, there were 31 cases that reported CU.

Because cases with urticaria relapse after vaccination were previously presented in PSUR #2, this discussion is focused on the 213 cases of patients who do not report CU in the MH.

Among the 213 patients, there were 26 reporting underlying autoimmune diseases (such as autoimmune thyroiditis, diabetes, sarcoidosis), 26 that reported hypersensitivity, asthma and/or multiple allergies suggesting a predisposition to autoimmune diseases. In addition, 14 individuals reported a MH of COVID-19 infection.

Out of the 213 cases, most patients reported the event after Dose 2, and 10 reported urticaria starting after Dose 1 and continuing or worsening after Dose 2. Table 3 presents the event by dose.

Table 4. Chronic Urticaria Event Reported by Dose	
Dose	**Number of Cases**
Dose 1	47
Dose 2	94
Dose 3	17
Dose 1 and continued/worsened after Dose 2	15
Unknown	40
Total	**213**

Time to onset ranged between same vaccination day up to 90 days post vaccination. Time to onset distribution is presented in Table 4.

Table 5. Chronic Urticaria Time to Onset Distribution	
Time to Onset	**Number of Cases**
Same vaccination day	28
Day 1-3	43
Day 4-7	29
8-10	9
>10	73 (range from 11 to 242 days, mean: 39.2 days)
Unknown	31
Total	**213**

Outcome was reported as not recovered at the time of reporting for 150 cases, recovered/recovering/recovered with sequelae in 35 cases, and for 28 cases, outcome was not provided.

Among the 213 cases, 35 reported urticaria duration lasting more than 6 weeks, therefore meeting the internationally agreed medical criteria for urticaria chronic. A focus on cases that have a time to onset where the vaccine administration may be considered the trigger (as a conservative approach we used 7 days), 16 cases remain. Among the 16, 3 reported a rechallenge generally described as worsening of the urticaria starting after Dose 1 also after vaccine Dose 2. Of note is that 7 out of the 16 cases reported a medical history and 6 of the 7 cases reported allergy, autoimmunity disease, hypersensitivity or previous COVID-19 infection, suggesting either a predisposition to urticaria and chronic urticaria or a different trigger than vaccination.

The 178 reports lacking information on how long the urticaria lasted do not allow a diagnosis of chronic urticaria. Among these cases, there were 83 that reported a time to onset following vaccination of 0 to 7 days); and among the 83 cases, there were 50 that did not provide any MH and this lack of information hampers a proper medical and causality assessment. Among the 33 remaining cases, there were 22 that reported histories of autoimmune diseases, allergy, atopy, and previous COVID-19 infection, suggesting a

possible predisposition to or alternate cause of urticaria. Among remaining 11 cases, there were 7 subjects that were taking concomitant medications (such as desogestrel, venlafaxine, quetiapine, dexamphetamine, doxycycline, sertraline) that may trigger urticaria. Among the remaining 4 cases, there was 1 case where the urticaria was thought to be due to insect bite, and 1 in a woman that was breastfeeding.[9]

Overall, 35 cases specifically reported that the urticaria lasted more than 6 weeks, and therefore meet the criteria for chronic urticaria. Only 16 cases reported a time to onset that was reasonably temporally associated with vaccination, and of note is that 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).

Rapporteur assessment comment:

Of the 244 retrieved cases reporting chronic urticaria through 09 May 2022, 35 cases reported a duration urticaria lasting more than 6 weeks. 16 cases had a TTO (within 7 days) where the vaccine administration may be considered the trigger. Seven of the 16 cases reported a medical history (allergy, autoimmunity disease, hypersensitivity or previous COVID-19 infection) suggesting either a predisposition to urticaria/ chronic urticaria or a different trigger than Comirnaty exposure. Overall, the number of case repots is low in the context of the large post-marketing exposure.

1.1.3.1. Clinical trial data

Phase 2/3 Study C4591001 placebo-controlled unblinded AEs in participants 12 years and older from Dose 1 to data cut-off date (15 April 2022) were reviewed. In the Phase 2/3 safety population, chronic urticaria was not reported in any of the 23,068 participants in the BNT162b2 group compared with 0 of 23,063 participants in the placebo group.

Phase 2/3 Study C4591031 placebo-controlled unblinded AEs in participants 12 years and older from booster vaccination to unblinding date were reviewed. In the Phase 2/3 safety population, chronic urticaria was not reported in any of the 5055 participants in the BNT162b2 group or in any of the 5020 participants in the placebo group.

Rapporteur assessment comment:

No chronic urticaria was reported in the clinical trials.

1.1.4. Observed versus expected analysis

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 244 CU cases reported cumulatively through 08 May 2022 globally. Observed cases were defined using the PT urticaria chronic. In Table 5, O/E results using both short and longer-term 21- and 42-day risk windows post Pfizer-BioNTech COVID-19 vaccines are provided using background rates in the general population for calculation of the expected cases in the denominator and all observed cases reported globally in the numerator. The O/E results are further stratified by age and dose for the United States (US) and European Economic Area (EEA) countries, because these regions provide detailed information about vaccine administration.

In the investigation for a background rate, 3 studies reported overall incidence rates of chronic urticaria ranging from 130 to 500 per 100,000 persons per year.[10,11,12] None of these studies reported age-specific rates. To take a conservative approach, the expected number of CU cases overall and in each age group was calculated based on a study from Italy that reported a background rate in the low end of the range of 130 per 100,000 person-years for 2013.[11] The study used data from the IMS Health Longitudinal Patient Database, which included patients registered with a total of 700 general practitioners across Italy. In the study, chronic spontaneous urticaria was defined as the presence of at least 1 outpatient ICD- 9-CM code of 708.1 (idiopathic urticaria), 708.8 (other specified urticaria) or 708.9 (unspecified urticaria) combined

with (i) a second diagnosis of 708.1, 708.8 or 708.9 coded ≥ 6 weeks later; (ii) an ICD-9-CM code of 995.1 for angio-oedema ≥ 6 weeks from the urticaria diagnosis; or (iii) a 90-day or longer period of an overlapping supply of a prescription antihistamine and a second prescription medication commonly used to treat chronic spontaneous urticaria (CSU); ie, a second antihistamine, montelukast, ciclosporin, methotrexate or oral corticosteroids) occurring within 6 months after the first ICD-9-CM diagnosis.

The expected chronic urticaria case counts were estimated based on this background incidence rate, the estimated number of Pfizer-BioNTech vaccine doses through 08 May 2022,[13,14,15] and the length of risk windows. COVID-19 vaccine administrations were limited to the Pfizer-BioNTech vaccine when available. For countries where the Pfizer--BioNTech COVID-19 vaccine is authorised, but manufacturer stratified data were not available, the doses administered were assumed to be divided equally by the number of brands of vaccines authorised during that period. The estimate of administered doses does not reflect COVID-19 vaccine doses administered in countries that did not publicly report.

Based on the background rates and the estimated number of exposure person-years through 08 May 2022, as shown in Table **5**, O/E ratios were well below one overall, by dose, and within strata of age groups for both risk windows of 21- and 42-days. This suggests that the number of observed cases of CU is not higher than expected in the absence of Pfizer-BioNTech COVID-19 vaccines overall and within the queried strata.

Table 6. Observed to Expected (O/E) Ratio for Spontaneously Reported Chronic Urticaria Cases Through 08 May 2022

Stratification	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY[a]	Expected Cases	O/E Ratio	Observed Cases	Time at Risk (PY)
21-day risk window							
US/EEA							
≤11 years	0	1,858,002	130	2415.40	0.000	0.000	0.001
12-17 years	6	3,272,834	130	4254.68	0.001	0.001	0.003
18-24 years	8	4,640,213	130	6032.28	0.001	0.001	0.003
25-49 years	89	19,192,688	130	24950.49	0.004	0.003	0.004
50-59 years	14	8,878,653	130	11542.25	0.001	0.001	0.002
60-69 years	14	7,714,168	130	10028.42	0.001	0.001	0.002
≥70 years	9	10,572,498	130	13744.25	0.001	0.000	0.001
Any dose	140	56,129,056	130	72967.77	0.002	0.002	0.002
Dose 1	51	22,872,174	130	29733.83	0.002	0.001	0.002
Dose 2	76	21,125,615	130	27463.30	0.003	0.002	0.003
Dose 3	13	12,131,267	130	15770.65	0.001	0.000	0.001
Global							

Table 6. Observed to Expected (O/E) Ratio for Spontaneously Reported Chronic Urticaria Cases Through 08 May 2022							
Stratification	**Observed Cases**	**Time at Risk (PY)**	**Background Rate Per 100,000 PY[a]**	**Expected Cases**	**O/E Ratio**	**Observed Cases**	**Time at Risk (PY)**
Overall	191	120,189,625	130	156246.51	0.001	0.001	0.001
42-day risk window							
US/EEA							
≤11 years	0	2,682,995	130	3487.89	0.000	0.000	0.001
12-17 years	7	5,019,355	130	6525.16	0.001	0.000	0.002
18-24 years	11	7,286,483	130	9472.43	0.001	0.001	0.002
25-49 years	96	30,271,381	130	39352.80	0.002	0.002	0.003
50-59 years	15	14,158,107	130	18405.54	0.001	0.000	0.001
60-69 years	16	12,483,992	130	16229.19	0.001	0.001	0.002
≥70 years	11	17,147,134	130	22291.27	0.000	0.000	0.001
Any dose	156	89,049,446	130	115764.28	0.001	0.001	0.002
Dose 1	55	22,872,174	130	29733.83	0.002	0.001	0.002
Dose 2	87	42,155,828	130	54802.58	0.002	0.001	0.002
Dose 3	14	24,021,444	130	31227.88	0.000	0.000	0.001
Global							
Overall	221	191,844,773	130	249398.21	0.001	0.001	0.001
a. Background rate source: Lapi F, et al 2016[1]							

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

With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Thus, the exposure is underestimated. In addition, country-specific dose volume data are dynamic and specific to the date of download from the websites, and subject to retrospective updates at the country level.[16] The expected count also assumes the background rates of the COVID-19 vaccinated population in the absence of vaccination is the same as those in the historical timeframe during which the source study was conducted. The background rates used in these analyses are derived from an administrative healthcare database in Italy prior to the COVID-19 era that did not report age-specific rates. A large proportion of COVID-19 vaccine dose administrations were derived from the US and other areas in the EU. It is possible that the delivery of healthcare, population demographics, and the underlying health status of the populations used for the background rate estimates differ from those expected in the vaccinated population.

Rapporteur assessment comment:

In the O/E analysis all retrieved 244 cases were used. All O/E ratios were well below 1.

1.1.5. Summary and Conclusion

Overall, of spontaneously reported cases, 35 specifically reported information that support a diagnosis of chronic urticaria and among them only 16 cases reported a likely temporal association to vaccination and among the cases that reported medical histories, 85.7% reported a predisposition to urticaria or an alternate trigger of urticaria. The cases that did not provide information about the length of urticaria did not meet the criteria of chronic urticaria. In some cases it was clearly mentioned urticaria lasting 1-2 days, which is not consistent with chronic urticaria diagnosis; in addition, most of the cases that reported medical history had pre-existing comorbidities/concomitant medication that were confounding factors. Considering that approximately 2.5 billion of doses have been administered worldwide, the number of reports of CU, even considering those that are not accurate diagnoses of chronic urticaria, is low, suggesting that it is unlikely to be correlated with vaccination.

The large clinical trials did not report any cases of chronic urticaria in either the BNT162b2 or placebo groups.

The ratio of O/E cases does not exceed 1 over either risk window.

Overall, the totality of the available information does not support a causal association between chronic urticaria and the vaccine. No changes in the risk minimisation measures or updates to the product information label are warranted at this time. The benefit risk profile of the vaccine remains favourable. The topic will continue to be monitored.

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Rapporteur assessment comment:

Of the 244 retrieved cases reporting chronic urticaria through 09 May 2022, 35 cases reported a duration urticaria lasting more than 6 weeks of which 16 cases had a TTO (within 7 days) where the vaccine administration may be considered the trigger. Seven of these 16 cases reported a medical history suggesting either a predisposition to urticaria/ chronic urticaria or a different trigger than Comirnaty exposure.

No chronic urticaria was reported in the clinical trial data.

All O/E ratios were well below 1.

Therefore, MAH's conclusion is accepted that the available information did not support a causal association between chronic urticaria and Comirnaty exposure.

Issue solved

Question 3

Regarding glomerulonephritis and nephrotic syndrome the MAH is requested:

a. To provide an updated literature review (DLP: 9 May 2022) concerning glomerulonephritis and nephrotic syndrome and for the identified case reports the MAH should include a WHO-UMC causality assessment per case regarding Comirnaty exposure.

MAH's response

Updated literature review

As previous cumulative reviews of the literature pertaining to this topic were included in the August 2021 Response to Questions from the PRAC Signal Assessment Report on Glomerulonephritis (GN) and Nephrotic Syndrome (NS) and PSUR #2 with a DLP of 18 December 2022, the literature was searched for the period of 19 December 2021 to 09 May 2022 for PTs in MedDRA v.25.0 HLT Glomerular Nephritis and Nephrotic syndrome and COVID [redacted] or PF07302048 or "PF 07302048" or PF-7302048 or PF7302048 or PF 7302048 or BNT162B2 or BNT162B2 or BNT162$ or BNT162$ or tozinameran or Comirnaty in the databases: Biosis, Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily.

In addition, literature articles resulting in case reports mentioned below in the Safety Database Review, are included in this literature section.

Results:

Twelve (12) relevant articles were retrieved from literature databases, and are summarized in **Error! Reference source not found.** below (not reproduced here). Some of these case reports were already in the global safety database, and some of these were captured in the Updated Safety Database Review below.

There were 10 literature articles from which respective cases are presented below in the Updated Safety Database Review. **Error! Reference source not found.** presents details of these articles (not reproduced here).

Rapporteur assessment comment:

As requested, the MAH provided an updated literature review on glomerulonephritis and nephrotic syndrome. For the period between 19 December 2021 to 9 May 2022, the MAH identified 12 relevant articles discussing 14 case reports from literature databases. Additionally, 10 articles were presented that included 14 other cases from MAH's safety database. Of the total of 28 cases, 3 cases were classified as unassessable, which is endorsed. The remaining cases were classified as unlikely to be related to Comirnaty (n=16) or possible related (n=9). For three of the cases that were classified by the MAH as possible related, the assessment is not agreed with. The case described in Arias et al. was considered to be confounded by previous Covid-19 infection according to the MAH. However, given that the Covid-19 infection was >1 year prior to the event, this is considered implausible and the case should be considered as probable related. Also, positive rechallenge was reported in this subject with no history of any renal disorder. The second possible case for which the causality assessment is not agreed with is the case described in Lim et al. This case describes a previously healthy subject with no evidence of renal disease that developed glomerulonephritis after the first Comirnaty dose. The patient had negative serologic testing results for multiple infections including Covid-19. The case is therefore considered to be probable related to Comirnaty. The third possible case for which the causality assessment is not agreed with is the case described in Baskeran et al. According to the MAH, no alternative explanation was available for the event following a work-up for potential aetiologies. Based on the information provided by the MAH, the case is considered to be probable related to Comirnaty.

Of the six possible cases that were agreed with the classification, four were reported in patients with a history of renal disease (positive rechallenge, n=1) and two reported new onset cases (positive rechallenge, n=1).

b. To provide an updated review (DLP: 9 May 2022) of cases reporting glomerulonephritis / nephrotic syndrome from their safety database and, when applicable, provide the WHO-UMC causality assessment per case regarding Comirnaty exposure.

MAH's response

Detailed Review of Cases Reported Through 18 December 2021

Case Describing Pre-existing Renal Disease and Exacerbations Following Vaccination

As presented in the previous review through 18 December 2021, out of the total of 226 cases, 102 cases described a pre-existing medical condition and/or use of co-suspect/concomitant medication representing a reasonable alternative cause of the relevant events; some examples of conditions are autoimmune disorders, immunodeficiencies, infections, diabetes, and some examples of medications are NSAIDs, immunosuppressants, cephalosporins. Out of these 102 cases, 61 cases (reporting a total of 69 relevant events) reported a pre-existing glomerulonephritis, nephrotic syndrome related events and/or acute kidney injury, renal impairment, renal transplant, chronic kidney disease, and/or renal cancer. 48 out of these 61 cases were healthcare professional/medically confirmed; and 24 of these 61 cases reported "aggravation, exacerbation, and/or worsening" of the renal events.

In 18 of these 24 cases laboratory work-up and/or diagnostic procedure for renal function/kidneys were provided confirming the diagnosis. Six out of these 18 cases originated from literature sources ([redacted]; [redacted]; [redacted]; [redacted]; [redacted]; [redacted]). The details of these articles are provided in the Updated literature review section above.

Out of the remaining 12 cases, in the following 3 cases the WHO-UMC causality assessment was *Unassessable* due to insufficient information for proper assessment:

A 59-year-old male patient had a complex medical history including Cardiovascular Accident (CVA) with impact on cardiac ejection fraction and diabetes which could contribute to development of relevant event; the only available laboratory test result in this case was proteinurea ([redacted])

A 43-year-old male patient with history of nephrotic syndrome and inflammatory bowel disease (both auto-immune and well controlled prior to vaccination; the patient received rituximab about 7 months prior to vaccination) who detected high levels of protein in urine on Combur Test strips 5 weeks after Dose 2 of the vaccine ([redacted]).

A 19-year-old male patient who had a history of pure idiopathic nephropathy from age of 3 years old and grass allergy, on mycophenolate. The patient had frequent relapses (1/year). A few months prior to vaccination, the patient had another relapse during the peak grass season; at that time corticosteroids were added to his mycophenolate. Two days post Dose 1, he experienced aggravation of his condition. The outcome of the relevant event was resolved ([redacted]).

Two other cases ([redacted]; [redacted]) of the remaining 9 cases provided minimal details and reported patients (17-year-old male; 39-year-old female, respectively) with a pre-existing IgAN and no other medical conditions, who experienced an aggravation of the disease with haematuria and proteinuria 1 day post Dose 2. The outcome for the relevant event was resolved in both cases, and the causality assessment was *Possible*.

The last 6 cases are presented in **Error! Reference source not found.** (not reproduced here). These cases reported varying amounts of details, but all were reports of exacerbation of renal disease (e.g., proteinuria) at some point following vaccination in otherwise stable disease.

Rapporteur assessment comment:

The MAH has provided information on the WHO causality assessments of the cases identified in the PSUR period (through 19 December 2021). Of the 61 cases describing pre-existing renal disease and exacerbations following vaccination, 48 were medically confirmed of which 24 reported "aggravation, exacerbation, and/or worsening" of the renal events. Of these 24 cases, 18 provided laboratory work-up and/or diagnostic procedure to confirm the diagnoses of which 6 were discussed above in the section describing the literature cases. Of the remaining 12 cases, 3 were considered unassessable since limited information was available. Although some more information was available, for 5 additional cases causality was also unassessable according to the MAH. Causality was classified as unlikely (n=1) and possible (n=3) in the remaining cases. For one case, information on causality seems to be missing.

Cases Without Pre-Existing Renal Disease Describing Events Following Vaccination

In the previous review (DLP 18 Dec 2021), there were 68 cases reporting patients without pre-existing relevant medical history who experienced relevant events and were hospitalised. Out of these 68 cases, 46 cases were medically confirmed; in 7 of these 46 cases, the co-reported events suggested that the renal conditions occurred as a result or in association with other conditions, such as infection (pneumonia, enterocolitis, etc.), auto-immune disorders (lupus, vasculitis, multi-inflammatory syndrome, etc.).

Out of the remaining 39 cases, 27 cases reported a plausible latency from 1 to 42 days post vaccination. Dose reported in a given case. Out of these 27 cases, 15 cases provided laboratory tests with results confirming the diagnosis. Details of these 15 cases are provided in **Error! Reference source not found.** (not reproduced here).

Rapporteur assessment comment:

The MAH has provided information on the WHO causality assessments of the cases identified in the PSUR period (through 19 December 2021). Of the 68 cases reporting patients without pre-existing renal disease, 46 were medically confirmed of which 7 were considered to be caused by other conditions. Of the 46 medically confirmed cases, 27 reported TTO from 1 to 42 days post vaccination of which 15 provided laboratory tests with results confirming the diagnosis. Of these, causality was classified as unassessable in 5 cases since limited information was available and 7 as unlikely given that these were confounded by underlying medical condition or concomitant infections and/or no information was available on other potential causes. For one case, information on causality seems to be missing.

Update of Cases Through 09 May 2022

The safety database was searched for all BNT162b2; BNT162b2S01 cases reported from 19 December 2021 through 09 May 2022 using MedDRA v 25.0 PTs within the HLT glomerulonephritis and nephrotic syndrome.

A total of 201 cases (reporting 914 events) were retrieved from the global safety database using the search strategy mentioned above. Some cases reported more than 1 of the relevant events in the HLT (a total of 236 relevant PTs were reported). **Table 10** below lists relevant PTs in this dataset and a respective number of cases.

Table 7. GN and NS Safety Database Search: Relevant PTs and Respective Number of Cases	
PT	**Number of Cases**
Nephrotic syndrome	75
IgA nephropathy	40
Glomerulonephritis	38
Glomerulonephritis minimal lesion	20
Glomerulonephritis membranous	9
Glomerulonephritis rapidly progressive	9
Nephritic syndrome	8
Focal segmental glomerulosclerosis	7
Microscopic polyangiitis	5
Glomerulonephritis acute	4
Goodpasture's syndrome	4
Anti-glomerular basement membrane disease	3
C3 glomerulopathy	3
Glomerulonephritis membranoproliferative	3
Granulomatosis with polyangiitis	2
Henoch-Schonlein purpura nephritis	2
Glomerulonephritis chronic	1
Glomerulonephritis proliferative	1
Mesangioproliferative glomerulonephritis	1
Post streptococcal glomerulonephritis	1

The majority of cases (171) were spontaneous; all 201 cases were serious. There were 105 females, 95 males, and gender was not reported in 1 case. When provided, the ages ranged as shown in **Table 11** below. The mean and median ages were 43.1 and 42 years, respectively (n=196).

Table 8. GN and NS Reported Age in 201 Cases

Age Range	Number of Cases	% of Total Cases
Less than or equal to 17 years	25	12.40%
18 – 30 years	39	19.40%
31 – 50 years	63	31.30%
51 – 64 years	29	14.40%
65 – 74 years	21	10.40%
Greater than or equal to 75 years	19	9.50%
Unknown	5	2.50%

The countries where these cases were most frequently reported are presented below in Table 12.

Table 9. GN and NS Top Reporting Countries in 201 Cases

Country	Number of Cases	% of Total Cases
Germany	50	24.90%
Japan	34	16.90%
France	24	11.90%
Australia	13	6.50%
Italy	10	5.00%

Further analysis was concentrated on 110 cases reporting relevant events with time to onset (latency) of 1 to 42 days post vaccination, as in the previous review (DLP 18 December 2021).

Out of these 110 cases, 38 cases described a pre-existing medical condition and/or use of co-suspect/concomitant medication representing a reasonable alternative cause of the relevant events; some examples of conditions are COVID-19, autoimmune disorders, immunodeficiencies, infections, diabetes, and some examples of medications are loop diuretics, immunosuppressants, other vaccines. Out of these 38 cases, 19 cases reported a pre-existing GN/NS.

Out of these 19 cases, 3 cases originated from literature ([redacted]; [redacted]; [redacted]). Details of these articles can be found in Updated literature review section above.

Out of the remaining 16 cases, 8 cases reported "aggravation or relapse" of the GN or NS related events. **Error! Reference source not found.** provides details of these 8 cases (not reproduced here).

The last 72 cases (with total of 315 events and 86 relevant events) described events that occurred post vaccination in patients without existing GN or NS. In 12 of these 72 cases, the co-reported events suggested the possibility of other conditions, such as infection (eg, influenza, urinary tract infection), immune/auto-immune conditions (eg, capillary leak syndrome, systemic inflammatory response, vasculitis, lupus) contributing to the events.

In the remaining 60 cases reporting 67 relevant events, when dose sequence was provided, it was Dose 1 for 17 relevant events, Dose 2 for 33 events and Dose 3 for 17 events. The outcome of the relevant events at the time of reporting was resolved/resolving for 30 events; not resolved for 22 events; resolved with sequelae for 4 events; outcome was unknown for 13 events. The latency was reported as: from 1 day to 3 days post vaccination for 21 relevant events, from day 4 to day 10 for 20 events, from day 11 to day 20 for 14 events, from Day 21 to Day 36 for 11 events.

Out of these 60 cases, 7 cases originated from literature ([redacted]). Details of these articles can be found in the Updated literature review section above.

Out of the remaining 53 cases, 13 cases reported hospitalisation and were health care medically confirmed. **Error! Reference source not found.** presents details of these 13 cases (not reproduced here).

Rapporteur assessment comment:

As requested, the MAH has provided an update of the cases reported as of 9 May 2022. The MAH identified a total of 201 additional cases of which 110 reported TTO between 1 to 42 days post vaccination. Of these 110 cases, 38 were considered to be caused by other conditions of which 19 reported pre-existing renal disorders. Of these 19 cases, 3 were discussed in the section describing the literature cases and 8 reported "aggravation or relapse". Of these 8 cases, 7 were classified as unassessable and one as unlikely. 72 cases were reported in patients without pre-existing renal disorders. Of these, 12 were considered to be caused by other conditions. Of the remaining 60 cases, 7 were discussed in the section describing the literature cases. For the 13 cases that reported medical history and were medically confirmed causality assessments were provided. Of the 13 cases, 9 were unassessable, 2 unlikely, and 2 possible related to Comirnaty.

MAH's summary and conclusion

MAH's safety database has received reports of reoccurrence of proteinuria in patients with underlying disease following vaccination (any dose) and cases describing new onset proteinuria in patients without histories of renal disease. Individual case assessments focusing on temporality, data confirming diagnoses and the presence or absence of alternative explanations are helpful but do not allow confirmation of a causal relationship.

In patients with underlying renal disease, it is possible that unreported or unknown factors, may be contributing to disease activity (eg, blood pressure and dietary changes, undulating or progressive nature of the disease course). Likewise, it is possible that patients without underlying renal disease would develop proteinuria or other renal disease regardless of vaccination. Therefore, consideration of the totality of data is important, as is consideration of the vast number of vaccine doses that have been administered in this current environment of high vigilance for any AE that occurs in the days to weeks following vaccination.

Currently, the literature on renal disease following vaccination consists of case reports rather than large observational studies. Clinical trial data in a population of patients with renal disease is also unavailable at this time. The development of renal disease has not been a safety signal in clinical trials suggesting that if there is a connection between it and vaccination, it is rare. The previous O/E analyses, with its caveats, was not supportive of an excess of cases compared to background rates.

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 renal disease such as GN or NS.

Rapporteur assessment comment:

As requested, the MAH provided the WHO causality assessments of relevant cases that were identified in the PSUR period. From MAH's safety database, three cases that were considered possible related to Comirnaty were identified in patients with pre-existing renal disease. No new onset cases assessed as causality probable or possible were identified.

Also, the MAH provided an updated literature review with DLP 9 May 2022 as requested. From literature, 28 additional cases were identified of which 3 were considered probable related (according to PRAC rapporteur's assessment), and 6 possible related of which 2 reported a positive rechallenge. These cases were both new onset cases (N=2) as well as cases that were reported in patients with pre-existing renal disorders (N=4). From the MAH's safety database, no additional cases considered possible or probable related were identified for patients with pre-existing renal disorders. For new onset cases that reported medical history and were medically confirmed, 2 possible related cases were identified.

To note, in the previous signal procedure (EPITT ref. 19722) with DLP 25 July 2021, a total of 7 (of which 5 from literature) probable cases and 3 possible cases were identified. Within this signal procedure, PRAC concluded that, based on available information, no update of the Comirnaty product information was warranted.

In conclusion, probable/possible related (literature) cases of both new onset (n=7) and cases in patients with pre-existing renal disease (n=7) were identified. However, given that O/E ratios were well below one, that the currently available data are in line with the previous PRAC conclusion, and taking into account Comirnaty exposure, it is agreed with the MAH that no new safety concern could be identified.

Issue solved

Question 4

The MAH is requested to confirm that there is no additional information during the current reporting period of the 2nd PSUR concerning clinical reactogenicity data on individuals previously exposed or not to SARS-COV-2. If not, the new data should be submitted.

MAH's response

Data are available from 2 analyses: 12–15-year-old adolescents (and 16–25-year-olds as comparator) and 5–11-year-old children, both receiving 2 primary doses of BNT162b2 (age-appropriately, 30 µg and 10 µg respectively).

12–15-year-old adolescents (from C4591001)

The reactogenicity data for subject subgroups based on their baseline SARS-CoV-2 positive or negative status are shown as tabular summary data for local reactions (Appendix 2 **Error! Reference source not found.**, not reproduced here) and systemic events (Appendix 2 **Error! Reference source not found.**, not reproduced here).

Local reactogenicity was generally similar between baseline positive and negative subjects, and numerically lower in baseline positive subjects. Systemic reactogenicity events were generally higher or similar for subjects positive at baseline compared to those negative at baseline, after the first dose. After the second dose, the pattern is reversed; systemic reactogenicity is lower for the subjects positive at baseline compared to those negative at baseline. The overall reactogenicity profile when one examines

the frequencies for any systemic reaction for either Dose 1 or Dose 2 was not substantially different between the baseline status subgroups.

The number of subjects in the baseline positive group is small, so results should be interpreted with caution.

5–11-year-old children (from C4591007)

Local reactions

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1378 BNT162b2 and 684 placebo participants with baseline negative SARS-CoV-2 status) (Appendix 2 **Error! Reference source not found.** [Positive] and Appendix 2 **Error! Reference source not found.** [Negative], not reproduced here). The frequencies of redness, swelling, and pain at the injection site after any dose of BNT162b2 was 20.3%, 12.8%, and 82.7% compared with 27.0%, 21.1%, and 84.5% for those positive and negative at baseline, respectively. The frequencies between individuals positive or negative at baseline were similar although numerically lower in those positive at baseline. Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

Systemic events

There were 133 BNT162b2 and 65 placebo participants with baseline positive SARS-CoV-2 status, and 1384 BNT162b2 and 685 placebo participants with baseline negative SARS-CoV-2 status (Appendix 2 **Error! Reference source not found.** [Positive] and Appendix 2 **Error! Reference source not found.** [Negative]). The frequencies of the most commonly reported systemic events of fatigue, headache, and muscle pain after any dose of BNT162b2 was generally similar, or numerically lower among those positive at baseline: fatigue, headache and muscle pain frequencies were 40.6%, 39.1% and 15.8% compared with 52.8%, 38.1%, and 17.7% for those positive and negative for SARS-CoV-2 at baseline, respectively. Fevers after any dose of BNT162b2 were reported at a slightly lower frequency in baseline positive compared to baseline negative participants (6.0% vs 8.5%). Note that the baseline SARS-CoV-2 positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

Rapporteur assessment comment:

The MAH provided additional data regarding clinical reactogenicity on individuals previously exposed or not to SARS-COV-2. In general, the baseline SARS-CoV-2 positive subgroups in the age groups 5-11 years, 12-15 years, and 16-25 years were considered small (N ranged from 30-133) and therefore results (clinical differences between positive and negative persons) should be interpreted with caution. No new important safety information could be identified.

Issue solved

7. Comments from member states

MS1, MS2

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

Rapporteur assessment comment:

The endorsements of the PSUR assessment are appreciated.

MS3

MS3 endorses the Rapporteur assessment report. However, MS3 has two additional comments regarding some cases of "neuralgic amyotrophy" and "acquired haemophilia".

Neuralgic amyotrophy syndrome

In the October MSSR (EMEA/H/C/005735/MEA/002.9), MS3 had reported 6 cases of neuralgic amyotrophy with a request for a cumulative review, which was not performed due to the absence of safety concern at the time. However, MS3 would like to rediscuss this topic.

Cases

In MS3, since the beginning of the vaccination with Comirnaty, 43 cases of neuralgic amyotrophy syndrome have been reported through the national pharmacovigilance network.

All reported cases have been reviewed and analysed with a neurologist expert taking into account the time to onset (TTO), the clinical data and complementary examinations. He confirmed the definite diagnosis of neuralgic amyotrophy syndrome in 25 cases.

The details are presented below.

Characteristics of reported cases	Serious cases N=25 (%)
Gender	
Male	16 (64%)
Female	9 (36%)
Median age, years	51 [25-75]
Groups of age	
0-18	0
19-29	2 (8%)
30-49	9 (36%)
50-64	5 (20%)
65 et +	9 (36%)
TTO (days)	21
0-7	6 (24%)
8-15	3 (12%)
16-22	5 (20%)
23-30	3 (12%)
31 et +	8 (32%)
Severity criteria	
Hospitalization	3 (12%)
Incapacity	5 (20%)
Medically significative	17 (68%)
Evolution	
Recovery	8 (32%)
Not recovered	14 (56%)
Recovered	1 (4%)
Recover with sequel	1 (4%)
Unknown	1 (4%)
Vaccine dose	
D1	7 (28%)
D2	14 (56%)
R1	4 (16%)
Additional examination performed	
Electrodiagnostic	19 (76%)
MRI	13 (52%)

Among those 25 cases, he reported 7 cases with particular forms potentially confounded:

- in their clinical expression: a focal form ([redacted]); an atypical form [redacted]; a beginning form ([redacted]);

- one case reports a contralateral neuralgic amyotrophy syndrome of the vaccinated arm [redacted];

- one case concerns a neuralgic amyotrophy syndrome occurring in a postpartum context (a period considered to be at risk for such a pathology) ([redacted]);

- 2 cases mention the existence of a trauma (fall while skiing [[redacted]], gardening effort [[redacted]]).

Therefore, among the 43 cases of neuralgic amyotrophy syndrome retrieved in MS3, the causal association with the vaccination cannot be ruled out in 18 cases, in particular one case of relapse in a patient with a history of neuralgic amyotrophy syndrome from which she had completely recovered[redacted]

Literature

The literature contains 10 case reports after vaccination with Comirnaty.

Mahajan et al. reported the case of a man presenting with a sudden severe painful symptomatology at D7 with the appearance of peripheral muscle weakness secondarily. EMG confirmed the diagnosis of Parsonage-Turner syndrome; the clinical picture improved with corticosteroid therapy. (*Mahajan S, Zhang F, Mahajan A, Zimnowdski S., Parsonage turner syndrome after COVID-19 vaccination, Muscle Nerve . 2021 apr23 doi :10.1002/mus.27255*).

Queler et al. mentioned the occurrence of Parsonage-Turner syndrome with painful symptoms in the left forearm 13 hours after D1 performed in the right upper limb. To note, a recent history of Lyme disease (which may have caused amyotrophic neuralgia) in the previous 2 months treated with doxycycline (*Queler SC, Towbin AJ, Milani C, Whang J, Sneag DB, Parsonage-Turner Syndrome following COVID-19 vaccination : MR Neurography, Radiology (2021) in press*).

Diaz-Segarra et al. reported a painless case of neuralgic amyotrophia syndrome at D9 after vaccination. There was a marked improvement with corticosteroid therapy (*Diaz-Segarra N, Edmond A, Gilbert C, McKay O, Kloepping C, Yonclas P., Painless idiopathic Neuralgic amyotrophy after COVID1-19 Vaccination. A case report, PM R 2021 , Apr 22*).

Coffman et al. reported on a 66 years old female patient with the onset of Parsonage Turner syndrome within days of the second dose of Comirnaty with an initial painful phase followed by a motor deficit. The EMG confirmed the diagnosis. The evolution was progressively favourable in 3 months with a disappearance of the pain at 1 month (*Coffmann JR, Randolph AC, Somerson JS., Parsonage- turner syndrome after Sars-Cov-2 BNT162b2 Vaccine. A case report, JBJS Case connector Vol 11 number 3 september 24 ,2021*).

Shields et al. reported 4 cases of neuralgic amyotrophy syndrome with repectively a TTO of 7 days (1 case); 15 days (2 cases) and 2 months (1 case) confirmed secondarily by EMG. Two patients noted a disappearance of the pain but a persistence of the motor disorders; 2 other patients noted a clinical improvement. (*Shields LBE, Lyer VG, Zhang YP, Burger JT, Shields CB. .Parsonage-Turner Syndrome Following COVID-19 Vaccination: Clinical and Electromyographic Findings in 6 Patients. Case Rep Neurol 2022*).

Koh et al. reported 2 cases of neuralgic amyotrophy syndrome in 2 patients; the (TTO was 25 days after D1 with a favourable evolution under corticotherapy in one case and 4 days after D2 with a spontaneous favourable evolution in the other case. (*Koh, JS, Goh Y, Tan BY-Q, Hui AC-F, Hoe RHM, Makmur A, Kei PL, Vijayan J, Ng KWP, Quek AML, Thirugnanm U. Neuralgic amyotrophy following COVID-19 mRNA vaccination. QJM 2021 Nov 5*).

Conclusions

Taking into account the 18 cases without other etiological cause, the 7 publications reporting 10 cases, and the fact that recent immunization is a known risk factor of neuralgic amyotrophy, a causal association between the occurrence of neuralgic amyotrophy syndrome and the vaccination cannot be ruled out.

Therefore, it is proposed to request from the MAH a cumulative review of cases reporting Neuralgic amyotrophy syndrome in the next PSUR, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccination. Based on this review, a discussion on the need to update the product information should be provided, if applicable.

Rapporteur assessment comment:

In MS3 there were 18 cases reporting neuralgic amyotrophy syndrome without other etiological cause in the cases descriptions and 7 publications were retrieved with 10 cases.

Neuralgic amyotrophy was/is considered a rare disease, with an estimated incidence of 1–3 per 100,000 per year, although there were some indications in the literature that the actual incidence may be higher. A study of van Alfen prospectively determined the 1-year incidence in a primary care population and found an incidence rate of 1 per 1,000 per year. [1] The total administered doses of Comirnaty in MS3 is estimated at 15,477,845 doses and therefore the observed 18 cases reporting neuralgic amyotrophy are considered well below the expected number of cases.

The CMS states that "recent immunization is a known risk factor of neuralgic amyotrophy" without further substantiation of this statement. Moreover, the exact pathophysiologic mechanism in neuralgic amyotrophy is not known, but it is thought to be complex and multifactorial. An interplay between environmental factors (i.e., infections or immune triggers), mechanical factors (repetitive or strenuous motor tasks), and individual (genetic) susceptibility is assumed to be the cause of neuralgic amyotrophy.[2]

During the interval period of the PSUR, no new important safety information could be identified for immune-mediated/autoimmune AESIs which included 179 cases reporting neuralgic amyotrophy.

Therefore a request for a cumulative review in the next PSUR of cases reporting neuralgic amyotrophy is not expected to change this conclusion.

References

1. van Alfen N, van Eijk JJ, Ennik T, Flynn SO, Nobacht IE, Groothuis JT, et al. Incidence of neuralgic amyotrophy (Parsonage Turner syndrome) in a primary care setting—a prospective cohort study. PLoS One 2015;10:e0128361.
2. Van Eijk, Groothuis 3, van Alfen. Neuralgic amyotrophy: An update on diagnosis, pathophysiology, and treatment. Muscle Nerve 2016 Mar;53(3):337-50. doi: 10.1002/mus.25008. Epub 2016 Jan 20.

Acquired haemophilia

The signal of acquired haemophilia has been closed in the last PSUR (PSUSA/00010898/202106) due to the limited information or confounding factors for the 11 reported cases at that time. However, MS3 would like to rediscuss this topic.

As a reminder, acquired hemophilia is a rare disease with an estimated prevalence of approximately 1 to 1.5 cases/million individuals/year that most often affects patients over 60 years old. Such inhibitory autoantibodies have been detected in autoimmune diseases, pregnancy, infections or malignant diseases. This isolated and acquired factor VIII deficiency can only be due to inhibitory autoantibodies directed against this coagulation factor. The term "acquired hemophilia", although often used, is therefore quite different from hemophilia, which is a constitutional, genetically modified deficiency. Taking into account the population concerned, the presence of antithrombotic treatment such as VKA or platelet inhibitors may delay the diagnosis because bleeding complications are then falsely attributed to anticoagulant treatment.

The diagnosis is most often evoked clinically but can only be confirmed by an isolated prolongation of the aPTT with an isolated factor VIII deficiency and on the identification of anti-factor VIII antibodies.

Cases

In MS3, since the beginning of the vaccination with Comirnaty, 18 cases of acquired haemophilia have been reported.

The 18 cases were all confirmed cases of acquired hemophilia, most of them presenting with a multiple hematomas and/or ecchymosis.

These 18 cases (10 women, 8 men; average age =75 years) occurred :

- For 5 cases after the first injection (D1)

  In 3 men and 2 women (ages ranging from 25 to 90 years)

  TTO: D4, D10, D12, D32, D90

- For 12 cases after the second injection (D2)

  In 4 men and 8 women (age ranging from 45 to 90 years)

  TTO: D2, D13, D15 (2 cases), D17, D21, D22, D23, D30, D49, D57, D60

- For 1 case after booster (R1)

  In a man over 70 years old,

  TTO: D60

All these cases were treated in hospital by specialized services for emergency treatment. Of these 18 cases, 3 were fatal, i.e. a mortality rate of 16.6%, which corresponds to the mortality rate reported in the literature (estimated between 8-20%).

To note among these 18 cases, we will describe 6 cases with a particularly evocative clinical data: 3 cases with a fatal outcome ([redacted]).

Determining a risk window, i.e., the time between exposure to the vaccine and the occurrence of acquired hemophilia, is therefore difficult because of the non-exceptional delay in diagnosis, which may have several causes (unexplored bleeding manifestations, unnoticed prolongation of the APTT, etc.). This is well known with this disease. The delays observed in our series of 18 cases are also variable.

Among the 18 cases in this analysis:

- 1 case occurred in a patient with rheumatoid arthritis;

- 1 case in a patient whose etiological work-up revealed a lymphopathy;

- 1 case corresponding to a relapse of a previously known acquired hemophilia, which is particular interesting because the patient was considered in remission ([redacted]).

For the other 15 cases, the etiological and extensive tests (autoimmune, infectious, neoplasic) were negative.

Literature

The scientific literature also reports several cases of acquired hemophilia in patients vaccinated with COMIRNATY vaccine[1,2,3,4,5,6].

From a mechanistic perspective, it is interesting to note published cases of acquired hemophilia post COVID-19 infection, as well as a recent publication that performed experimental work to evaluate whether the vaccine-induced antibody response against the SARS-COV2 spike protein could have FVIII inhibitory functions[7,8,9].

Conclusions

Taking into account the 18 cases, in particular the 3 cases of fatal outcome and the 3 cases where the link between vaccination and acquired haemophilia is plausible, the literature data and the potential mechanism of action, a causal association between acquired haemophilia and the vaccination cannot be ruled out.

Therefore, MS3 proposed to re-open the signal of acquired haemophilia and it is proposed to request from the MAH a cumulative review of cases reporting acquired haemophilia in the next PSUR, 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 provided a comprehensive discussion of literature and mecanism of action. Based on this review, a discussion on the need to update the product information should be provided, if applicable.

[1] *Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. J Thromb Haemost. 2021 Jun;19(6):1515-1518.*

[2] *Murali A, et al. Acquired Hemophilia A following Pfizer-BioNTech SARS CoV-2 mRNA vaccine, successfully treated with prednisolone and rituximab. J Oncol Pharm Pract. 2022 Jan 28:10781552221075545.*

[3] *Al Hennawi H, et al. Acquired Hemophilia A Post-COVID-19 Vaccination: A Case Report and Review. Cureus. 2022 Feb 4;14(2):e21909.*

[4] *Leone MC, et al. Four cases of acquired hemophilia A following immunization with mRNA BNT162b2 SARS-CoV-2 vaccine. Thromb Res. 2022 Mar;211:60-62.*

[5] *Farley S, et al. Autoimmunity after Coronavirus Disease 2019 (COVID-19) Vaccine: A Case of Acquired Hemophilia A. Thromb Haemost. 2021 Dec;121(12):1674-1676.*

[6] *Ai Vuen L, et al. Case of acquired haemophilia a in Southeast Asia following COVID-19 vaccine. BMJ Case Rep. 2022 Mar 9;15(3):e246922.*

[7] *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*

[8] *Olsen GM, et al. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. Transfusion. 2020;61(3):989-991.*

[9] *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:

In MS3 there were 18 confirmed cases of acquired hemophilia reported of which 2 are considered confouded by medical history and 1 case reported a relapse of acquired hemophilia. There seems to be no clear pattern regarding the time to onset that ranged from 12 to 90 days after Comirnaty exposure and it is not clear if the cases were tested positive or negative for SARS-CoV-2 infection.

In the presented literature cases of acquired hemophilia, the reported medical histories (diabetes, adenocarcinoma of the prostate, benign prostatic hyperplasia, breast cancer, rheumatoid arthritis) could be another explanation of the cause for the occurrence of acquired hemophilia. Besides in the literature cases it is not described if the cases were currently tested negative for SARS-CoV-2 infection which could have triggered the occurrence of acquired hemophilia.

However, the background incidence of acquired hemophilia is estimated to be 1-1.5 per 1,000,000 persons/year and the estimated cumulative exposure in MS3 is 15,477,845 administered doses of Comirnaty. With 15 acquired hemophilia cases reported in MS3 the total observed cases of acquired hemophilia are considered around the expected number of cases (O/E ratio around 1). Also acquired hemophilia is considered a serious adverse event with a potentially life-threatening course. Therefore, the

PRAC Rapporteur agees to request a cumulative review of cases reporting acquired haemophilia in the next PSUR from the MAH, 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 provided a comprehensive discussion of the literature, mechanism of action and a discussion on the need to update the Comirnaty product information, if applicable. **Request for next PSUR**

MS4

MIS:

Until May 8th, in MS4 12 cases* were registered in MS4 database: 5 cases involving patients < 21 years (analysed in consideration of MIS-C) and 7 cases ≥ 21 years (analysed in consideration of MIS-A).

These cases were reviewed and assessed according to Brighton Collaboration (BC): 5 cases were classified as BC level 1; 2 cases as BC level 2b and 5 cases as BC level 4. In 6 of the 7 cases with the necessary information for a proper evaluation, no alternative explanations were found.

In addition, in the age-stratified analyses, the O/E ratio exceeds 1 for MIS for most age group, included the 12-17 years age group.

For analysing cases according to Brighton collaboration criteria, it is essential to have access to the narratives, since relevant information is not always codified. It will be therefore important to make sure that the MAH has access to the case narratives; this is of relevance for other issues under evaluation where specific diagnostic criteria need to be applied.

A cumulative review of MIS-C/A cases analysed according to the BC criteria should be presented in the next PSUR.

**Search criteria: Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in children and Multisystem inflammatory syndrome in adults.*

Rapporteur assessment comment:

Here the member state provided data outside the PSUR interval period and proposes a cumulative review in the next PSUR. However, following the initial signal procedure the MAH is already requested to present all new cases of MIS-C/A in PSURs, SSRs, and other relevant safety reports including assessments using the 'BC criteria' and the 'WHO-UMC system for standardised case causality assessment'. The MS4 comment is therefore considered to be covered.

PREGNANCY:

Overall, we agree with the Rapporteur evaluation However, the foetal defects associated with stillbirths (17 cases), elective pregnancy termination (29 cases) together with those found in livebirth should be described in detail in order to rule out a common pattern. Since spontaneous abortion is the most frequently reported outcome, an analysis of O/E is expected.

Rapporteur assessment comment:

At the moment, the Comirnaty exposure in pregnant women is not known and therefore O/E analyses cannot be performed. However, the PRAC Rapporteur agrees that it is unclear if the frequency of AEs reported including spontaneous abortion is consistent with the expectation. This can however not be determined from spontaneous reporting. Future results from studies (including PASS addressed in the RMP) evaluating the safety in pregnancy should give more clarity regarding pregnancy outcomes in relation to Comirnaty exposure.

HERPES ZOSTER:

This signal was assessed and closed in the 9th monthly report. Since then, new studies and case reports on the potential relationship between herpes zoster and COVID vaccine-19 have been published. To note the article by Hertel et al based on real-world data from over 120 healthcare organizations across 19 countries that includes information from two cohorts with more than 1,000,000 subjects each. The study found that the frequency of herpes zoster diagnoses within 1-60 days post-COVID-19 vaccination was higher among patients who received COVID-19 vaccines (Cohort I) versus those who were not vaccinated (cohort II). Risk ratio and OR were around 1.8, being statistically significant.

Moreover, according to the summary tabulation, the number of spontaneous AE of herpes zoster has doubled compared to that included in the 9th monthly report. The number of cases of herpes zoster meningitis and herpes zoster meningoencephalitis has also increased. Therefore, we consider that this signal should be re-evaluated in the next PSUR including a review of literature, cases of herpes zoster with neurologic involvement, as well as cases from adolescents and children.

M. Hertel, M. Heiland, S. Nahles, M. von Laffert, C. Mura, P.E. Bourne, R. Preissner, S. Preissner. Real-world evidence from over one million COVID-19 vaccinations is consistent with reactivation of the varicella-zoster virus. Journal of the European Academy of Dermatology and Venereology Supplement : 2 May 2022.

Rapporteur assessment comment:

Regarding herpes zoster, a cumulative review was assessed in the 8th SSR (procedure EMEA/H/C/005735/MEA/002.9) and it was concluded that there was no new important safety concern, and signal was closed.

The presented article of Hertel et al. is published in May 2022 and therefore after DLP of the interval period of the current 2nd PSUR. However, other AESIs including herpes zoster were continue monitored in the SSRs for Comirnaty during the reporting period of the PSUR (and beyond, till the 14th SSR with data through 15 Apr 2022) and there was no new important safety concern. The PRAC Rapporteur is expecting that the presented article will be included in the next PSUR with MAH's assessment of herpes zoster, as applicable.

CVST:

CVST has been reviewed in the 13th SSR. An O/E analysis has been provided with overall ratios <1. However, the O/E ratio was >1 using a 21-day risk window for males and females 18-24 and 25-49 and for females 60-69 years, when applying the low background rates.

In addition, in the PSUSA, an O/E analysis by EMA has been presented; there seems to be an imbalance for CVST in the younger age groups in the 20-29 age group: (D14) O/E ratio 7.85 (95%CI 5.72 - 10.5); (D30) O/E ratio 5.04 (95%CI 3.87 - 6.47).

A qualitative analysis of the cases has been performed concluding that the issue does not represent a signal for Comirnaty at this stage. However, taking into account the consistency in the disproportionality analysis in the young adult population, this should be monitored in the next PSUR.

Rapporteur assessment comment:

Here the member state provided data outside the PSUR interval period. In the 14th Comirnaty SSR (safety data through 15 Apr 2022), the MAH provided an updated review of CVST and included WHO-UMC causality assessments for the relevant cases as requested by the PRAC. Although several of the O/E ratios of the age-stratified analyses were >1, the review of the spontaneous reports only identified three

cases that were classified as possible related to Comirnaty. Furthermore, the identified literature articles did not indicate that there is a causal association between CVST and Comirnaty. PRAC (June 2022) therefore agreed with the MAH that based on the data provided no new safety concern was identified and that the signal could be closed.

MS5

We overall support the PRAC Rapporteur assessment however we have the following comments below. Please also note that for subacute thyroiditis we sent in our comment in the comment form for the SSR.

We find the data presented and the analyses provided by the MAH to have an overall inadequate quality level.

- On the presentation of the MS5 signals *on chronic urticaria (CU)* and *polymyalgia rheumatica* (PMR), pAR sections 2.2.1.3 and 2.2.1.4 and *exacerbations of autoimmune and inflammatory disease* 2.2.1.1, we consider it premature based on the inadequate quality of the MAH data presentation to conclude if a causal association between Comirnaty and these safety topics exist or not.
- In relation to sections 2.1 *RMP*, and 2.4.2 *Description of missing information* the MAH restricts its presentation of missing information to the exact conditions mentioned in the RMP. We find this inadequate.

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

In the PSUR, many other frailties, co-morbidities are broadly deemed "confounders" with the MAH excluding large amounts of cases with potentially valuable information on patients with predispositions from further analysis. In the PMR analysis (2.2.1.4), 2/3 of cases are excluded on a group level on the grounds of involved patients allegedly belonging to broad confounding disease/disposition-groups. The groups are potentially rendering them frail or susceptible to the event analysed and thereby the exclusion methodology is inadequate in the realm of the general purpose of PSURs and RMPs. Frailty with co-morbidities information need to be analysed per se as to increase information leading for the safe use of the product; information regarding patients with potential pre-dispositions for developing ADRs should not be discarded by default as may appear to have been done.

- We find

- the inclusion and exclusion criteria for ICSR analyses concerning, not sufficiently described, relevant for sections 2.2.1.1, 2.2.1.2, 2.2.1.4

- the lack of detailed clinical justification for the high levels of exclusion of ICSRs from the analyses is unacceptable. Potential positive dispositions, risk factors for developing disease are broadly and without detailed explanation classified as confounding thereby excluding massive numbers of cases from clinically important analysis. This is not in line with the RMP safety specification on missing information.

- the level of exclusion of cases based on TTO restrictions is questionable, especially but not restricted to "too short" TTO in ICSRs associated with a second or later doses and concerning immunogenic/ inflammatory reactions.

- exclusion of ICSRs on the grounds of lack of detailed lab results in the reports are unjustified, especially regarding medically confirmed cases. We believe there is no reason why a reported diagnosis of an ADR

(eg PMR) should not be accepted as true to a similar degree as the MAH accepts other clinical diagnoses in the ICSRs' medical histories which in turn are used to exclude cases from the case series.

It is not reasonable to exclude every report which is not perfect; a reasonable overview of the pattern of all reporting which is not definitely invalid should be expected.

- We find the MAH ICSR causality assessments methodology concerning, and of questionable quality. The MAH claims to have used the WHO-UMC causality assessment system. Where individual causality assessments are presented, e.g. section 2.2.1.4, the results markedly deviate (away from causality) both from what would be expected using the WHO-UMC method and also from a separate assessment of the cases (tabular analysis provided at the end of the document) conducted by us. The assessments further exhibit inter-report assessment inconsistencies, lack of exclusion of miscoded cases, apparent misunderstanding of clinical information in reports and there are further examples where less typical but scientifically acknowledged signs and symptoms associated with diseases (eg PMR), go unacknowledged as such, thereby deeming cases unlikely/unclassifiable and excluding them from further analysis instead of understanding the information to be supportive of the diagnosis.

- Rechallenge information, a vital causality assessment criterion is absent in the PSUR. It hence lacks acknowledgement of positive rechallenge (PR), an indicator of causality, even where plausible PR cases are present e.g. sections 2.2.1.3, 2.2.1.4. The MAH in places does not distinguish between positive rechallenge and exacerbation of pre-existing disease, in some cases excluding such cases from analysis as confounded.

- O/E analyses presented are held on a general level with some limitations mentioned. As Comirnaty is truly globally distributed, more elaborate sensitivity considerations in the O/E analyses would be of relevance e.g. underreporting, backlog and global variations.

- MAH literature reviews do not in our opinion adequately reflect the conclusions of articles presented in the PSUR. E.g in section 2.2.1.1. in general study authors, in parallel with finding the vaccines well tolerated, also overall do find a slight increased level of clinical deterioration, small increases in exacerbation frequency of disease. The latter is not reflected in the MAH review.

- For clinical trial data presented in relation to potential signals to be at all meaningful and possible to interpret, relevant level of ("stand alone") information needs to be provided by the MAH, for example regarding exclusion criteria, age, gender, geographic location, size of study populations and follow up time of the studies in relation to expected time to diagnosis (eg 2.2.1.1, 2.2.1.3)

Overall, we find a concerning lack of a well-balanced analysis of data.

4. B/R Balance:

We support the conclusion that the benefit-risk balance of Comirnaty remains positive.

5 Request for supplementary information

The MAH should be requested to clarify points and re-analyse data taking the above into account.

Comparative causality assessment table PMR, MAH/MS, 48 cases

CRP + ESR cases n=16	MAH assessment in PSUR	MS assessment on narrative as presented in PSUR	MS Comment
[redacted] 65/M [redacted]	Possible	Possible/Probable	
[redacted] 74/M [redacted]	Unlikely	Possible	MAH conclusion without support of data in report as presented.
[redacted]	Possible	Possible/Probable	
[redacted] 46/M [redacted]	Possible	Possible/Probable	
[redacted] 70/F [redacted]	Unclassifiable	Possible regarding co-reported GCA. Unclassifiable regarding PMR	Is narrative accurately reproduced? GCA and PMR are closely interrelated clinical diagnoses.
[redacted] 75/M [redacted]	Unlikely	Possible	
[redacted] 8 decade/M [redacted]	Unlikely	Possible	MAH conclusion without support of data in report as presented.
[redacted] 78/F [redacted]	Unlikely	Possible	MAH conclusion without support of data in report as presented.
[redacted] 59/F [redacted]	Unclassifiable	Unclassifiable/ possible	Notably the diagnosis of PMR by rheumatologist. Sudden blindness may be related to GCA, but not more closely described. Is narrative accurately reproduced?
[redacted] 65/F [redacted]	Unclassifiable	Possible	
[redacted] 71/M [redacted]	Unlikely	Possible	MAH conclusion without support of data in report as presented. Inventing (?) a possible other aetiology; infection
[redacted] 67/M [redacted]	Unclassifiable	Possible	Arguments against a possible causality weak.
[redacted] 74/M [redacted]	Unclassifiable	Possible	Arguments against a possible causality weak: An elderly person with muscular pain and stiffness (e.g. from PMR) may very well experience muscle weakness (exclusion reason by MAH) as a result. Lack of clinical insight.
[redacted] 83/M [redacted]	Possible	Possible/probable	
[redacted] 59/F [redacted]	Unclassifiable	Possible	MAH conclusion without support of data in report as presented. Inventing (?) a possible other etiology; infection
[redacted] 78/M [redacted]	Unlikely	Unclassifiable	Non-typical signs and symptoms in addition to typical PMR signs and symptoms should not be used for deeming diagnosis unlikely. Peripheral synovitis is indeed a less common, clinical feature of PMR (see reference).

CRP (no ESR) cases n=26	MAH assessment in PSUR	MS assessment of narrative as presented in PSUR	MS Comment
[redacted] 73/M [redacted]	Unclassifiable	Possible	
[redacted] 57/M [redacted]	Unclassifiable	Possible	
[redacted] 76/F [redacted]	Unclassifiable	Possible	MAH conclusion without support of data in report as presented. Absence of morning stiffness in fingers (potentially relevant and possibly reported to exclude a diagnosis of RA; not common symptom of PMR) is "rebranded" in the assessment as "no morning stiffness", i.e. to a lack of a typical PMR symptom, thereby downgrading the case.
[redacted] 50/M [redacted]	Unclassifiable	Possible	MAH reasoning for labelling the case as a questionable PMR case not valid.
[redacted] 73/F [redacted]	Unclassifiable	Possible/probable	Unclear why the causality conclusion has been reached. Case well described.
[redacted] 82/F [redacted]	Unclassifiable	Possible	Reasons for classifying the case as unclassifiable invalid. Case clearly described.
[redacted] 84/F [redacted]	Unlikely	Possible	Labs consistent w a PMR diagnosis. WBC elevation is indeed common in PMR (se reference).
[redacted] 52/M [redacted]	Unlikely	Probable/Possible	MAH drawing conclusion without support of data in report as presented. (Inventing a possible other aetiology; infection). A person with muscular pain and stiffness may very well experience muscle weakness (exclusion reason by MAH) as a result.
[redacted] 87/M [redacted]	Unclassifiable	Possible	Typical symptoms and lab findings. Adequately described case
[redacted] 71/M [redacted]	Possible	Probable/possible	Positive rechallenge (EULAR classification used in report)
[redacted] 68/M [redacted]	Unclassifiable	Possible	Adequately described case. Typical signs and symptoms of PMR are mentioned in the narrative while the MAH states that there is no clinical description of the case.
[redacted] 71/M [redacted]	Unclassifiable	-	**Case potentially miscoded** Potentially the patient did not have a diagnosis of PMR but of what is mentioned as a pseudo-rheumatoid arthritis. Which term did the reporter report?
[redacted] 65/F [redacted]	Unclassifiable	Probable/possible	Narrative describes a positive rechallenge where the symptoms worsen significantly after dose two.
[redacted] 60/M [redacted]	Unlikely	-	**Case potentially miscoded**- diagnosis was according to report concluded to be RA- by reporter
[redacted] 74/F [redacted]	Unclassifiable	Possible	Typical case of PMR. Unclear why the MAH has classified it as unclassifiable.

[redacted] 76/F	Unclassifiable	Possible	Typical case of PMR including regression of symptoms on steroids.
[redacted] 79/F [redacted]	Possible	Possible	Typical case of PMR including regression of symptoms on steroids
[redacted] 78/M	Unclassifiable	Possible	Patient w PMR diagnosed and treated by a specialist.
[redacted] 87/F [redacted]	Unlikely	Possible	Unclear why case is classified as unlikely. Because the patient had several ongoing, likely unrelated diseases?
[redacted] 82/F [redacted]	Possible	Possible	
[redacted] 50/M [redacted]	Unclassifiable	Possible	Thoroughly described case where symptoms, signs, investigation all support the PMR diagnosis, as does recovery on steroids. Unclear why noted as unclassifiable. Information on a potential second dose missing.
[redacted] 84/M France	Unlikely	Possible	Described oedema of extremities is a less well known but described sign in PMR (see ref). Hence the diagnosis of PMR is supported rather than as the MAH claims, disproved
[redacted] 81/M [redacted]	Unclassifiable	Possible	Fairly typical PMR case with recovery on treatment.
[redacted] 67/F [redacted]	Unclassifiable	Possible	Typical case where reaction diagnosed as PMR required hospitalization and successful treatment was given. It is unclear why the case is considered unclassifiable.
[redacted] 63/M [redacted]	Unclassifiable	Possible	Patient with results from several advanced investigations included by reporter alongside diagnosis and successful treatment. Hence no clear reason for being noted as "unclassifiable"
[redacted] 79/Unknown [redacted]	Unclassifiable	Possible/ unclassifiable	The case as presented does not contain a lot of information but there is no clear reason to contradict the reported diagnosis. Treatment not included as presented.
Cases with ESR values (no CRP) n=6	**MAH assessment in PSUR**	**MS assessment of narrative as presented in PSUR**	**MS Comment**
[redacted] 79/F [redacted]	Unclassifiable	Possible	No clear reason to doubt the clinical diagnosis reported, causality assessment possible to perform.
[redacted] 71/M [redacted]	Unclassifiable	Possible	No clear reason to doubt the clinical diagnosis reported, causality assessment possible to perform.
[redacted] Unknown/F [redacted]	Unclassifiable	Possible	No clear reason to doubt the clinical diagnosis reported, causality assessment possible to perform.
[redacted] 83/M [redacted]	Unclassifiable	Possible	Typical symptoms and signs and labs as well as response to treatment described.
[redacted] 69/F [redacted]	Unclassifiable	Possible	No clear reason to doubt the clinical diagnosis reported, causality assessment possible to perform.

[redacted] 84/F [redacted]	Unclassifiable	Possible	No clear reason to doubt the clinical diagnosis reported, causality assessment possible to perform. Description of a potentially possible positive rechallenge although unclear narrative to decipher as the timeline (as in several other cases) is presented in an unnecessarily convoluted manner in the report in the PSUR.

References to table:

Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. Ann Rheum Dis. 2001 Nov;60(11):1021-4. R Caporali et al

Soluble interleukin 2 receptors in polymyalgia rheumatica/giant cell arteritis. Clinical and laboratory correlations. J Rheumatol. 1992 Jul;19(7):1100-6. C Salvarani et al.

Rapporteur assessment comment:

The member state stated that they overall find a concerning lack of a well-balanced analysis of data, that results in a RfSI which includes a comparative causality assessment table of 48 polymyalgia rheumatica cases, MAH versus member state. Here 35 of the 48 cases assessed by the MAH as unclassifiable or unlikely, were classified as possible by the member state. The 'WHO-UMC system for standardised case causality assessment' as any other standardisation criteria for causality assessment has a certain (high) degree of subjectivity that is difficult to resolve. Therefore, requesting the MAH to clarify their causality assessment compared to the member states causality assessment and re-analyse the data will probably result in a subjectivity difference concerning the WHO criteria with no altered conclusion which is not considered helpful. Moreover, for the large majority of cases, it is unclear how why the MS arrives at a different conclusion than the MAH.

Also noted is that in the O/E analysis of the 628 new onset cases of polymyalgia rheumatica reported through 18 December 2021, all O/E ratios are well below 1.

In conclusion, considering the safety information provided in the current PSUR (post-marketing cases, clinical trial data, literature, O/E analyses) concerning Comirnaty exposure and reports of polymyalgia rheumatica and exacerbation or flare-up hereof, the PRAC Rapporteur accepts the MAH's conclusion that the data does not suggest a causal association between Comirnaty and polymyalgia rheumatica.

MS6

Rapporteur assessment comment:

Regarding **dizziness**, cumulatively in the 2nd PSUR through 18 Dec 2021 there were 61,935 cases reporting dizziness of which 15,129 cases were considered serious cases. The MS6 has received 4,648 reports of dizziness of which 57 were considered serious. They noted that there seem to be cases reporting dizziness (around 10%) that are considered not anxiety/stress-related reactions as mentioned in the SmPC section 4.4 which could be considered an ADR from Comirnaty and should be listed in the ADR table of the SmPC section 4.8, if applicable.

Dizziness is labelled in the Comirnaty SmPC section 4.4: "*Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.*"

Therefore, for the next PSUR the MAH is requested to provide a cumulative review of cases reporting dizziness after Comirnaty exposure that were not reported in the context of anxiety/stress-related reactions (as already labelled in the Comirnaty SmPC section 4.4) and a discussion to add dizziness (including a proposal for the frequency of occurrence) to the ADR table of the Comirnaty SmPC section 4.8, as applicable. **Request for next PSUR**