COMIRNATY : Periodic safety update report assessment

19 December 2020 to 18 June 2021

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period 19 December 2020 to 18 June 2021, and;

2. The Comirnaty PSUR itself.

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

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

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

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

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

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

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

EMA/25323/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202106

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

Period covered by the PSUR: 19/12/2020 To: 18/06/2021

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:	16 September 2021	16 September 2021
☐	PRAC Rapporteur's preliminary assessment report (AR)	15 November 2021	11 November 2021
☐	MS/PRAC members and MAH comments	15 December 2021	15 December 2021
☐	PRAC Rapporteur's updated assessment report following comments	30 December 2021	27 December 2021 10 January 2022
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	13 January 2022	13 January 2022

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Table of contents

1. Background information on the procedure 4
2. Assessment conclusions and actions 4
3. Recommendations 7
4. Issues to be addressed in the next PSUR 7
5. PSUR frequency 8
6. Other considerations 8

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 1st EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 19 August 2021) covering the period 19/12/2020 through 18/06/2021.

Comirnaty (single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike [S] protein of SARS-CoV-2) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.

During the current reporting interval, approximately 765,980,340 doses of Comirnaty were shipped worldwide, corresponding to 635,763,682 estimated administered doses.

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

- Seizure,
- Thromboembolic events (since the thromboembolic events of myocardial infarction, stroke, pulmonary embolism, and deep venous thrombosis are being closely monitored in the MSSRs, which is considered acceptable at the moment. Furthermore, all TTS cases are under close scrutiny in the MSSRs),
- Delayed syncope,
- Eye pain and eye swelling,
- Herpes zoster including ophthalmic herpes zoster,
- Appendicitis,
- Hearing loss and tinnitus,
- Overdose,
- Deaths (including elderly or frail individuals).

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

- Delayed skin reaction (erythema multiforme was added as an ADR in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/SDA/034),
- Extensive swelling of the limbs (extensive swelling of vaccinated limb was added to section 4.8 of the Comirnaty SmPC after the assessment of the 4th MSSR - EMEA/H/C/005735/MEA/002.3),
- Reaction associated with dermal fillers (regarding dermal filler reactions, section 4.8 of the Comirnaty SmPC was updated with "Facial swelling" in the ADR table, including the footnote "Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase" - EMEA/H/C/005735/SDA/023),

- Injection site pruritis (at the time of product conditional approval by EMA, this was added as an ADR to section 4.8 of the EU SmPC per EMA request),
- Insomnia (at the time of product conditional approval by EMA, this was added as an ADR to section 4.8 of the EU SmPC per EMA request),
- Facial nerve palsy (at the time of product conditional approval by EMA, this was added as an adverse reaction to section 4.8 of the EU SmPC per EMA request),
- Dizziness (included in section 4.4 of the Comirnaty SmPC was "Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself" - EMEA/H/C/005735/II/0038/G)),
- Hyperhidrosis, Night sweats, Asthenia, Lethargy, Decreased appetite (added as ADRs in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/II/0036),
- Vaccine stress-related responses (Added as warning in section 4.4 of the Comirnaty SmPC - EMEA/H/C/005735/II/0038/G),
- Tachycardia (Added as warning in section 4.4 of the Comirnaty SmPC - EMEA/H/C/005735/II/0038/G),
- Diarrhoea (added as ADR in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/II/0016/G),
- Pain in extremity (Arm) (added as pain in extremity that refers to the vaccinated arm in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/II/0016/G),
- Anaphylaxis (added as ADR in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/LEG/022 and added as an important identified risk to the Comirnaty RMP at the time of product conditional approval by EMA),
- Vomiting (added as ADR in section 4.8 of the Comirnaty SmPC - EMEA/H/C/005735/II/0016/G),
- Hypersensitivity, other than anaphylaxis (at the time of product conditional approval by EMA, hypersensitivity e.g. rash, pruritus, urticaria, angioedema were added as ADRs to section 4.8 of the EU SmPC per EMA request),
- Paraesthesia (PRAC requested to add paraesthesia and hypoesthesia as ADRs in section 4.8 of the Comirnaty SmPC following assessment of the 9th MSSR - EMEA/H/C/005735/MEA/002.8).

The following are ongoing signals:

- After the DLP of this PSUR, immune thrombocytopenia signal was closed and categorized as no risk, Trigeminal neuralgia and Hypertensive crisis with intracranial haemorrhage were closed as non-validated signals.
- After DLP of this PSUR, based on the signal of myocarditis and pericarditis for Comirnaty (EPITT No. 19712) - EMA/PRAC/325882/2021 recommendation dated 08 July 2021, the MAH updated the EU SmPC to include information about myocarditis and pericarditis following vaccine administration and has distributed a DHPC to address these findings in July 2021 to all EU member states.

After DLP, the EU RMP version 2.3 was submitted to EMA in August 2021, to include myocarditis and pericarditis as important identified risk in the list of safety concerns and the pharmacovigilance plan was consequently updated.

The signal has been reopened based on preliminary information from a Nordic study and concluded that the risk for both of these conditions is overall "very rare" and the data show that the increased risk of myocarditis after vaccination is highest in younger males. The product information has been updated accordingly.

During the reporting period, monitoring was requested or was proposed by the MAH in previous MSSRs for the following topics for which no safety signal was identified based on the information provided in the PSUR and close monitoring can be discontinued:

- Lymphopenia
- Hearing loss and tinnitus
- Hypoglycemia
- Serious hypertension
- Haemophagocytic syndrome
- Serious arrhythmias
- Acute pancreatitis
- Acquired haemophilia
- Menstrual disorders

For Immune thrombocytopenia, monitoring was requested in the MSSR. Based on the information provided by the MAH in the PSUR, additional information was requested as an RSI because a case by case causality assessment of BC level 1 an level 2 cases and thorough literature discussion was lacking in the PSUR. As requested, the MAH provided more information on the BC level 1 and level 2 cases as well as a thorough literature discussion. Based on the information provided, no new safety issue is identified. Routine monitoring will continue.

In alignment with the European Union Risk Management Plan version 1.0 (EU RMP) in effect at the beginning of the reporting period the important identified risk is Anaphylaxis; 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.

Based on the evaluation of the interval data, no new significant 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 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

The MAH should 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 and on the actions done and foreseen in the near future in order manage all the AE reports received.
2. Of concern are the backlog cases and the impact thereof on the O/E analyses. Besides the O/E analyses that include the processed cases, no sensitivity O/E analysis is presented which include the processed cases plus the backlog cases. In future PSURs and similar to the O/E analyses reported in the MSSRs, the MAH is requested to perform overall O/E analyses using at least no risk window, 14-day risk window and 21-day risk window and additionally perform sensitivity O/E analyses which include the processed cases plus the backlog cases.
3. 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).
4. In the PSUR under off-label use and in other relevant sections, the MAH should assess:
    a. 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.
    b. the safety profile of Comirnaty when used in heterologous vaccination schedules with other vaccines.
5. 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.
6. Regarding O/E analyses for AESIs, the MAH is requested to clarify which terms have been considered for the background incidence estimate for the multiple concerned AESIs including haemorrhage when using the Pfizer Internal Data Healthcare.
7. 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.

8. 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.

9. 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.

10. 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.

5. PSUR frequency

☒ No changes to the PSUR frequency

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

6. Other considerations

Not Applicable

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submitted the first PSUR for BNT162b2 (Comirnaty®) covering the period 19 December 2021 to 18 June 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 individuals 12 years of age 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.

Overall, BNT162b2 is approved in a total of 82 countries.

Rapporteur assessment comment:
The provided information is noted.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The following actions have been taken for safety reasons during the reporting interval:

- On 15 January 2021, following fatal events involving elderly patients vaccinated with BNT162b2 in Norway, the Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.
- On 05 February 2021, Health Canada requested to issue a joint Pfizer-Health Canada Health Product Risk Communication to communicate revisions to Product Monograph (addition of 6-dose vial information and text on anaphylaxis). Final Health Product Risk Communication (HPRC) was approved on 08 February 2021.
- In March 2021, complaints for leakages were reported to the MAH in Hong Kong, with 19 vials with leakages reported from 3 different vaccination sites in the country; overall 26 vials with leakages and/or loose caps were reported. All vials were from 1 batch, the only batch in use for vaccination in Hong Kong and Macau. During the investigation, it became apparent that the root cause of the reported product quality complaints is a combination of the container closure process (crimping) at 1 single contract manufacturing organization

(CMO) and of the specific transport conditions on dry ice that are required for BNT162b2. Vaccination in Hong Kong and Macau was stopped as soon as the issue became apparent (24 March 2021). A total of 2 batches (210102 and 210104) have been affected (including the one being used and another one already shipped to Hong Kong, but still in storage) and were quarantined. The root cause of the reported product quality complaints was clearly identified through analysis of the data generated and collected as of 31 March 2021. Due to the identified root cause the MAH could exclude any influence on batches that were on the market anywhere outside of Hong Kong and Macau. The CMO in question has not manufactured any batch that was released for any market other than Hong Kong and Macau.

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 4.0 dated 19 May 2021, which is located in Appendix 1 of the PSUR. The previous CDS versions (1.0 dated 12 February 2021, 2.0, dated 02 March 2021 and 3.0, dated 20 April 2021) 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 SmPC is in line with the CDS. Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, and Night sweats have been added as adverse drug reaction to the product information of Comirnaty (EMEA/H/C/005735/II/0036). Following the PRAC meeting in July 2021, myocarditis and pericarditis were added to sections 4.4. and 4.8 of the SmPC, and the package leaflet accordingly (EMEA/H/C/005735/II/0059).

1.3.3. Estimated exposure and use patterns

Clinical trials

Cumulatively up to 18 June 2021, 53,499 subjects have participated in the BNT162b2 clinical development program, comprising several clinical candidates:

- BNT162a1: 30 subjects;
- BNT162b1: 411 subjects;
- BNT162b3: 96 subjects;
- BNT162c2: 96 subjects;
- BNT162b2: 46,577 subjects (of which, 23,514 subjects received BNT162b2, 21,235 subjects received BNT162b2 post-unblinding and had received placebo before, 959 had received BNT162b2/placebo and 869 subjects received a blinded boost with either BNT162b2 or BNT162b2s01 and had received BNT162b2 before);
- BNT162b2s0114: 330 subjects;
- Blinded therapy: 4757 subjects, and
- Placebo: 1202 subjects.

Post-marketing experience

This estimation is based on the proportion of doses administered (83%) out of those shipped upon review of data currently available for the EU countries and the US.

The MAH estimated that approximately 774,478,440 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorization for emergency supply on 01 December 2020 through 18 June 2021, corresponding to 642,817,105 estimated administered doses.

Within the reporting interval, approximately 765,980,340 doses of BNT162b2 were shipped worldwide, corresponding to 635,763,682 estimated administered doses.

Post-marketing exposure data in the EU

Table 3 presents the cumulative and interval number of administered doses by age group and dose 1 and dose 2 in the EEA.

Table 3. EEA - Cumulative and Interval Number of Administered Doses by Age Group and Dose 1 and Dose 2

	<18 years		18-24 years		25-49 years		50-59 years		60-69 years		70-79 years		≥80 years		All[b]	
Countries	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Austria			167555	47702	971199	342616	641838	314720	546224	395763	393795	343964	355207	333226	3135921	1785206
Belgium			166728	64131	1408198	429906	849729	432004	840119	736020	536927	523117	379786	368636	4193346	2557731
Bulgaria	266	189	15278	11513	159468	133713	99168	85240	121185	102251	92622	76077	28906	23204	517254	432452
Croatia	2280	255	42259	8569	317338	102782	198754	84438	222771	128620	135422	96913	60943	47868	977487	469190
Cyprus			17984	10944	116794	78539	47914	42806	38710	34614	23140	18821	25185	23655	269737	209366
Czechia	16771	521	124179	27930	1465870	351932	727173	335423	730020	551387	545166	488903	247876	233858	3843810	1990215
Denmark			160444	22357	447539	156710	629283	113376	555667	406034	518812	508466	238233	235276	2550785	1443219
Estonia	2738	217	19446	4813	121570	46108	56404	41242	51754	43140	56113	51820	41253	38412	346867	225631
Finland			61362	8770	831073	85286	481133	71374	348956	69582	449416	240046	256030	236973	2427970	712031
France															24326612	12868715
Germany															28250232	20472529
Greece			26492	14949	771439	360626	699135	528149	476183	383765	599397	555891	501387	479715	3090855	2331578
Hungary	140853	80059	163126	76516	867158	595910	310562	251589	370538	333408	307408	291502	203466	195665	2360581	1828050
Iceland			12113	3307	50143	27544	16532	14965	14290	13542	9173	8743	12410	12334	114697	80434
Ireland			41574	22891	529757	182446	341416	243352	78469	60161	306069	278298	169889	158073	1472938	948542
Italy	236199	4016	911472	228860	5613161	1811641	4626670	1727223	3069219	2100315	2426244	2010958	3490947	3320810	20902474	11212843
Latvia			22531	15621	114418	96539	40493	33501	31994	25690	14130	11102	6068	4803	263132	204368
Liechtenstein															5483	3831
Lithuania	13981	707	56909	26792	255693	171088	141155	120218	152207	139020	99695	94176	57027	48916	764295	600966
Luxembourg			1520	1239	73003	18864	50700	48169	31139	30120	13128	12717	18550	18135	194297	134808
Malta			18843	12790	89993	78043	21670	21705	18653	19610	36278	37112	21583	19858	207544	193777
Netherlands															6213306	3484049
Norway															1306486	937807
Poland			608505	197615	3690822	1951594	1702115	1220780	1931938	1542381	1966597	1836281	961394	915070	11251269	7683325
Portugal	2201	765	33504	25324	693279	315197	749493	298839	598816	511126	477845	445734	575661	552248	3128600	2148468
Romania	26558	23235	266386	219774	1309771	1219816	644430	609328	750019	718764	444435	426774	146176	138833	3589468	3355093
Slovakia			75234	28771	457959	250535	169916	127800	249662	220386	231902	219288	82806	77104	1267479	923884
Slovenia	5059	726	17768	5571	114339	59404	94655	72449	106076	92438	99017	91676	67672	61190	499527	382728
Spain	4641	2745	105814	84748	3436349	868561	4278583	2549569	1051898	969309	3513927	3448266	2680133	2635045	15071210	10558191
Sweden			59666	35857	703182	238904	814215	267874	695462	577755	557804	527731	424263	403758	5254592	2051890
Grand Total	**451547**	**113435**	**3196692**	**1207354**	**24609515**	**9974284**	**18433136**	**9656133**	**13081969**	**10206201**	**13854462**	**12645376**	**11052851**	**10582665**	**145798254**	**92230917**

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6, cumulative period as of week 24, 2021).
b. Population may include also subjects of unknown age.

Rapporteur assessment comment:

Cumulatively up to 18 June 2021, it is estimated that approximately 642 Mio doses of BNT162b2 were administered worldwide. Within the reporting period of this PSUR, approximately 635 Mio doses were administered worldwide.

1.3.4. Data in summary tabulations

Within the reporting interval, 702 clinical trial cases (883 SAEs) and 327,125 post-marketing cases (1,172,004 events) were reported.

Clinical trial data

Across all age groups, there were slightly more male than female patients reporting adverse events. Overall, the proportion of cases with a fatal outcome is higher when comorbidities are reported.

The overall safety evaluation, provided in Table 7, 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 June 2021.

Table 7. Clinical Trial Data: Events Reported in ≥2%* Cases

	Reporting Period 19 Dec 2020 - 18 Jun 2021	Cumulatively through 18 Jun 2021
MedDRA SOC MedDRA PT	AEs (AERP%) N = 702	AEs (AERP%) N = 1048
Cardiac disorders		
Acute myocardial infarction	15 (2.14%)	20 (1.91%)
Atrial fibrillation	15 (2.14%)	25 (2.39%)
General disorders and administration site conditions		
Condition aggravated	29 (4.13 %)	36 (3.44%)
Infections and infestations		
Appendicitis	19 (2.71%)	32 (3.05%)
Pneumonia	15 (2.14%)	24 (2.29%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	13 (1.85%)	21 (2.00%)
Total number of events	**883**	**1306**

* Reporting proportion (% of total CT cases) in the current reporting period or cumulatively.

The frequently reported events are not listed or consistent with listed events as per the current Investigator's Brochure. However, it should be noted that none of these events were considered to be related to BNT162 by either the Investigator or Sponsor.

Rapporteur assessment comment:

The MAH presented the most frequently reported adverse event in the clinical trials. All of the events were considered not to be related to BNT162 according to the investigator/sponsor.

Post-authorisation data

Across all age groups, there were many more female than male patients reporting adverse events.

The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (405,301); Nervous system disorders (181,899); Musculoskeletal and connective tissue disorders (146,042); Gastrointestinal disorders (94,762); Skin and subcutaneous tissue disorders (65,167); Respiratory, thoracic and mediastinal disorders (52,493); Injury, poisoning and procedural complications (37,587); Infections and infestations (26,765); Blood and lymphatic system disorders (23,448); Investigations (22,448); Vascular disorders (19,979); Cardiac disorders (19,219); Psychiatric disorders (18,193); Eye disorders (14,890); Ear and labyrinth disorders (10,753); Immune system disorders (8531); and Metabolism and nutrition disorders (6884).

The overall safety evaluation, provided in Table 8, 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 reporting interval as compared to the cumulative period through 18 June 2021.

No quality related quality issues were identified for the most frequently reported lot numbers.

Table 8. Post-Authorization Data: Events Reported in ≥2%* Cases

	Reporting Period 19 Dec 2020 - 18 Jun 2021	Cumulatively through 18 Jun 2021
MedDRA SOC MedDRA PT	**AEs (AERP%) N = 327,125**	**AEs (AERP%) N = 327,603**
Blood and lymphatic system disorders		
Lymphadenopathy[a]	18,545 (5.67%)	18,553 (5.66%)
Gastrointestinal disorders		
Nausea[a]	37,730 (11.53%)	37,768 (11.53%)
Diarrhoea[a]	13,182 (4.03%)	13,194 (4.03%)
Vomiting[a]	11,416 (3.49 %)	11,423 (3.49%)
General disorders and administration site conditions		
Pyrexia[a]	64,242 (19.64%)	64,284 (19.62%)
Fatigue[a]	54,683 (16.72%)	54,724 (16.70%)
Chills[a]	41,227 (12.60%)	41,256 (12.59%)
Vaccination site pain[a]	36,986 (11.31%)	37,046 (11.31%)
Pains	25,715 (7.86%)	25,748 (7.86%)
Malaise[a]	27,788 (8.49%)	27,805 (8.49%)
Asthenia[a]	24,391 (7.46%)	24,404 (7.45%)
Injection site pain[a]	10,105 (3.09%)	10,105 (3.08%)
Influenza like illness	8603 (2.63%)	8608 (2.63%)
Infections and infestations		
COVID-19[b]	8154 (2.49%)	8157 (2.49%)
Musculoskeletal and connective tissue disorders		
Myalgia[a]	49,382 (15.10%)	49,402 (15.08%)
Arthralgia[a]	35,410 (10.82%)	35,426 (10.81%)
Pain in extremity[a]	28,312 (8.65%)	28,346 (8.65%)
Nervous system disorders		
Headache[a]	83,686 (25.58%)	83,758 (25.57%)
Dizziness[a]	23,935 (7.32%)	23,978 (7.32%)
Paraesthesia[a]	9532 (2.91%)	9543 (2.91%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea[c]	11,042 (3.38%)	11,058 (3.38%)
Cough[c]	7701 (2.35%)	7707 (2.35%)
Skin and subcutaneous tissue disorders		
Pruritus[a]	11,302 (3.45%)	11,318 (3.45%)
Rash[a]	10,665 (3.26%)	10,686 (3.26%)
Erythema[a]	7888 (2.41%)	7900 (2.41%)
Sensitive skin	7434 (2.27%)	7434 (2.27%)
Total number of events	**1,172,004**	**1,173,395**

a. Listed or consistent with listed AEs in current RSI.
b. Listed per case processing conventions, except for fatal cases; for summary of relevant cases of COVID-19 see Section 16.3.3.1.3 *COVID-19 AESIs*.
c. Consistent with anaphylactic reactions listed in the current RSI.
* Reporting proportion (% of all post-authorization cases) in the current reporting period.

Analysis of the occurrences of the AEs by doses for the post-marketing cases is displayed in Table 10. Out of the 327,125 post-marketing cases, the dose was reported in 206,221 distinct cases; in the majority of the cases the events occurred after the first dose.

Table 10. Post-Authorization Cases – Analysis by Dose[a]

	Number of Distinct Cases	Number of AEs
Dose 1	127356	171554
Dose 2	83653	114738
Totals	206221	286292

a. Dose number was evaluated based on the reported Dose number or with availability of both Therapy and Event Onset Dates.

MAH's conclusion

Overall, the majority of adverse events were reported for female patients. The greatest number of events occurred in patients in the 31-50 age group. The majority of events were non-serious (non-serious [850,284] vs serious [321,919]), and in most cases the events were resolved or resolving at the time of the report (where outcome was known). Fatal events occurred mainly in patients 75 years of age and older. The proportion of cases with a fatal outcome was higher in cases for which additional comorbidities were reported. The reporting rates for fatal outcomes were similar for male and female patients, both in the presence and in the absence of comorbidities.

Rapporteur assessment comment:

The presented data is in line with the data assessed in the MSSRs. The majority of the events reported in ≥2% of the cases are considered to be covered or listed in the product information. As requested in the 7th/8th MSSR, an analysis of cases reporting hypoaesthesia and paraesthesia was provided in the 9th MSSR. After assessment, the MAH was requested to add hypoesthesia and paraesthesia to the product information (SmPC section 4.8 and PIL section 4) of Comirnaty (EMEA/H/C/005735/MEA/002.8).

No new significant safety information was identified from the provided information on the post-marketing cases.

General overview – unlocked cases (Unlocked cases are those cases either in the drug safety unit (DSU), Primary Review or the Medical Review workflows that are not yet in the Distribution workflow which locks the cases and the system automatically runs reporting rules, schedules and subsequently generates expedited reports as appropriate)

A total of 145,825 unlocked case reports (28 from CT and 145,797 from PM) containing 496,718 events fulfilled criteria for inclusion in this PSUR. These 145,825 cases represent 44.5% of the all cases included in the PBRER dataset summarized above. Table 11 displays selected characteristics of the unlocked cases at the end of the reporting interval.

Table 11. Selected Case Characteristics - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases	CT No. of Cases[a]	PM No. of Cases
No. of Cases		145,825	28	145,797
Gender	Female	107,027	12	107,015
	Male	32,177	16	32,161
	Unknown/No Data	6621	0	6621
Age (years)	N	126,274	25	126,249
	Min-Max[b]	6 days – 120 years	12 – 81 years	6 days – 120 years
	Mean	50.3	50.7	50.3
	Median	49	52	49
Age group	≤ 17	954	5[c]	949[d]
	18-30	19,735	0	19,735
	31-50	49,102	9	49,093
	51-64	33,242	6	33,236
	65-74	10,819	3	10,816
	≥ 75	12,893	4	12,889
	Unknown	19,080	1	19,079[e]
Country of occurrence (≥2% of all cases)	Italy	32,469	0	32,469
	US	32,265	13	32,252
	France	12,618	0	12,618
	Netherlands	10,732	0	10,732
	UK	9598	0	9598
	Mexico	9196	0	9196
	Spain	8431	0	8431
	Germany	4664	3	4661
	Austria	3531	0	3531
Case Seriousness	Serious	10,576	28	10,548
	Non-serious	135,249	0	135,249
Case Outcome	Resolved/Resolving	85,761	14	85,747
	Resolved with sequelae	890	2	888
	Not resolved	25,480	6	25,474
	Fatal	646	4	642
	Unknown	33,048	2	33,046
Presence of comorbidities	Yes	15,658	8	15,650
	No	130,167	20	130,147

a. BioNTech is the Sponsor of all Clinical Trials; for the following Clinical Trials (C4591001, C4591005, C4591015, C4591017, C4591020), Pfizer acts as lead development party and for the Clinical Trials (BNT162-03, BNT162-06), BioNTech Third Party act as lead development party.
b. Includes only patients to whom BNT162b2 or study therapy was administered directly; does not include exposure during pregnancy or via breastfeeding.
c. Includes 2 cases involving exposure during pregnancy.
d. Includes 26 cases with contradictory demographic information (physical characteristics not matching with the reported age value), 4 cases which upon review were determined not to involve paediatric patients, 27 cases involving exposure during pregnancy, and 133 cases involving exposure via breastfeeding.
e. Includes 234 cases involving exposure during pregnancy and 123 cases involving exposure via breastfeeding.
Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, Frail patients with co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis) described as special populations in Section 16.3.5.5, Section 16.3.5.6 and Section 16.3.5.7, respectively.

Rapporteur assessment comment:

The MAH presents the general characteristics of the unlocked cases (i.e. cases being processed at the MAH but not included in the PSUR or reported to EudraVigilance), which represent 44.5% of the total PSUR dataset. The backlog in processed cases is of concern. 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. **Request for next PSUR.** The progress on the actions done and foreseen in the near future in order manage all the AE reports is being monitored in the MSSRs.

Clinical trial data – unlocked cases

The only event reported more than once in clinical trial cases that were unlocked at the end of the reporting interval was coded to the PT Maternal exposure during pregnancy (2 cases).

Post-authorisation data – unlocked cases

The overall safety evaluation, presented in Table 12, includes a review of the most frequently reported events by SOC and by PT for events reported in ≥2% of unlocked cases at the end of the reporting interval.

Table 12. Post-Authorization Data: Events Reported in ≥2%* of Unlocked Cases

MedDRA SOC MedDRA PT	AEs (AERP%) N = 145,797
Blood and lymphatic system disorders	
Lymphadenopathy[a]	9073 (6.22%)
Gastrointestinal disorders	
Nausea[a]	17,569 (12.05%)
Diarrhoea[a]	5848 (4.01%)
Vomiting[a]	4667 (3.20%)
General disorders and administration site conditions	
Pyrexia[a]	34,635 (23.76%)
Fatigue[a]	25,066 (17.19%)
Chills[a]	21,564 (14.79%)
Vaccination site pain[a]	17,497 (12.00%)
Pain[a]	11,570 (7.94%)
Malaise[a]	15,001 (10.29%)
Asthenia[a]	13,875 (9.52%)
Injection site pain[a]	9721 (6.67%)
Influenza like illness	4691 (3.22%)
Musculoskeletal and connective tissue disorders	
Myalgia[a]	28,609 (19.62%)
Arthralgia[a]	19,542 (13.40%)
Pain in extremity[a]	11,542 (7.92%)
Nervous system disorders	
Headache[a]	41,883 (28.73%)
Dizziness[a]	9413 (6.46%)
Paraesthesia[a]	3763 (2.58%)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea[b]	3008 (2.06)
Skin and subcutaneous tissue disorders	
Pruritus[a]	4572 (3.14%)
Rash[a]	4231 (2.90%)
Erythema[a]	3212 (2.20%)
Sensitive skin	4758 (3.26%)
Total number of events	**496,671**

a. Listed or consistent with listed AEs in current RSI.
b. Consistent with anaphylactic reactions listed in the current RSI.
* Reporting proportion (% of total cases) at the end of the current reporting period.

MAH's conclusion

The data contained in the unlocked cases is consistent with the overall dataset.

Rapporteur assessment comment:

The events reported in ≥2% of the unlocked cases is in line with the events reported in ≥2% of the processed cases.

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 interval, there were 10 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.
- 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: there were 9 ongoing clinical trials:
    - C4591001, A phase 1/2/3, placebo-controlled, randomized, observer-blind, dosefinding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.
    - C4501007, 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.
    - 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.
    - BNT162-0326, 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.
    - BNT162-06,26 Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy subjects: A phase II, randomized, placebo-controlled, observer-blind study.

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

Remaining trials:

- There were 2 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.

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

Long-term follow-up

There is no new safety information beyond 6-months follow-up of clinical trial subjects for this reporting period.

Other therapeutic use of medicinal product

There is no relevant information 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 significant safety information was identified by the MAH from the clinical 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 5 ongoing sponsor-initiated non-interventional studies.

Safety Studies:

- PASS: Non-interventional studies C4591008 and C4591012. No clinically important information has emerged from these 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:

There were 3 ongoing non-interventional studies:

- C4591006, General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early postapproval stage).
- C4591014, C4591029 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

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

Rapporteur assessment comment:

No new significant 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 period, the MAH was committed to demonstrating real-world vaccine effectiveness (VE) through test-negative design (TND) study(s) for the BNT162b2 (COVID-19) vaccine as a post-authorization commitment to FDA, EMA and MHRA. To meet this commitment, the MAH is conducting three VE studies at three different study sites. The C4591014 study is a retrospective noninterventional database study (CT24) described above in the section Findings from Non-Interventional Studies. In addition, there are two ongoing research collaborations conducting prospective respiratory disease surveillance which have been amended to include BNT162b2 VE objectives. Both studies are low-interventional non-Pfizer sponsored research being conducted in collaboration with Pfizer and are briefly described below.

- Study WI235284 (Emory University Sponsor) (PAM-MEA-024)

  Study Title: Respiratory Syncytial Virus (RSV) in older adults and pregnant women study (ROAPS) amendment for BNT162b2 post-authorization vaccine effectiveness: This study is a prospective population-based surveillance study originally conducted to estimate incidence for RSV hospitalizations among older adults and pregnant women (ROAPS), which has been ongoing since October 2018 at 2 hospitals in Atlanta Georgia. The study protocol has been amended to include COVID VE objectives. All patients admitted to the hospitals with acute respiratory illness are screened for eligibility and invited to participate if appropriate. Enrolled patients have a nasopharyngeal swab collected for viral testing, undergo a patient interview for data collection on vaccination history (including BNT162b2), comorbidities, COVID-19 related risk behaviors and other risk factors, and electronic medical record review for hospitalization and outcome data collection. No Pfizer products are administered as part of the study protocol. The study aims to enroll approximately 6000 patients.

- Study WI25588632 (Bristol University, UK, Sponsor)

  Study Title: Avon Community Acquired Pneumonia Study (Avon CAP): A panpandemic acute lower respiratory tract disease surveillance study: This is a prospective population-based observational study, including adults aged ≥18 years, admitted to one of two hospitals in Bristol (UK) with symptoms of lower respiratory tract disease. The study has been enrolling participants since mid-2020. The protocol has been amended to include COVID VE objectives. COVID VE will be estimated using a TND analysis, utilizing data on vaccination history (BNT162b2, influenza and pneumococcal vaccinations given as standard of care), comorbidities, preadmission COVID test and current admitting condition from electronic medical records, and a COVID risk-behaviors questionnaire which will be completed on patient interview.

No new safety information has emerged from these studies at the time of this report.

During the reporting interval, there was 1 ongoing MAH-sponsored clinical trial, that was not part of the BNT162b2 development program, where BNT162b2 is administered as part of the study drug.

- B7471026: A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when co-administered with a booster dose of BNT162b2 in adults 65 years of age and older.

No new significant safety finding for BNT162b2 was identified from this study.

During the reporting interval, there was 1 ongoing clinical trial conducted by National Institute of Allergy and Infectious Diseases on delayed heterologous booster doses.

- Study 21-0012 (NCT04889209)

  Study Title: A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA Vaccines

  A phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial was designed to assess the safety, reactogenicity and immunogenicity of a delayed (>/=12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273, and mRNA-1273.211 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).

During this reporting period, no new safety information from other clinical trial studies was reported about mixed dose schedules, antibody waning, booster dose or revaccination.

Rapporteur assessment comment: No new significant safety information was identified by the MAH from other clinical trial studies.

Medication errors

During the reporting period no serious clinical trial cases indicative of medication errors were reported. Since the post-marketing cases regarding medication errors are being reviewed in the MSSRs, these are not reproduced here.

Rapporteur assessment comment: No serious clinical trial cases indicative of medication errors were reported. Post-marketing cases have been monitored in the MSSRs, and no new significant safety information was identified regarding medication errors.

1.3.5.4. Non-clinical data

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

Rapporteur assessment comment: No new significant safety information was identified by the MAH from non-clinical data.

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 9 studies that presented important new safety findings for BNT162b2.

Frail subjects:

1. *Grupper A, Sharon N, Finn T, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol 2021;doi: 10.2215/CJN.03500321.*

   Conclusion: Although most patients on maintenance hemodialysis developed a substantial humoral response following the BNT162b2 vaccine, it was significantly lower than controls. Age was an important factor in the humoral response, regardless of chronic medical conditions.

2. *Goupil R, Benlarbi M, Beaubien-Souligny W, et al. Short-term antibody response after 1 dose of BNT162b2 vaccine in patients receiving hemodialysis. Canadian Medical Association Journal 2021; 193 (22) E793-E800; DOI:* doi.org/10.1503/cmaj.210673.

   Interpretation: A single dose of BNT162b2 vaccine failed to elicit a humoral immune response in most patients receiving hemodialysis without previous SARS-CoV-2 infection, even after prolonged observation. In those with previous SARS-CoV-2 infection, the antibody response was delayed. The patients receiving hemodialysis should be prioritized for a second BNT162b2 dose at the recommended 3-week interval.

3. *Ali H, Aribi A, Arslan S, et al. Safety and Tolerability of SARS-CoV-2 Emergency-Use Authorized Vaccines Allogeneic Hematopoietic Stem Cell Transplant Recipients. Transplant Cell Ther 2021; S2666-6367(21)01073-3. doi: 10.1016/j.jtct.2021.07.008*

   Conclusions: This study provides preliminary data that both EUA mRNA vaccines were generally safe and well tolerated in an allogeneic HCT population despite some limitations

4. *Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021; 137(23):3165-73.*

   In conclusion, antibody-mediated response to BNT162b2 mRNA COVID-19 vaccine in patients with CLL is markedly impaired and affected by disease activity and treatment.

Pregnancy and lactation:

5. *Collier A-RY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. JAMA 2021; 325(23):2370-80.*

   Conclusion and Relevance: In this exploratory analysis of a convenience sample, receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.

6. *Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Efficient maternofetal transplacental transfer of anti-SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis 2021: ciab266. doi: 10.1093/cid/ciab266. (Accepted manuscript).*

   Maternal and cord blood sera were collected from 20 parturients who received the BNT162b2 vaccine. All women and infants were positive for anti S- and anti-RBD-specific IgG. Cord blood antibody concentrations were correlated to maternal levels and to time since vaccination. Antenatal SARS-CoV-2 vaccination may provide maternal and neonatal protection.

7. *Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest 2021; 131(13):e150319.*

   Conclusions: Antenatal BNT162b2 mRNA vaccination induces a robust maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy.

8. *Kelly JC, Carter EB, Raghuraman N, et al. Anti-SARS-CoV-2 antibodies induced in breast milk after Pfizer-BioNTech/BNT162b2 vaccination: Am J Obstet Gynecol. 2021: S0002-9378(21)00211-8. doi: 10.1016/j.ajog.2021.03.031.*

   Conclusions: The Authors characterized longitudinal breast milk levels of antispike IgG/A following Pfizer-BioNTech BNT162b2 vaccination, demonstrating sustained elevation of IgG/IgA levels. This response is similar to previous studies on maternal vaccination, which have shown high levels of breast milk IgA/G production for up to 6 months after vaccination for influenza and pertussis. A concurrent decrease in infant respiratory illness rates suggest that maternal vaccination confers protection against infection in breastfed infants. Thus, the Pfizer-BioNTech/BNT162b2 vaccination may also confer protection against COVID-19 to breastfed infants as well. Our studies limited by a small number of participants, but we report data that suggest a potential immune benefit to infants of lactating people up to 80 days after COVID-19 vaccination. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination

Thrombosis and intracranial haemorrhage:

9. *Shimazawa R, Ikeda M. Potential adverse events in Japanese women who received tozinameran (BNT162b2, Pfizer-BioNTech). Journal of Pharmaceutical Policy and Practice 2021: 14(1)*

   Reports of CVST and intracranial haemorrhage (ICH) following the administration of coronavirus vaccines have raised concerns regarding their safety. Although no regulatory authority has recognized ICH as an adverse event associated with tozinameran (BNT162b2, Pfizer-BioNTech), fatal and non-fatal cases have been reported. In Japan, 10 fatal cases (five men and women) have been reported to date. Four of the five women died of ICH and the other died of aspiration pneumonia, whereas all five men died of causes other than stroke. This imbalance is incompatible with the mortality data on cardiovascular diseases in the National Statistics, which show no apparent disparity between sexes or between haemorrhagic and ischemic stroke. Cumulatively, our analysis reveals a disproportionately high incidence of death by ICH in Japanese women who received tozinameran, suggesting a potential association of ICH with the vaccine. Although we

understand that the benefits of tozinameran still outweigh the risks, we believe that a causal link with the vaccine is not proven but possible and warrants further analysis.

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 identified a total of nine relevant scientific publications. Four studies describe vaccination with BNT162b2 in frail subjects (patients receiving hemodialysis, allogeneic hematopoietic stem cell transplant recipients, patients with chronic lymphocytic leukemia). Within these studies it is reported that the effectiveness may be impaired in these patients, however, no specific safety issues were described. Four studies describe vaccination with BNT162b2 in pregnant and lactating women for which no specific safety issues were reported. The remaining publication was related to thrombosis and intracranial haemorrhage and was discussed within the 7th MSSR for which it was concluded that no further action was warranted.

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.

1.3.6. Lack of efficacy in controlled clinical trials

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

1.3.7. Late-breaking information

After the DLP, based on the Signal of Myocarditis and pericarditis for COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY (EPITT No. 19712) - EMA/PRAC/325882/2021 recommendation dated 08 July 2021, the MAH updated the RSI (CDS version 5.0 dated 14 July 2021) and EU-SmPC to include information about myocarditis and pericarditis following vaccine administration and has distributed a DHPC to address these findings. The DHPC was distributed starting from 19 July 2021 to all EU member states where the respective vaccines are authorised. The EU-RMP was accordingly updated (version 2.3) and was submitted to EMA on 06 August 2021. With respect to approved version 2.0, the list of safety concerns was updated with the inclusion of myocarditis and pericarditis as important identified risk and the Pharmacovigilance plan was consequently updated.

After DLP, Immune thrombocytopenia was closed and categorized as no risk, Trigeminal neuralgia and Hypertensive crisis with intracranial haemorrhage were closed as non-validated signals.

Rapporteur assessment comment:

Please refer regarding the evaluation of the signal of myocarditis and pericarditis to the separate procedure EMEA/H/C/005735/SDA/032, EPITT ref. 19712.

Please refer to section 2 of this AR for the assessment of "immune thrombocytopenia", "trigeminal neuralgia", and "hypertensive crisis with intracranial haemorrhage".

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:

Table 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
Missing information (Cont'd)	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

As per EU RMP ver. 1.0 (dated 21 December 2020).

After DLP, 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. The MAH proposes the following list of safety concerns for the next reporting period, subject to the PRAC approval of the EU-RMP version 2.3:

Table Ongoing Safety Concerns

Important identified risks	Anaphylaxis Myocarditis and pericarditis[a]
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. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory Disorders
	Interaction with other vaccines
	Long-term safety data

a. Search criteria: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Rapporteur assessment comment:

Please refer regarding the inclusion of myocarditis and pericarditis as an important identified risk in the list of safety concerns (after DLP of current PSUR) to the separate procedure

EMEA/H/C/005735/II/0059.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 19.12.2020 to 18-06-2021.

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
Signals Determined NOT to be Risks							
Seizure	01 Mar 2021	Closed	06 May 2021	Competent authority	Spontaneous reports	Clinical study reports and safety database	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Thromboembolic events	12 Mar 2021	Closed	31 Mar 2021	Competent authority	Spontaneous reports	Clinical study reports and safety database	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Delayed skin reaction	08 Mar 2021	Closed	24 Mar 2021	Routine PV (literature) Competent authority	Spontaneous reports	Safety database and literature	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Delayed syncope	04 Feb 2021	Closed	24 Feb 2021	Competent authority	Spontaneous reports	Clinical study reports, safety database	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened 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
Eye pain and eye swelling	22 Jan 2021	Closed	03 Feb 2021	Competent authority	Spontaneous reports	Safety database	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Herpes zoster including ophthalmic HZ *Updated from "Herpes Zoster to Herpes Zoster including Ophthalmic herpes zoster" on 07 May 2021	05 Oct 2020 Reopened 21 Feb 2021 05 Oct 2020 Reopened 21 Feb 2021 Reopened 26 Apr 2021	Closed	30 Apr 2021	Routine PV (review of clinical study and spontaneous data), Competent authority	Routine PV: Clinical study reports Re-opened 2/21/21: Routine PV (case review) Routine PV: Clinical study reports Re-opened 2/21/21: Routine PV (case review) Re-opened 4/26/21: Competent authority	Clinical study reports, safety database, O/E analyses	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Appendicitis	18 Sep 20 Reopened 18 Sep 20 Reopened 06 May 2021	Closed	13 May 2021	Routine review of clinical study data and Competent authority	Clinical study and spontaneous reports	Clinical study reports, safety database, O/E analyses	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened 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
Hearing Loss and Tinnitus	08 Feb 2021	Closed	17 Feb 2021	Routine review of clinical study data and Competent authority	Clinical study and spontaneous reports	Clinical study report, safety database, O/E analyses	Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Extensive Swelling of the Limbs	18 Mar 2021	Closed	06 Apr 2021	Competent authority	Spontaneous reports	Safety database and clinical study reports	Added to EU-SPC as ADR at request of EMA CDS: Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Reaction associated with dermal fillers	02 Mar 2021	Closed	24 Mar 2021	Routine PV (literature) and Competent authority	Spontaneous reports	Safety database, Clinical study reports	Added to EU-SPC as ADR at request of EMA CDS: Based on available data (DLP: 18 June 2021) a causal association between the vaccine and this event has not been established. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Injection site Pruritis	19 Dec 2020	Closed	20 Jan 2021	Competent authority	Clinical study data (DLP 14 Nov 2020)	Clinical study reports and safety database	At the time of product conditional approval by EMA, this was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request CDS: Based on available data (DLP 18 Jun 2021), a causal association between the vaccine and this event is not established
Insomnia	19 Dec 2020	Closed	20 Jan 2021	Competent authority	Clinical study data (DLP 14 Nov 2020)	Clinical study reports and safety database	At the time of product conditional approval by EMA, this was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request CDS: Based on available data (DLP 18 Jun 2021), a causal

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
							association between the vaccine and this event is not established
Overdose	27 Dec 2020	Closed	20 Jan 2021 27 Dec 2020	Routine PV (case review)	Spontaneous reports	Safety database medication errors	Based on available information (DLP 18 Jun 2021), it is determined that the OD language in the CDS is adequate
Deaths (including in elderly or frail individuals)	18 Jan 2021	Closed	20 Jan 2021	Competent authority	Spontaneous reports	Safety database and O/E analyses	Based on available data (DLP 18 Jun 2021), a causal association between the vaccine and this event is not confirmed. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available
Facial Nerve Palsy	13 Apr 2021	Closed	23 Apr 2021	Competent authority	Clinical study and spontaneous reports	Safety database and clinical study reports	At the time of product conditional approval by EMA, this was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request CDS: Based on available data (DLP 18 Jun 2021), a causal association between the vaccine and this event is not established. PV monitoring and active surveillance will continue, and the topic will be revisited when relevant new 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
Signals Determined to be Risks							
Dizziness for the process of vaccination rather than the vaccine substrate	18 Jan 2021	Closed	31 March 2021	Enquiry from a competent authority Post-authorization reports Enquiry from a competent authority Post-authorization reports	Initially the MHRA noted to Pfizer/BNT in routine PV discussion that they have noted frequently reported events of dizziness and the EMA PRAC Final assessment report for the Jan 2021 SMSR contained a request to provide a safety evaluation of dizziness Provided in SMSR 3 and then was evaluated in the context of the Stress related analysis.	Clinical study and safety database case review	Labelling update to the Warnings and Precautions Section of the CDS for Vaccine Stress Related Responses which Dizziness is included as a stress/anxiety related reaction. This is considered an identified risk for the process of vaccination rather than the vaccine substrate and was closed as an identified risk. *Dizziness was also reviewed outside of the context of vaccine stress related – refer to Safety topics determined NOT to be validated signals

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
Hyperhidrosis	27 Apr 2021	Closed	27 Apr 2021	Clinical study data	Clinical study data (DLP 13 Mar 2021)	Clinical study reports	Added as ADR to CDS
Night sweats	27 Apr 2021	Closed	27 Apr 2021	Clinical study data	Clinical study data (DLP 13 Mar 2021)	Clinical study reports	Added as ADR to CDS
Asthenia	27 Apr 2021	Closed	27 Apr 2021	Clinical study data	Clinical study data (DLP 13 Mar 2021)	Clinical study reports	Added as ADR to CDS
Lethargy	27 Apr 2021	Closed	27 Apr 2021	Clinical study data	Clinical study data (DLP 13 Mar 2021)	Clinical study reports	Added as ADR to CDS
Decreased appetite	27 Apr 2021	Closed	27 Apr 2021	Clinical study data	Clinical study data (DLP 13 Mar 2021)	Clinical study reports	Added as ADR to CDS
Vaccine stress related responses	10 Feb 2021	Closed	31 Mar 2021	Routine PV (case review)	Spontaneous reports of potential stress/anxiety related AEs perivaccination	Safety database	The concept determined to be related to process of vaccination, not the vaccine itself. The concept will be added as Warning/Precaution to CDS and CO written for CDS and local labels for submission per regulatory processes; referred to Labelling Team for implementation. Concepts included: dizziness, fainting, palpitations, heart rate increase, blood pressure changes, shortness of breath, tingling sensations (paraesthesias), sweating, anxiety
Tachycardia	28 Jan 2021	Closed	31 Mar 2021	Health authority PV report	Spontaneous reports	Safety database and clinical study reports	Added to CDS and local labels as potential symptom of Vaccination stress-related response

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
Diarrhea	16 Nov 2020 Reopened 18 Jan 2021 following Receipt of SMSR #1 PRAC assessment report.	Closed	10 Feb 2021	Clinical study data (DLP 14 Nov 2020) Re-opened due to Competent authority request	Clinical study data review for initial submission (DLP Nov 2020) Spontaneous reports	Clinical study reports and safety database	Based on evaluation of post-authorization spontaneous data, Diarrhea will be added to the CDS and local labels as adverse reaction
Pain in Extremity (Arm)	19 Dec 2020	Closed	20 Jan 2021	Competent authority	Request to include as an adverse reaction in EU SmPC at time of conditional approval	Safety database and clinical study reports	Based on evaluation of data, added to EU-SPC at time of conditional approval in EU and also added to CDS and USEUA Fact Sheets
Anaphylaxis	08 Dec 2020	Closed	30 Dec 2020	Competent authority	Spontaneous reports of anaphylaxis	Safety database and clinical study reports	Based on evaluation of post-authorization spontaneous data, Anaphylaxis identified as adverse reaction and will be added to IB, EU-SPC and US-EUA Fact Sheets; also, Anaphylaxis will be added as an Important identified risk to EURMP, US-PVP
Vomiting	16 Nov 2020 Reopened 18 Jan 2021 following receipt of SMSR #1 PRAC assessment report	Closed	10 Feb 2021	Clinical study data (DLP 14 Nov 2020) Re-opened due to Competent authority request	Clinical study data review for initial submission (DLP Nov 2020) Spontaneous reports	Clinical study reports and safety database	Based on evaluation of post-authorization spontaneous data, Vomiting will be added to the CDS and local labels as adverse reaction

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
Hypersensitivity, other than anaphylaxis	19 Dec 2020 Reopened 07 Jan 2021	Closed	13 Jan 2021	Competent authority	Spontaneous reports	Safety database and clinical study reports	At the time of product conditional approval by EMA, Hypersensitivity was added as an adverse reaction (not important) to Section 4.8 of the EU SmPC per EMA request. "Hypersensitivity (e.g. rash, pruritus, urticaria, angioedema)" was added to the CDS and EUA PI as an adverse reaction
Paraesthesia	29 Dec 2020	Closed	31 Mar 2021	Routine PV (case review) and Competent Authority	Spontaneous reports	Safety database and clinical study reports	This event has been included in the description of Vaccination stress related responses which was added as a W/P to the Core Data Sheet
Safety Topics Determined NOT to be Validated Signals (i.e. Non-Validated Signals)							
Dizziness (Note: This topic has been reviewed in the context of Vaccination stress responses and as a stand-alone	10 May 2021	Closed	09 Jun 2021	Competent Authority	Spontaneous reports that may not be associated with vaccination stress responses	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Abnormal behavior/Mental disorder	13 May 2021	Closed	28 May 2021	Competent Authority	Request for literature and opinion	Safety database and literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute disseminated encephalomyelitis (ADEM)	09 May 2021	Closed	26 May 2021	O/E Competent Authority	SMSR #5 O/E > 1 and competent authority	O/E analyses and safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new 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
					request		
Cranial nerve palsy	13 Apr 2021	Closed	23 Apr 2021	Competent Authority	Request for comment on cases	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Nephrotic syndrome	29 Apr 2021	Closed	06 May 2021	Routine PV (literature)	Literature Case Report	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hemolytic anemia	16 Apr 2021	Closed	23 April 2021	Routine PV (case review)	Spontaneous report	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Optic neuritis	13 Apr 2021	Closed	23 Apr 2021	Competent authority	Spontaneous reports received	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hepatic events	01 Mar 2021	Closed	19 Apr 2021	Routine PV (case review)	Spontaneous report	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Dysphagia	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Voice Hoar seness (Dysphonia)	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hypertension	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new 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
Arrhythmia	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Polyneuropathy/Peripheral neuropathy	11 Mar 2021	Closed	25 Mar 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Transverse myelitis	11 Mar 2021	Closed	07 June 2021	O/E	O/E >1 and competent authority request	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Anosmia/Ageusia	11 Mar 2021	Closed	06 Apr 2021	O/E	O/E >1 and competent authority request	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Myasthenia gravis	11 Mar 2021	Closed	25 Mar 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Meningitis	11 Mar 2021	Closed	25 Mar 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Guillain- Barre Syndrome (GBS)	25 Feb 2021 Reopened 21 May 2021	Closed	26 May 2021	O/E Competent authority	O/E >1 and competent authority request	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Severe cutaneous adverse	21 Feb 2021	Closed	03 Mar 2021	Routine PV (case review)	Spontaneous reports	O/E analyses and safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be

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
reactions (SCAR)							revisited if relevant new information becomes available
Increased international normalized ratio (INR)	14 Jan 2021	Closed	20 Jan 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Gastrointestinal obstruction	18 Sep 2020	Closed	24 Sep 2020	Routine PV (clinical study AE review)	Blinded clinical study report (Study C4591001)	Clinical study data	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hypoglycemia	16 Mar 2021	Closed	31 Mar 2021	Competent authority	Request for review	Review for hypoglycemia and hyperglycemia; vaccine label review; safety database review	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Disseminated Intravascular Coagulation (DIC)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA Office of Biostats and Epi signal detection	Safety database and epidemiology analysis (internal and external databases)	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Pulmonary Embolism (PE)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA Office of Biostats and Epi signal detection	Safety database and epidemiology analysis (internal and external databases)	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute Myocardial Infarction (AMI)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA Office of Biostats and Epi signal detection	Safety database and epidemiology analysis (internal and external databases)	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acquired Hemophilia	25 May 2021	Closed	04 Jun 2021	Competent authority	Spontaneous reports	Safety database, clinical study	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal.

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
						reports, O/E analyses, literature	Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute Pancreatitis	21 May 2021	Closed	04 Jun 2021	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analyses, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Menstrual disorders	10 May 2021	Closed	19 May 2021	Competent authority	Spontaneous reports	Safety database, clinical study reports, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Ongoing Safety Topics/Signals							
Immune Thrombocytopenia	21 Jan 2021 Reopened 25 June 2021 (PSUR #1 request)	Closed	8/4/2021 *Closed after DLP	Competent Authority	Spontaneous reports	Safety database clinical reports, O/E analyses, literature	TBD
Trigeminal neuralgia	29 Apr 2021 Reopened 07 June 2021	Closed	7/2/2021 *Closed after DLP	Competent Authority	Spontaneous reports Re-opened due to Competent Authority request for review in SMSR #7	Safety database, clinical study reports, O/E analyses	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new 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
Myocarditis and Pericarditis	15 Feb 2021 Reopened 19 Apr 2021 Reopened 24 May 2021 Reopened 24 June 2021 Reopened 30 June 2021	Closed	30 June 2021 *Closed after DLP	Competent Authority	Spontaneous reports	Safety database clinical reports, O/E analyses, literature	Added to EU-SmPC, USEUA Fact Sheets multiple local labels as W/P and ADR at request of Competent authorities. Added to EU-RMP and US-PVP as Important identified risk. CDS: Based on available data, a causal association between the vaccine and this event is not established; PV monitoring and active surveillance will continue, and the topic will be revisited when relevant new information
Hypertensive crisis with intracranial hemorrhage	07 June 2021	Closed	30 June 2021 *Closed after DLP	Competent Authority	Spontaneous reports	Safety database, clinical study reports, literature Serious HTN was again reviewed for PSUR #1	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Vaccine stress-related responses	10 Feb 2021	Closed	31 Mar 2021	Routine PV (case review)	Spontaneous reports of potential stress/anxiety related AEs peri-vaccination	Safety database	The concept determined to be related to process of vaccination, not the vaccine itself. The concept will be added as Warning/Precaution to CDS and CO written for CDS and local labels for submission per regulatory processes; referred to Labelling Team for implementation. Concepts included: dizziness, fainting, palpitations, heart rate increase, blood pressure changes, shortness of breath, tingling Sensations (paraesthesias), sweating, anxiety

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
Tachycardia	28 Jan 2021	Closed	31 Mar 2021	Health authority PV report	Spontaneous reports	Safety database and clinical study reports	Added to CDS and local labels as potential symptom of Vaccination stress-related response
Diarrhea	16 Nov 2020 Reopened 18 Jan 2021 Following receipt of SMSR #1 PRAC Assessment report	Closed	10 Feb 2021	Clinical study data (DLP 14 Nov 2020) Re-opened due to competent authority request	Clinical study data review for initial submission (DLP Nov 2020) Spontaneous reports	Clinical study reports and safety database	Based on evaluation of post-authorization spontaneous data, Diarrhea will be added to the CDS and local labels as adverse reaction
Pain in extremity (Arm)	19 Dec 2020	Closed	20 Jan 2021	Competent authority	Request to include as an adverse reaction in EU SmPC at time of conditional approval	Safety database and clinical study reports	Based on evaluation of data, added to EU-SPC at time of conditional approval in EU and also added to CDS and USEUA Fact Sheets
Anaphylaxis	08 Dec 2020	Closed	30 Dec 2020	Competent authority	Spontaneous reports of anaphylaxis	Safety database and clinical study reports	Based on evaluation of post-authorization spontaneous data, Anaphylaxis identified as adverse reaction and will be added to IB, EU-SPC and US-EUA Fact Sheets; also, Anaphylaxis will be added as an Important identified risk to EURMP, US-PVP

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
Vomiting	16 Nov 2020 Re-opened 18 Jan 2021 Following receipt of SMSR#1 PRAC assess ment report	Closed	10 Feb 2021	Clinical study data (DLP 14 Nov 2020) Re-opened due to Competent authority request	Clinical Study data review for initial submission (DLP Nov 2020) Spontaneous reports	Clinical study reports and safety database	Based on evaluation of post-authorization spontaneous data, Vomiting will be added to the CDS and local labels as adverse reaction
Hypersensitivi ty, other than anaphylaxis	19 Dec 2020 Re-opened 07 Jan 2021	Closed	13 Jan 2021	Competent authority	Spontaneous reports	Safety database and clinical study reports	At the time of product conditional approval by EMA, Hypersensitivity was added as an adverse reaction (not important) to Section 4.8 of the EU SmPC per EMA request. "Hypersensitivity (e.g. rash, pruritus, urticaria, angioedema)" was added to the CDS and EUA PI as an adverse reaction
Paraesthesia	29 Dec 2020	Closed	31 Mar 2021	Routine PV (Case review) and competent authority	Spontaneous reports	Safety database and clinical study reports	This event has been included in the description of Vaccination stress-related responses which was added as a W/P to the Core Data Sheet
Safety Topics Determined NOT to be Validated Signals (i.e. Non-Validated Signals)							
Dizziness (Note: This topic has been reviewed in the context of Vaccination stress responses and	10 May 2021	Closed	09 Jun 2021	Competent authority	Spontaneous reports that may not be associated with vaccination stress responses	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new 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
as a stand-alone topic)							
Abnormal behavior/Mental disorder	13 May 2021	Closed	28 May 2021	Competent authority	Request for literature and opinion	Safety database and literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute disseminated encephalomyelitis (ADEM)	09 May 2021	Closed	26 May 2021	O/E Competent authority	SMSR #5 O/E >1 and competent authority request	O/E analyses and safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Cranial Nerve palsy	13 Apr 2021	Closed	23 Apr 2021	Competent authority	Request for comment on cases	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Nephrotic syndrome	29 Apr 2021	Closed	06 May 2021	Routine PV (literature)	Literature case report	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hemolytic anemia	16 Apr 2021	Closed	23 Apr 2021	Routine PV (case review)	Spontaneous report	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Optic neuritis	13 Apr 2021	Closed	23 Apr 2021	Competent authority	Spontaneous report received	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hepatic events	01 Mar 2021	Closed	19 Apr 2021	Routine PV (case review)	Spontaneous report	Safety database and clinical study reports	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Dysphagia	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV

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
							monitoring will continue, and the topic will be revisited if relevant new information becomes available
Voice hoarseness (dysphonia)	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hypertension	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Arrhythmia	16 Mar 2021	Closed	25 Mar 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Polyneuropathy/Peripheral neuropathy	11 Mar 2021	Closed	25 Mar 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Transverse myelitis	11 Mar 2021 Re-opened 01 Jun 2021	Closed	07 Jun 2021	O/E	O/E >1 and competent authority request	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Anosmia/Ageusia	11 Mar 2021	Closed	06 Apr 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Myasthenia gravis	11 Mar 2021	Closed	25 Mar 2021	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Meningitis	11 Mar	Closed	25 Mar	O/E	O/E >1	Safety database	Based on information as of the data-lock date of 18 Jun

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
	2021		2021				2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Guillain-Barre syndrome	25 Feb 2021 Re-opened 21 May 2021	Closed	26 May 2021	O/E Competent authority	O/E >1 and competent authority request	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Severe cutaneous adverse reactions (SCAR)	21 Feb 2021	Closed	03 Mar 2021	Routine PV (case review)	Spontaneous report	O/E analyses and safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Increased INR	14 Jan 2021	Closed	20 Jan 2021	Competent authority	Request for review	Safety database	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Gastrointestinal obstruction	18 Sep 2020	Closed	24 Sep 2020	Routine PV (clinical study AE review)	Blinded clinical study report (Study C4591001)	Clinical study data	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Hypoglycemia	16 Mar 2021	Closed	31 Mar 2021	Competent authority	Request for review	Review for hypoglycemia; vaccine label review; safety database review	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Disseminated intravascular coagulation (DIC)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA office of Biostats and Epi signal detection	Safety database and epidemiology analysis (internal and external databases)	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Pulmonary embolism (PE)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA office of Biostats and	Safety database and epidemiology	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV

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
					Epi signal detection	analysis (internal and external databases)	monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute myocardial infarction (AMI)	14 Jun 2021	Closed	16 Jun 2021	Competent authority	FDA office of Biostats and Epi signal detection	Safety database and epidemiology analysis (internal and external databases)	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acquired hemophilia	25 May 2021	Closed	04 Jun 2021	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analysis, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Acute pancreatitis	21 May 2021	Closed	04 Jun 2021	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analysis, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Menstrual disorders	10 May 2021	Closed	19 May 2021	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analysis, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available
Ongoing safety topics/signals							
Immune thrombocytopenia	21 Jan 2021 Re-opened 25 Jun 2021 (PSUR #1 request)	Closed	8/4/2021 *Closed after DLP	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analysis, literature	TBD
Trigeminal neuralgia	29 Apr 2021 Re-opened 07 Jun	Closes	7/2/2021 *Closed after DLP	Competent authority	Spontaneous reports Re-opened due to	Safety database, clinical study reports, O/E analysis, literature	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new 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
	2021				competent authority request for review in SMSR #7		
Myocarditis and pericarditis	15 Feb 2021 Re-opened 19 Apr 2021 Re-opened 24 May 2021 Re-opened 24 June 2021 Re-opened 30 June 2021	Closed	30 Jun 2021 *Closed after DLP	Competent authority	Spontaneous reports	Safety database, clinical study reports, O/E analysis, literature	Added to EU-SmPC, USEUA Fact Sheets and multiple local labels as W/P and ADR at request of Competent authorities. Added to EU-RMP and US-PVP as Important identified risk CDS: Based on available data, a causal association between the vaccine and this event is not established; PV monitoring and active surveillance will continue, and the topic will be revisited when relevant new information becomes available
Hypertensive crisis with intracranial hemorrhage	07 Jun 2021	Closed	30 Jun 2021 *Closed after DLP	Competent authority	Spontaneous reports	Safety database, clinical study reports, literature Serious HTN was again reviewed for PSUR #1	Based on information as of the data-lock date of 18 Jun 2021, this topic is a non-validated signal. Routine PV monitoring will continue, and the topic will be revisited if relevant new information becomes available

2.2.1 Safety reviews requested by health authorities in the context of the MSSRs and considered by the MAH as non-validated signals (hypoglycemia and serious hypertension), as safety topics (lymphopenia and haemophagocytic syndrome) or for which the MAH committed to closely monitor (immune thrombocytopenia, hearing loss and tinnitus, serious arrhythmias, acute pancreatitis, acquired haemophilia and menstrual disorders)

2.2.1.1 Lymphopenia

***PRAC request 2nd MSSR*:** The MAH was requested to provide a cumulative review of lymphopenia (including cases from post-marketing experience, clinical trial data, as well as relevant literature). Based on this review, the need for a PI update should be discussed.

Results

Search criteria:

PT lymphopenia

Non-clinical data:

Decreases in lymphocytes were not observed on Days 4 or 17 after BNT162b2 administration in the repeat-dose toxicity studies in rats.

Clinical trial data:

In Phase 1 laboratory assessments of C4591001, there were observations of transient decreases in lymphocytes (< 0.8 x lower limit of normal) noted 1-3 days after Dose 1. These decreases returned to normal by the next measurement (within 6-8 days of the first dose). Most decreases were grade 1 or 2. RNA vaccines are known to induce type I interferon and type I interferons regulate lymphocyte recirculation and are associated with transient migration and/or redistribution of lymphocytes. This rapid rebound of lymphocytes supports that the lymphocytes were not depleted, but temporarily migrated out of the peripheral blood, and subsequently re-entered the bloodstream by the time of the next assessment.

Post-authorization data:

- Number of cases: 73 (0.02% of 327,603 cases, the total cumulative PM dataset)
- 64 medically confirmed cases. 9 non-medically confirmed
- Subjects' gender: female (41), male (31) and unknown (1)
- Subjects' age in years (n = 70), range: 16-100, mean 61.4, median 63.5
- Medical history (n = 50): The most frequently (≥2 occurrences) reported relevant medical history included thrombocytopenia (3), arthritis, prostate cancer, rheumatoid arthritis (2 each).
- COVID-19 Medical history (n = 10): Medical conditions reported were coded to the PTs COVID-19 (7), Coronavirus infection, COVID-19 pneumonia, Suspected COVID-19 (1 each).
- Co-suspects (n=4): Relevant co-suspects included atovaquone, and venetoclax (1 each).
- Time to event onset (n = 51), range: <24 hours to 53 days, median 4 days.
    - <24 hours: 3 events;
    - 1 day: 11 events;
    - 2-7 days: 18 events;
    - 8-14 days: 9 events;
    - 15-30 days: 9 events;

    - 31-181 days: 1 event.
- Duration of events (n = 7 out of 18 occurrences with outcome of resolved), range: 1-15 days, median 3.5 days.
    - 1 day: 1 event;
    - 2-7 days: 4 events;
    - 8-14 days: 1 event;
    - 15-30 days: 1 event.
- Relevant event outcome: fatal (3 – PT: Lymphopenia), resolved/resolving (26), not resolved (9), unknown (35).

The three fatal cases are further described:

- The case concerned a 72-year-old male patient with a medical history of bladder catheter permanent, hypoacusis, hypothyroidism, urinary tract infection, end-stage Parkinson's disease, and transient ischaemic attack received single vaccine dose. The patient was reported as at risk of developing a severe form of COVID-19 disease. On day 18, the patient experienced septic shock, lymphopenia, malaise, muscle rigidity, livedo reticularis, and skin discolouration. Laboratory investigations on the same day (day 18) were: white globules 7.5 G/L, polynuclear neutrophils 6.72 G/L, lymphocytes 0.5 G/L, platelets 248 G/L, and haemoglobin 14.9 g/dL. The patient was treated with antibiotics. The patient died on day 24, due to septic shock and lymphopenia. An autopsy was not performed.
- This case described an 88-year-old male patient who received first dose of vaccine and on day 17 developed COVID-19, Drug ineffective (reported as symptomatic COVID-19 Infection), lymphopenia and thrombopenia (values not provided). Medical history and concomitant medications were not reported. The patient died on an unspecified date and it was not reported if an autopsy was performed. All events coded to the PTs COVID-19, Drug ineffective, Lymphopenia and Thrombopenia reported a fatal outcome.
- This case described an 84-year-old female patient with a medical history of tachyarrhythmia absoluta, atrial fibrillation, arterial hypertension received vaccine dose 2. On day 3 after dose 2, the patient experienced pyrexia, pneumonia, leukopenia, and lymphopenia which resulted in hospitalization. Laboratory data were not provided. On day 12, the patient died, and an autopsy was performed but results were not provided. All events coded to the PTs Pyrexia, Pneumonia, Leukopenia, and Lymphopenia reported a fatal outcome.

Literature: A search of OVID databases, Embase, OVID Medline (R), and Pubmed was conducted cumulatively through 22 July 2021 for Covid-19 vaccine AND "idiopathic CD4-positive T-lymphocytopenia" or "idiopathic CD4-positive T-lymphocytopenia" or "lymphocytopenia" or "lymphopenia" or "lymphopenia" or "lymphopenia" or "T-lymphocytopenia, idiopathic cd4-positive" or "T-lymphocytopenia, idiopathic CD4-positive" or "lymphocytopenia. The search resulted in a total of 15 articles, 1 of which was relevant (see section 1.3.5 of this AR).

This study provides preliminary data that both EUA mRNA vaccines were generally safe and well tolerated in an allogeneic HCT population despite some limitations.

MAH's conclusion:

Transient lymphopenia is an expected association with immunization due to migration of lymphocytes from the bloodstream to lymphoid tissues as part of the expected immune response to the vaccine. Upon review of the fatal and non-fatal cases, a transient decrease in lymphocytes was reported in 38 out of 73 cases however, most cases involved patients with underlying conditions (such as thrombocytopenia, urinary tract infection, COVID-19), malignancies (prostate

cancer), and/or other chronic diseases (arthritis, rheumatoid arthritis, atrial fibrillation, arterial hypertension), which should be taken into account. Based upon review of the available information from non-clinical, clinical phase 1 and post-authorization, no new significant safety information has emerged. No additional change to the RSI is warranted at this time. Safety surveillance will continue.

Rapporteur assessment comment:

As requested in the 2nd MSSR, the MAH has provided a review of lymphopenia. In the clinical trial program, transient decreases in lymphocytes were observed that occurred 1-3 days after dose 1 and returned to normal within 6-8 days after dose 1. The MAH describes that this is an expected effect of the vaccination given that lymphocytes migrate to lymphoid tissues as part of the immune response.

In the post-marketing phase, a total of 73 lymphopenia cases were reported of which 64 were medically confirmed. In the cases that reported TTO (n = 51), 32 occurred within 7 days after vaccination. Duration of the event was available for 7 cases and ranged from 1-15 days with a median of 3.5 days. The three fatal cases were described in further detail, had multiple comorbidities and concomitant Covid-19 infection.

Given the nature of the reported events that seem to resolve within several days and the relative limited number of reported cases compared to the BNT162b2 exposure, it is agreed with the MAH that currently the data do not support a new safety issue.

2.2.1.2 Immune thrombocytopenia

PRAC request 3rd MSSR: The MAH reviewed this topic, and committed to review this topic again in the upcoming PSUR.

A review of thrombocytopenia following vaccination with BNT162b2 was included in the 3rd SMSR (01 February 2021 – 28 February 2021). This is an updated review with data-lock date of 18 June 2021. Thrombocytopenia is an AESI.

MAH's database was searched for BNT162b2 adverse event reports using MedDRA v 24.0 search strategy HLT Thrombocytopenias, received cumulatively to 18 June 2021.

Cases were assessed using the Brighton Collaboration SPEAC AESI Case Definition Companion Guide for Thrombocytopenia (v 1.0, 08 February 2021).

Results

Using this search strategy, 760 cases were retrieved. The 760 cases were individually reviewed. One case was eliminated from further review because it was a duplicate report. The 759 cases were assessed as follows:

- BC Level 1: 215 cases
- BC Level 2: 293 cases
- BC Level 4: 63 cases
- BC Level 5 (not thrombocytopenia): 188 cases

Brighton Collaboration Criteria Level 1

All 215 BC Level 1 cases were categorized as serious. Sex was reported in 213 cases (111 females, 102 males). Age was reported in 208 cases and ranged from 17 to 100 years (63.8 mean, 69.5 median). Country of case origin: UK (64), France (38), Italy (19), US (16), Spain (15), Germany

and Japan (11 each), Sweden (9), Netherlands (8), Norway (5), Switzerland (4), Czech Republic (3), Denmark and Belgium (2 each) and Austria, Costa Rica, Croatia, Finland, Greece, Mexico Slovenia and Poland (1 case each).

Potentially alternative explanations for thrombocytopenia were noted for 63 cases. These included autoimmune diseases such as rheumatoid arthritis; concurrent infections such as urosepsis, concurrent DIC; current COVID-19 or history of COVID-19, and malignancies including hematologic malignancies. An additional 36 cases described histories of thrombocytopenia, mostly immune thrombocytopenia. Of the remaining 116 cases, 26 described current use of 1 or more medications that note thrombocytopenia as an adverse reaction in product labelling. It is acknowledged that a history of immune thrombocytopenia does preclude the possibility that the vaccine may still affect these patients if, indeed, there is a causal association between the vaccine and thrombocytopenia.

For the remaining 90 cases, an alternative cause was not reported for the thrombocytopenia event; 45 were reported following dose 1, 29 following dose 2 and 16 cases did not specify the dose. Time to thrombocytopenia following vaccination was:

- 1: <24 hours
- 22: 1 to 6 days (inclusive)
- 24: 7 to 13 days (inclusive)
- 11: 14 to 20 days (inclusive)
- 23: > 20 days
- 9: Unspecified

Reported platelet nadirs were:

- 49: < 10
- 11: > 10-20
- 13: >20-50
- 5: >50-100
- 6: > 100-150
- 6: Unspecified

Outcomes of the thrombocytopenia at the time of reporting were provided in 60 of the 90 cases and were:

- 27 Resolved/Resolving
- 25 Not resolved
- 8 Fatal (case outcome)

Rapporteur assessment comment:

The MAH provided a summary of the cases with fatal outcome (n=8, not reproduced in this AR). In 2 cases the lack of detail precluded an assessment. In the other 6 cases the lack of detail provided regarding the work-up of the thrombocytopenia, possible separate pathological process (n=4), and previous (asymptomatic) COVID-19, leaves doubts to its cause due to the vaccination.

No case by case causality assessment of the remaining 82 BC level 1 cases is reported which is not accepted. These cases seem well documented to be assessed as BC level 1 cases. Subsequently, a case by case causality assessment is expected. Although the O/E ratios are below 1, there are backlog cases and an unknown underreporting of adverse events including reports of immune thrombocytopenia, therefore the MAH is requested to provide a case by case causality assessment of the immune thrombocytopenia cases considered BC level 1 cases. **RfSI**

Brighton Collaboration Criteria Level 2

All 293 BC Level 2 cases were categorized as serious. Sex was reported in 289 cases (151 females, 138 males). Age was reported in 279 cases and ranged from 16 to 96 years (65.5 mean, 72.0 median). Country of case origin: UK (79), France (46), Spain (27), Italy (25), US (20), Germany (18), Sweden (15), Netherlands (17), Denmark and Norway (6 each), Austria, Belgium and Japan (5 each), Greece (4), Malta (3), Czech Republic, Slovenia and Switzerland (2 each), and Finland, Poland, Hong Kong, Ireland, Israel and Portugal (1 each).

Potentially alternative explanations for thrombocytopenia were noted for 97 cases. These included autoimmune diseases (e.g. rheumatoid arthritis), sepsis, hematologic and other malignancies, COVID-19 (current or history), HCV and multi-organ failure. An additional 44 cases described histories of thrombocytopenia. Of the remaining 152 cases, 38 described current use of 1 or more medications that note thrombocytopenia as an adverse reaction in product labelling.

This left 114 cases without a reported alternative cause for the thrombocytopenia; 44 were reported following dose 1, 49 following dose 2 and 21 cases did not specify the dose. Time to thrombocytopenia following vaccination was:

- 3: <24 hours
- 38: 1 to 6 days (inclusive)
- 25: 7 to 13 days (inclusive)
- 9: 14 to 20 days (inclusive)
- 26: > 20 days
- 13: Unspecified

Reported platelet nadirs were:

- 24: < 10
- 7: > 10-20
- 17: >20-50
- 25: >50-100
- 36: > 100-150
- 5: Unspecified

Outcomes of the thrombocytopenia at the time of the report were provided in 80 of the 114 cases and were:

- 45 Resolved/Resolving
- 27 Not resolved
- 8 Fatal (case outcome)

Rapporteur assessment comment:

The MAH provided a summary of the cases with fatal outcome (n=8, not shown in this AR). In 2 cases the lack of detail of the cases and on the course of hospitalisation precluded an assessment. In the other 6 cases the lack of detail provided of the thrombocytopenia etiology (n=2), underlying medical conditions (n=3), and concomitant infection /use of antibiotics, leaves doubts to its cause due to the vaccination.

No case by case causality assessment of the remaining 106 BC level 2 cases is reported which is not accepted. These cases seem well documented to be assessed as BC level 2 cases. Subsequently, a case by case causality assessment is expected. Therefore, the MAH is requested to provide a case by case causality assessment of the immune thrombocytopenia cases considered BC level 2 cases. **RfSI**.

Brighton Collaboration Criteria Level 4

Thrombocytopenia is reported for BC Level 4 cases, but a platelet value is not reported. Therefore, the severity of thrombocytopenia (e.g. <150) is not known.

All 63 BC Level 4 cases were categorized as serious. Sex was reported in 62 cases (38 females, 24 males). Age was reported in 52 cases and ranged from 21 to 95 years (63.1 mean, 65 median). Country of case origin: Germany (16), UK (9), Japan (6), Australia, Italy (5), US (4), Netherlands, Norway, Slovakia, Spain, Sweden (2 each), Albania, Belgium, France, Hong Kong, Hungary, Iceland, Poland, South Africa (1 each).

Potentially alternative explanations for thrombocytopenia were noted for 14 cases. These included autoimmune diseases such as systemic lupus erythematosus; hematologic and other malignancies, COVID-19 (current or history), liver and multi-organ failure. An additional 3 cases described histories of thrombocytopenia. Of the remaining 46 cases, 4 described current use of 1 or more medications that note thrombocytopenia as an adverse reaction in product labelling.

This left 42 cases without a reported alternative cause for the thrombocytopenia; 19 were reported following dose 1, 9 following dose 2 and 14 cases did not specify the dose. Time to thrombocytopenia following vaccination was:

- 1 <24 hours
- 11 1 to 6 days (inclusive)
- 6 7 to 13 days (inclusive)
- 6 14 to 20 days (inclusive)
- 5 > 20 days
- 13 Unspecified

Outcomes of thrombocytopenia were provided in 30 of the 42 cases and were:

- 10 Resolved/Resolving
- 15 Not resolved
- 5 Fatal (case outcome)

Of the 5 fatal cases, the lack of detail regarding severity of thrombocytopenia makes an assessment of the contributory role of thrombocytopenia less reliable. The lack of detail on temporality between vaccination and thrombocytopenia in 2 of the reports further compromises a meaningful assessment. In a third case, the reported occurrence of thrombocytopenia >20 days after vaccination makes a relationship with vaccination less likely.

Clinical study data

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).

O/E analyses

The observed to expected analyses of clinical trial and spontaneously reported adverse events of Idiopathic thrombocytopenia purpura, Autoimmune thrombocytopenia were < 1 for all analyses:

- 14 day risk window: O/E ratio 0.185 (95% CI 0.172; 0.199).
- 21-day risk window: O/E ratio 0.128 (95% CI 0.119; 0.138).

Rapporteur assessment comment:

In current PSUR reporting period, the MAH is using in the O/E analyses 14-day and 21-day risk windows. In the MSSRs, the MAH reports overall OE ratios in a 21-day risk and no risk windows and in the age-stratified analyses OE ratios in 14-day and 21-day risk windows.

Of concern are the backlog cases. Besides the O/E analyses that include the processed cases, no sensitivity O/E analysis is presented which include the processed cases plus the backlog cases. In future PSURs and similar to the O/E analyses reported in the MSSRs, the MAH is requested to perform overall O/E analyses using at least no risk window, 14-day risk window and 21-day risk window and additionally perform sensitivity O/E analyses which include the processed cases plus the backlog cases. **Request for next PSUR**

Literature

A literature search was conducted using OVID MEDLINE (R) 1946-present, OVID MEDLINE (R) In-Process & Epub Ahead of Print, BIOSIS Previews and Embase for thrombocytopenia and COVID-19 vaccines. Additionally, articles obtained through routine PV were also reviewed. The relevant articles are summarized:

A study of the VAERS database published by the FDA Division of Epidemiology, Office of Biostatistics and Epidemiology assessed cases of thrombocytopenia reported as of 04 Feb 2021 following vaccinations with BNT162b2 and Moderna mRNA COVID-19 vaccines. They used as a basis an annual incidence rate of 3.3 ITP case per 100,000 adults. There were 15 reports of thrombocytopenia following >18 million doses of BNT162b2 vaccine and 13 cases following >16 million doses of Moderna vaccine. The reporting rate was 0.80 per million doses for both vaccines and the number of all thrombocytopenia cases did not exceed the number of ITP cases expected. [Welsh KJ, Baumblatt J, Chege W, et al. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2021; 39(25):3329-32.]

Authors including hematologists wrote a case series describing 20 patients with thrombocythemia after vaccination with either BNT162b2 or Moderna COVID-19 vaccine that they collated via a search of data from the CDC, FDA and VAERS. Four of the 20 patients (11 females, 12 males) who ranged in age from 22 to 73 years, had previous diagnoses of ITP or episodes of thrombocytopenia prior to vaccination and 3 other patients had known autoimmune conditions. Fourteen presented with bleeding symptoms and most presenting platelet counts were <10. All responded to treatment except the index patient who died from a cerebral hemorrhage and a patient whose treatment details were not known beyond 3 days. The authors state that distinguishing vaccine-induced ITP from coincidental ITP is impossible at the time of the publication. [Lee EJ, Cined DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. Am J Hematol 2021; 96(5):534-7.]

Another article described a 39-year old woman in the [redacted] with a history of polycystic ovary disease on norgestimate-ethinyl estradiol, and a normal CBC 6 months prior, who received the 2nd dose of the BNT162b2 and presented 3 days later with a petechial rash. She had experienced fatigue and myalgias about 12 hours after vaccination. She was found to be afebrile with normal blood pressure and mild tachycardia, petechiae on her legs, arms, abdomen and chest extending to her neck. Her platelet count was 1000/µL, coagulation studies were normal and ESR was increased 75 mm/h (0.0-20.0). A peripheral smear confirmed low platelets and an ultrasound of her spleen was normal. Hemolysis was ruled out and tests for viral hepatitis, HIV and H. pylori were negative as

was an antinuclear antibody test. She was transfused 1 unit of platelets and received 1000 mg IV methylprednisolone. Within 6 hours her platelet count increased to 16000/µL, but the following day decreased to 4000/µL. She was given a 2nd transfusion of platelets and IVIG was administered that day and the next. A report was made to VAERS as the team and a consulting hematologist felt the most likely cause of the ITP was vaccination, based on her history (no preceding illness, no new medications, no travel, no other vaccinations and age-appropriate cancer screening) and lab tests. She spent 3 days in the hospital and her platelet count was 92,000/µL at discharge. The next day they were 243,000/µL. She was tested after discharge for antiplatelet antibodies (negative). Of note, she was not tested for COVID-19. The authors hypothesize that vaccination caused the ITP. [King ER, Towner, E. A case of immune thrombocytopenia after BNT162b2 mRNA COVID-19 vaccination. Am J Case Rep 2021; 22: e931478.]

A case study described a 53-year old man in [redacted] with a history of obesity, diabetes and hypertension on lercanidipine losartan, doxazocin, hydrochlorothiazide and aspirin, who presented with epistaxis and thrombocytopenia 2 weeks after his 1st vaccination with BNT162b2. One week prior to presentation he had taken 2 doses of levofloxacin for suspected otitis (as he had on numerous occasions in the past). On exam, he had purpura on his palate and petechiae on the trunk and limbs, no lymphadenopathy or splenomegaly. His platelet count was 1 x 10^3/µL, kidney, liver and coagulation tests were normal. CMV, EBV, HBV, HCV and HIV were negative. Mycoplasma antibody was borderline positive (1:80), ANA, complement, anti-cardiolipin and anti β2-glycoprotein were negative. He was treated with dexamethasone 20 mg/d and IVIG with an increase in platelets that normalized in 5 days. The 2nd vaccine was not administered due to the severity of the thrombocytopenia which the doctors thought was likely due to the vaccine. [Ganzel C, Ben-Chetrit E Immune thrombocytopenia following the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine IMAJ 2021; 23(6): 341.]

Another article from [redacted] was a case series of 4 patients diagnosed with a TTP following vaccination:

1. A 40-year-old healthy woman presented 8 days after dose 2 with somnolence, fever, hematuria and petechiae and ecchymosis of the lower limbs.
2. A 28-year-old healthy male with obesity and an episode of dysarthria lasing 15 minutes who had received dose 2 of vaccine 28 days earlier. His neurological exam and brain CT were normal.
3. A 31-year old woman with recurrent TTP who was in remission, presented 13 days after dose 1 with vaginal bleeding and purpura. ADAMTS-13 test showed 0% activity.
4. A 30-year old man with history of one episode of TTP in 2013, presented with purpura on his limbs 8 days after dose 2 of BNT162b2. ADAMTS-13 activity was normal.

All patients improved following treatment to a platelet count >150 k/µL within a mean of 4 days following presentation. All patients received plasma exchange, corticosteroids and caplacizumab; 3 received rituximab. The authors estimate that 2-3 cases/year are diagnosed in any [redacted] hospital and that this number alerted them to a possible association with BNT162b2 vaccine. [Tarawneh O, Tarawneh H. Immune thrombocytopenia in a 22-year-old post COVID-19 vaccine. Am J Hematol 2021; 96(5):E133-4.]

In another case report, a 41 year old woman with multiple food and drug allergies and a history of hypothyroidism, hypertension, and pre-diabetes on enalapril and levothyroxine, presented to the ED with a 12 hour history of fever tachycardia and nausea She had received the BNT162b2 vaccine 12 hours prior to that. She was afebrile with a HR of 108 bpm, blood pressure 154/99 and had a normal physical examination except for some mild dehydration. Labs showed normal WBC, and platelet count was 65 x 10^9. She had a previously normal platelet count 4 months prior. CRP and

IgE were elevated but all other tests were within normal range: C3, C4 levels, ANA, anti-SSA, anti-SSB and antiDNA. The peripheral smear was not remarkable. Antiplatelet antibodies and bone marrow smear were not done. After 12 hours in the ED platelets were 38 and she had mucosal bleeding (e.g. gums). She received methylprednisolone and IVIG and a CT of the head had no evidence of intracerebral hemorrhage. After the 2nd dose of IVIG and dexamethasone, gingival bleeding stopped, and platelets began to increase. She received a total of 4 doses of dexamethasone and 3 doses of IVIG. She was discharged after 5 days with a normal platelet count. One week later, her platelet count was 629 x 10^9. The authors say their purpose in publishing this case is to raise awareness of the disease. [Maayan H, Kirgner I, Gutwein O, et al. Acquired thrombotic thrombocytopenic purpura: a rare disease associated with BNT162b2 vaccine. J Thromb Haemost 2021 Jun 8:10.1111/jth.15420.doi.]

A case of a 22-year old man with no medical history and no medication use who developed petechiae and bleeding gums 3 days following his first dose of BNT162b2 was published. He had no history of adverse reactions to vaccines and no personal or family history of bleeding or autoimmune disorders. His complete blood count was normal except a platelet count of 2 x 10^9/L. Two months prior, during an evaluation for upper respiratory symptoms he was COVID-19 negative with a normal platelet count of 145 x 10^9/L (140-400 x 109/L). He was again COVID-19 negative and remaining labs, including HIV, HBV, HCV and EBV were normal/negative except mildly elevated ALT and AST (resolved the next day). He was treated with dexamethasone 40 mg daily for 4 days and IVIG for 2 days. Studies on postvaccination day 6 included an autoimmune workup that was negative except an elevated Sjogren's Syndrome A antibody at 2.8 (normal <1 AI). His platelet count had risen to 28 x 10^9/L on Day 6 so he was discharged; his diagnosis was ITP. By the 11th day after vaccination, his platelet count was 173 x 10^9/L and Sjogren's syndrome A antibody had decreased to 1.5 AI; also on that day complement C3 was normal and complement C4 was low (complement had not been tested previously). He remains healthy without signs of autoimmune disease at the time of publication. The authors state that the temporal relationship and abrupt and severe drop in platelet count is reminiscent of drug-induced thrombocytopenia suggests the possibility of the vaccine as the culprit. [Fueyo-Rodriguez O, Valente-Acosta B, Jimenez-Soto R, et al. Secondary immune thrombocytopenia supposedly attributable to COVID-19 vaccination. BMJ Case Rep 2021; 14e242220.doi:10.1136/bcr-2021-242220.]

A prospective study over approximately 2 months at a [redacted] hospital studied 52 routine long-standing ITP patients who were advised to obtain platelet counts 1-7 days before vaccination for COVID-19 and 3-14 days after. An exacerbation of thrombocytopenia was defined as a platelet count reduced by 66% from pre-vaccination baseline plus new bleeding symptoms. The patients had guideline-defined chronic ITP present for a median of 12 years, 71% were female and median age was 65.5 years; 16 (31%) were on active treatment for ITP and 18 (35%) were not. Only 4 patients received Johnson & Johnson vaccine and 24 each received BNT162b2 or Moderna vaccines. The results:

- 8/52 (15%) – no worsening of ITP symptoms, but did not have platelet counts drawn within 14 days post-vaccination
- 38/52 (73%) – no worsening of ITP symptoms and no significant change in platelet counts (about 50% of these patients had decreases in counts but they could not be distinguished from their usual fluctuations in number and none decreased by more than 50% from previous counts)
- 6/52 (12%) – developed a severe exacerbation and worsening bleeding symptoms

Of the vaccinated patients with ITP, there were no thromboses and decrease in platelets generally occurred 2-5 days after the vaccination. Of the 6 with severe exacerbations, lowest platelet counts

post-vaccination ranged from 1 to 17 x 10^9/L. 4/6 had been in remission for over one year (2 still on active treatment). Bleeding beyond ecchymoses, petechiae and oral blood blisters did not occur and 5 of 6 responded to prednisone +/- IVIG; with the 6th patient also requiring treatment with romiplostim and rituximab. The 6th patient and one other with a severe exacerbation had previously had a decrease in platelets following other vaccinations (Neisseria meningitis and Streptococcus pneumoniae). Two of the 6 received dose 2 prior to obtaining platelet counts; they had had bleeding symptoms following dose 1 that were attributed to their concurrent warfarin anticoagulation. Four of the six did not receive the 2nd dose. Four of the 6 received BNT162b2 vaccine, 1 received Moderna and 1 received Johnson & Johnson vaccine. The authors were not able to identify any specific predictors among these patients in terms of age, gender, duration of ITP, baseline platelet count, remission status, concurrent ITP therapy or vaccination type. They concluded that the results suggest that some ITP patients have a transient exacerbation of thrombocytopenia within 1 week of COVID-19 vaccination. [Kuter D. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. British Journal of Hematology doi: 10.1111/bhj.17645.]

Rapporteur assessment comment:

No details of the literature search method and no detailed results of the literature search are presented in the PSUR. The MAH summarized 8 articles, one study of VAERS data with 28 thrombocytopenia cases after mRNA vaccination, four case reports, two case series of which one reporting on 20 thrombocytopenia patients after mRNA vaccination and the other one reporting on 4 patients diagnosed with TTP after vaccination, one prospective study concerning 52 chronic ITP patients and exacerbation of thrombocytopenia after vaccination. However, no detailed conclusion regarding the literature search results is provided by the MAH which is expected. Therefore, the MAH is requested to provide a thorough discussion and conclusion of the retrieved literature following the literature search. **RfSI**

MAH's conclusion

This review of thrombocytopenia consists of clinical study data, post-authorization 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. 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. Routine pharmacovigilance will continue.

Rapporteur assessment comment:

The MAH provided a review of ITP cases with DLP 18 June 2021 (an update of the review reported in the 3rd MSSR with DLP 26 Feb 2021 which resulted in 83 cases). The comprehensive cumulative review retrieved 760 cases reporting thrombocytopenia (including one duplicate case) and classified in BC Level 1: 215 cases, BC Level 2: 293 cases, BC Level 4: 63 cases, and BC Level 5 (not thrombocytopenia): 188 cases. However, the MAH did not provide a case by case causality assessment (and case line listings) of at least of all the BC level 1 and 2 cases which is not accepted.Also, a thorough discussion and conclusion of the retrieved literature following the literature search is lacking. Therefore, the MAH is request regarding ITP cases to provide: 1) a

case by case causality assessment of the immune thrombocytopenia cases considered BC level 1 cases, 2) a case by case causality assessment of the immune thrombocytopenia cases considered BC level 2 cases, and 3) a thorough discussion and conclusion of the retrieved literature following the literature search.

2.2.1.3 Hearing loss and tinnitus

PRAC request 3rd and 5th MSSR: The MAH reviewed these topics in the 3rd SMSR (01 February 2021 – 28 February 2021), and committed to review of this topic again in the upcoming PSUR. In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), considering the report raised recently by UMC on this issue for COVID-19 vaccines, the number of cases that are being received occurring soon after vaccination, and some positive rechallenges after the second dose, a review is expected in the upcoming PSUR.

Rapporteur assessment comment:

The included updated cumulative reviews of cases reporting hearing loss (including deafness) and cases reporting tinnitus were also submitted and assessed in the 8th MSSR.

MAH's safety database was searched for all cases reporting HLT hearing loss, PT Tinnitus after BNT162b2 vaccination through 18 June 2021.

A total of 980 serious cases of hearing loss were reported.

A total of 2499 cases reported tinnitus using the search criteria mentioned above. A total of 1325 cases were assessed as serious and 1174 as non-serious.

MAH's conclusion

Hearing loss, including deafness and sudden hearing loss, have been reported following vaccination with BNT162b2 vaccine.

Out of a total of 980 cases, most spontaneous cases of hearing loss are confounded by a medical history reporting a pre-existing ear disorder or other significant clinical risk factors (as acoustic neurinoma, tympanoplasty, autoimmune disorder and cancer). A bucket of 124 cases reported hearing loss in the context of other adverse events that may explain the symptomatology (e.g., cerebrovascular accident, encephalitis, infections).

A total of 2499 subjects reported tinnitus. Among these cases there were 558 reports confounded by a medical history reporting a pre-existing ear and/or autoimmune/infection disorder (tinnitus, deafness, acoustic neurinoma, COVID infection, autoimmunity, etc) and additional 638 cases describing tinnitus in the context of different diseases known to be associated with tinnitus (as cerebrovascular accident, facial paralysis, migraine, blood pressure issues etc). All other cases reported insufficient information to perform a meaningful assessment.

Clinical study results do not demonstrate an imbalanced number of events between placebo and vaccine. At this time, statistical signal detection in the safety database has not shown a signal of disproportionate reporting for hearing losses and tinnitus. Further, O/E analysis does not suggest an increased rate for these topics.

Given the totality of the available information, a causal association with the vaccine is unlikely for hearing loss and for tinnitus and changes to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable.

Rapporteur assessment comment:

Please refer to the assessment of the cumulative reviews (DLP 18 June 2021) of cases reporting hearing loss (including deafness) and cases reporting tinnitus in the 8th MSSR, procedure EMEA/H/C/005735/MEA/002.7. For both, hearing loss and tinnitus, no causal association with Comirnaty is suggested based on current data. Considering the seriousness of the event, close TTO and considerable number of cases without confounding medical history, medication, conditions, or risk factors, the MAH is requested to keep hearing loss under close monitoring and discuss any new patterns/trends. Particular focus should be on cases without confounding or alternative etiologies (request for 9th MSSR). No new safety information could be identified in the assessment of this request in the 10th MSSR (EMEA/H/C/005735/MEA/002.9).

2.2.1.4 Hypoglycaemia

PRAC request 4th MSSR: In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested to "discuss hypoglycaemia not only limited in patients with diabetes type 1 after vaccination with Comirnaty."

Search criteria

SMQ Hypoglycaemia (Narrow).

Non-clinical data

Changes in serum glucose in the rat repeat-dose toxicity studies were monitored and no vaccine-related effects were observed.

Clinical trial data

- Number of cases: 4 (0.4% of 1048 cases, the cumulative CT dataset; 3 were blinded therapy and 1 BNT162b2).
- Country of incidence: Argentina (2), US (2).
- Subjects' gender: female (3), male (1).
- Subjects' age in years (n = 4), range 28 - 47, mean 42.3, median 47.
- Medical history (n = 4): the relevant reported medical conditions included type 1 diabetes mellitus, type 2 diabetes mellitus (2 each), chronic kidney disease, diabetes mellitus, and hypothyroidism (1 each). Of note, more than 1 relevant medical history was reported in some cases.
- There were no cases that reported medical history of COVID-19.
- Co-suspects (n = 3): insulin aspart, insulin glargine, insulin human, isophane insulin (1 each).
- Reported relevant PT: Hypoglycaemia (4). None of the relevant events were related to BNT162b2 or blinded therapy.
- Relevant event outcome: fatal (1), resolved (3).

PT Hypoglycaemia with fatal outcome: 1 case:

In this case a 47-year-old female subject with a medical history of tobacco user, type II diabetes and hypertension, gallstones, cholecystectomy, right foot ulcer, right pinky toe infection and right pinky toe amputation; on medications for her conditions received the fourth dose of study vaccine BNT162b2 on 17 March 2021. On 13 May 2021, the subject experienced hypoglycaemia and died. An autopsy was performed, autopsy report was not available at the time of the report. The investigator and the Sponsor considered there was not a reasonable possibility that the event

hypoglycaemia was related to blinded and open label study vaccine, concomitant drugs, or any clinical trial procedure.

Post-authorization data

- Number of cases: 390 (0.1% of 327,603 cases, the total cumulative PM dataset).
- Medically confirmed cases (204), non-medically confirmed cases (186).
- Country of incidence: UK, US (98 each), France (30), Netherlands (17), Italy (16), Spain (15), Germany (13), Sweden (11), Belgium, Mexico (10 each). The remaining 72 cases were distributed among 23 countries.
- Subjects' gender: female (266), male (119) and unknown (5).
- Subjects' age in years (n = 347), range 12 - 99, mean 54.7, median 52.
- Medical history (n = 284): the most frequently (≥2%) reported medical conditions included Diabetes mellitus (73), Type 1 diabetes mellitus (58), Type 2 diabetes mellitus (40), Hypothyroidism (14), Disease risk factor (8), Chronic kidney disease (7), Cardiac failure and, Hypoglycaemia (6 each).
- COVID-19 Medical history (n = 17): COVID-19, Suspected COVID-19 (7 each), COVID-19 pneumonia, SARS-CoV-2 antibody test positive, and SARS-CoV-2 test positive (1 each).
- Co-suspects (n = 11): Relevant co-suspects included insulin (4), insulin aspart (3), insulin glargine (2), insulin detemir, and semaglutide (1 each).
- Number of relevant events: 396.
- Relevant event seriousness: serious (189), non-serious (207).
- Reported relevant PTs: Hypoglycaemia (241), Blood glucose decreased (147), Hypoglycaemic coma, Hypoglycaemic unconsciousness (2 each), Glycopenia, Hypoglycaemic seizure, Postprandial hypoglycaemia, and Shock hypoglycaemic (1 each).
- Time to event onset (n = 287), range: <24 hours to 40 days, median <24 hours.
    - <24 hours: 158 events;
    - 1 day: 58 events;
    - 2-7 days: 50 events;
    - 8-14 days: 14 events;
    - 15-30 days: 5 events;
    - 31-181 days: 2 events.
- Duration of relevant events: (n = 72 out of 163 occurrences with outcome of resolved/resolved with sequelae), range: 30 minutes to 29 days, median 1 day.
    - <24 hours: 21 events;
    - 1 day: 34 events;
    - 2-7 days: 13 events;
    - 8-14 days: 1 event;
    - 15-30 days: 3 events.
- Relevant event outcome: fatal (5), resolved/resolving (222), resolved with sequelae (10), not resolved (39), unknown (121).
- The lot/batch number #EM0477 was reported in more than ≥3% of cases.
- PT Hypoglycaemia with a fatal outcome: 5 cases:
    - This case concerned a 95-year-old female patient with medical history of atrial fibrillation, moderate aortic stenosis, pulmonary hypertension, possible papillary fibroelastoma, "non-specifically lethargic (for 1-2 weeks)" (as reported) within the month of administration; on medications for her conditions. In the 24-48 hours following vaccination, she developed headache and chills; she reduced oral intake, fell twice and became confused nine days post dose 1; was admitted to the hospital the next day; she was hypothermic, leg ulcers and bilateral leg oedema were noted,

supplemental oxygen commenced due to low saturations. She was drowsy and found to be hypoglycaemic overnight two days later, was given IV treatment, and glycaemia improved. The next morning post this episode, she was hypotensive, hypoxic, tachypnoeic, unresponsive and died. An autopsy was performed but results were not available.

  - This case described an 85-year-old female patient with medical history of atrial fibrillation, hypothyroidism (from Hashimoto), sepsis, dementia, and cardiac pacemaker insertion (reported as pacemaker probe), all from an unknown date; on medications for her conditions. The patient experienced severe hypoglycaemia 4 days post dose 1; she was given Glucagon, but the hypoglycaemia did not respond at all to Glucagon. The patient died the next day due to severe hypoglycaemia. An autopsy was not performed.
  - This case involved an 83-year-old female patient with a medical history of diabetes mellitus insulin-dependent (treatment insulin glargine), dementia, hypothyroidism, chronic lumbago, hysterectomy, cataract, knee prosthesis insertion received second dose of vaccine. On next day (day 2), the patient experienced vomiting and pyrexia and was treated with paracetamol. Six days (day 8) later, the patient experienced feeding disorder, hypoglycaemic coma, hyperglycaemia. On day 10, the patient died due to diabetic metabolic decompensation and diabetic ketoacidosis. Autopsy was not performed.
  - This case described a 60-year-old male patient with a medical history of diabetes, coronary artery disease, and back surgery received vaccine dose 1. On day 8, the patient's blood glucose decreased and died due to diabetic coma. It was not reported whether an autopsy was performed.
  - This case involved a 74-year-old female patient who received second dose of vaccine and after 30 minutes of vaccination experienced headache, syncope, cyanosis, hypothermia, hypoglycaemia, and respiratory acidosis. She was admitted to the hospital and was treated with epinephrine, and atropine. The patient died on an unspecified date due to the events. It was unknown if an autopsy was performed.

- Number of subjects with comorbidities: 224 (57.4% of the cases reporting hypoglycaemia).
- The reporting proportion of hypoglycaemia related events with fatal outcome (1.8%) and not resolved (11.5%) is slightly higher in individuals with co-morbid conditions when compared to the reporting proportion observed in the individuals without co-morbidities (0.6% of events with fatal outcome and 7.8% of events with outcome not resolved), but this is expected considering that underlying comorbidities are likely to be contributory to individual's death and delayed recovery.

MAH's conclusion

Upon review of the fatal and non-fatal cases, most cases involved patients with underlying conditions including other chronic diseases (such as diabetes mellitus- type 1 and type 2, hypothyroidism, disease risk factor, chronic kidney disease, cardiac failure and, hypoglycaemia), which should be taken into account. Based upon review of the available information, no new significant safety information has emerged. No additional change to the RSI is warranted at this time. Safety surveillance will continue.

Rapporteur assessment comment:

The MAH provided a review of cases reporting hypoglycaemia, not limited to only patients with diabetes type 1 after vaccination with Comirnaty. The RCT data did not report an imbalance, 1 case in treatment group and 3 cases in placebo group. Post-marketing, 390 cases were retrieved

of which 204 medical confirmed. In 170 of the cases medical history of diabetes was reported for which the occurrence of hypoglycaemia not unexpected. Furthermore, hypoglycemia can occur in non-diabetic individuals for which the estimated frequency (based on noncritical care hospital admissions) is 36 per 10,000 admissions. Limited information is available on hypoglycemia in the outpatient setting (UpToDate). Given this, the number of reports may not be worrisome. No new safety concern is identified based on the available information.

2.2.1.5 Serious hypertension

PRAC request 4th MSSR: In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested "to perform a cumulative review focused on serious hypertension, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of any plausible mechanisms, the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable. Any findings from the MAH's review of stress/anxiety related reactions should be taken into account, if relevant."

Search criteria

HLT Accelerated and malignant hypertension (Primary Path).

Non-clinical data

Blood pressure was not monitored during nonclinical toxicity studies.

Clinical trial data

- Number of cases: 10 (1.0% of 1048 cases, the total cumulative CT dataset; 5 were blinded therapy and 5 were BNT162b2).
- Country of incidence: US (5), Argentina (4) and Turkey (1).
- Subjects' gender: female (3), male (7).
- Subjects' age in years (n = 10), range: 40 - 66, mean 51.3, median 49.5.
- Medical history (n = 10): Hypertension (7), Obesity (4), Type 2 diabetes mellitus (3), Coronary artery disease, Ex-tobacco user (2 each), Cerebellar stroke, Cerebrovascular accident, Cholelithiasis, Chronic kidney disease, Depression, Diabetes mellitus, Drug abuse, Food allergy, Gastroesophageal reflux disease, Glaucoma, Gout, Hyperlipidaemia, Intervertebral disc protrusion, Knee operation, Ligament rupture, Seasonal allergy, Sleep apnoea syndrome, and Substance use (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Relevant PTs (10): Hypertensive emergency, Hypertensive urgency (4 each), Accelerated hypertension and Hypertensive crisis (1 each). One event was related to BNT162b2 and 9 to blinded therapy.
- Time to event onset (n = 9):
    - <24 hours: 3 events;
    - 1 day: 1 event;
    - 2-7 days: 4 events;
    - 8-14 days: 1 event.
- Duration of event (n = 9):
    - 15-30 days: 3 events;
    - 31-181 days: 5 events
    - >181 days: 2 events.
- Relevant event outcome: resolved (9), resolved with sequelae (1).

Post-authorization data

- Number of cases: 634 (0.2% of 327,603 cases, the total cumulative PM dataset).
- Medically confirmed cases (546), Non-medically confirmed cases (88).
- Country of incidence (≥2%): France (205), Italy (133), Mexico (96), Spain (53)
- Germany (25), Austria (24), Greece (16), and UK (14).
- Subjects' gender: female (480), male (148) and unknown (6).
- Subjects' age in years (n = 621), range: 20-98, mean 62.1, median 60.
- Medical history (n = 364): the most frequently (≥2%) reported medical conditions included Hypertension (200), Hypersensitivity (28), Atrial fibrillation, Drug hypersensitivity (22 each), Asthma (17), Hypothyroidism (16), Myocardial ischaemia, Type 2 diabetes mellitus (15 each), and Dyslipidaemia (14).
- COVID-19 Medical history (n = 17): COVID-19.
- Co-suspects: enzalutamide (1).
- Number of events: 2488 (of which 635 were events of interest).
- Relevant event seriousness: serious (621), non-serious (14).
- Most frequently reported relevant PTs (≥2%): Hypertensive crisis (590), and Hypertensive emergency (20).
- Time to relevant event onset (n = 296), range: <24 hours to 25 days.
    - <24 hours: 191 events (3 of which had a fatal outcome);
    - 1 day: 37 events;
    - 2-7 days: 42 events (1 of which had a fatal outcome);
    - 8-14 days: 20 events;
    - 15-30 days: 6 events.
- Duration of relevant event (n = 155):
    - <24 hours: 38 events;
    - 1 day: 50 events;
    - 2-7 days: 54 events;
    - 8-14 days: 9 events;
    - 15-30 days: 4 events.
- Relevant event outcome: fatal (4), resolved/resolving (446), resolved with sequelae (6), not resolved (82), unknown (97). The reported cause of death in the 4 fatal cases coded to the PTs Hypertensive crisis (3), Asthenia, Cardiac arrest, Death, Haemorrhagic stroke, Hyperthermia, Lung disorder, Vaccination site inflammation, Pulmonary oedema (1 each). All these 4 fatal cases involved elderly patients. In 3 of the 4 cases, medical history was reported, and significant medical conditions included Hypertension (3) and Dyslipidaemia (1).
- When comparing the events of elderly to those of the non-elderly population, the PTs that were reported with a greater reporting rate in the elderly population were: Herpes zoster, Fall, Aphasia, Balance disorder, Speech disorder, Transient ischaemic attack and Pallor (1 case each); however, these increases in reporting proportion were associated with small number of cases in the elderly dataset and are an artifact of the small elderly dataset resulting in unstable reporting proportion.
- Number of subjects with comorbidities: 374 (0.1% of 327,827 cases, the total dataset).
- There are no differences between the group with comorbidities and the one comorbidities.

MAH's conclusion

There is no plausible mechanism to explain any sustained elevated serious hypertension caused by BNT162b2. The topic of serious hypertension has emerged as a concern for some COVID-19 vaccines and is being carefully monitored for BNT162b2. In 32% of the post-marketing cases,

events indicative of anxiety stress related reactions was co-reported and coded to the PTs Dizziness, Dyspnoea, Paraesthesia, and Tachycardia. No other safety signals have emerged based on a review of these cases and of the O/E analysis performed. No labelling change is needed at this time. Surveillance will continue.

Rapporteur assessment comment: A review of cases reporting serious hypertension is provided by the MAH. The RCT data did not report an imbalance, 5 cases in treatment group and 5 cases in placebo group. Post-marketing 634 cases were retrieved of which 546 medical confirmed. It is noted that the MAH did not perform O/E analysis because relevant background rates of hypertension could not be identified. MAH's conclusion is accepted that no safety signals have emerged based on a review of cases reporting serious hypertension.

2.2.1.6 Haemophagocytic syndrome

PRAC request 4th MSSR: The MAH was requested to provide a review of cases suggestive of Haemophagocytic syndrome (aka macrophage activation syndrome). Upon evaluation of the causative role alternative aetiologies such as genetic predisposition, viral infections (e.g. EBV, SARS-CoV2), concomitant medication should be taken into account.

Results

Search criteria: PT Haemophagocytic lymphohistiocytosis

Non-clinical data:

There was no nonclinical evidence for haemophagocytic syndrome in rats (eg, no hemophagocytosis in bone marrow or in macrophages in other tissues; no anemia).

Clinical trial data:

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

Post-marketing data:

- Number of cases: 10 (0.003% of 327,603 cases, the total cumulative PM dataset)
- MEDICALLY CONFIRMED cases (8), NMEDICALLY CONFIRMED cases (2)
- Country of incidence: France (4), Spain, US, Netherlands, Switzerland, Belgium, and Japan (1 each).
- Subjects' gender: female (4) and male (6).
- Subjects' age in years (n = 10), range: 22-98, mean 63.6, median 68.
- Medical history (n = 9): Hypertension (4), Type 2 diabetes mellitus, Diabetes mellitus, Myocardial infarction, Hypercholesterolaemia (2 each), Asthma, COVID-19, COVID-19 pneumonia, Herpes zoster, Infectious mononucleosis, Oesophageal candidiasis, Pharyngotonsillitis, Pulmonary tuberculosis, Seasonal allergy, Bone disorder, Disease progression, Metastatic malignant melanoma, Neuroblastoma, Surgery, Hip surgery, Myocardial ischaemia, Arrhythmia, Bartholinitis, Breast neoplasm, Breast cancer, Depression, Haemodialysis, Collagen disorder, Hyponatraemia, Liver disorder, Sjogren's syndrome, Systemic lupus erythematosus, Coronary artery disease, Angioplasty, Arterial catheterisation, Atrial fibrillation, Cardiac pacemaker insertion, Cardioversion, Chemotherapy, Chronic kidney disease, Chronic obstructive pulmonary disease, Continuous positive airway pressure, Coronary artery bypass, Coronary artery occlusion, Coronary artery stenosis, Device malfunction, Dyspnoea, Hospitalisation, Hypoperfusion, Implantable

defibrillator insertion, Ischaemic cardiomyopathy, Left ventricular dysfunction, Mastectomy, Mitral valve incompetence, Peripheral arterial occlusive disease, Peripheral artery angioplasty, Peripheral artery stenosis, Peripheral artery stent insertion, Radiotherapy, Sleep apnoea syndrome, Tachycardia, and Vascular stenosis (1 each).
- COVID-19 Medical history (n = 2): COVID-19 and COVID-19 pneumonia (1 each).
- Co-suspects: amoxicillin/clavulanic acid, dexketoprofen trometamol, ipilimumab, metamizole magnesium, methylprednisolone, nivolumab, paracetamol, prednisone, and tocilizumab (1 each).
- Number of events: 73 AEs, (including 10 serious AEs coded to the relevant PT Haemophagocytic lymphohistiocytosis).
- Time to relevant event onset: (n = 9), < 24 hours to 663 days, median 5.5 days
    - < 24 hours: 1 event;
    - 1 day: 1 event;
    - 2-7 days: 3 events;
    - 8-14 days: 1 event;
    - > 14 days: 3 events;
- Duration of the relevant event: (n = 1), 4 days
- Relevant event outcome: fatal (4 – PT: Haemophagocytic lymphohistiocytosis), not resolved (3), resolved/resolving (2), and unknown (1).
- Relevant Lot/Batch number: EL1491, EJ6788, EL9264, EP2163 (1 each), and unknown (6).

PT Haemophagocytic lymphohistiocytosis with a fatal outcome: 4 cases

- The case described a 26-year-old male patient who had the medical history of COVID-19 pneumonia about 3 months before he received the first vaccine dose. The patient also had the medical history of asthma, herpes zoster, infectious mononucleosis, oesophageal candidiasis, pharyngotonsillitis, pulmonary tuberculosis, and seasonal allergy, who started with symptoms of pharyngotonsillitis on day 17 after the vaccination and was treated with various antibiotics. However, his general condition aggravated on day 21 and the patient died of liver failure, refractory shock, hepatitis acute, suspected haemophagocytic syndrome, and multiple organ failure on day 24. In lung biopsy and liver post-mortem, HSV-1 was in high quantity.
- The case involved a 59-year-old female patient, with the medical history of type 2 diabetes mellitus, who experienced haemophagocytic lymphohistiocytosis on day 10 after receiving the second vaccine dose and died on the same day despite of treatments with etoposide and steroids. The patient was not diagnosed with COVID-19 before the vaccination, while COVID was tested post vaccination with an unknown result. Haemophagocytic lymphohistiocytosis reported a fatal outcome and an autopsy was not performed in this case. The investigation of this batch (Lot number: EL9264) was performed and no related quality issues were identified.
- The case described an 82-year-old male patient who had the medical history of COVID-19 before he received the COVID-19 immunization and he also had the medical history of diabetes mellitus, haemodialysis, and myocardial infarction. Concomitant medications included pregabalin, insulin, metoprolol, vancomycin, nadroparin, and dexamethasone for unspecified indications from an unknown date. The patient had no adverse events following the first vaccine dose; while he experienced haemophagocytic lymphohistiocytosis, chills, pancytopenia, inflammation, hyperpyrexia, serum ferritin abnormal, myalgia, hypertriglyceridaemia, hypotension, fatigue, malaise, and arthralgia after receiving the second vaccine dose and died due to haemophagocytic syndrome. The extensive microbiological examination showed the patient was EBV seropositive, which expressed the

severe weakening of the immune system and could be a confounding factor.

- The case described a 76-year-old male patient, with the medical history of coronary artery disease and hypertension, who experienced fever, chills, lymphadenopathy, asthenia, flu syndrome on the same day after receiving the second vaccine dose (Lot number was not reported). The patient's concomitant medications were not reported. The patient was treated with paracetamol. It was reported that "the patient, more than 1 month later, died due to macrophage activation syndrome linked to B lymphoma possibly activated / accelerated by the vaccine". An autopsy was not performed. All events coded to the PTs Haemophagocytic lymphohistiocytosis, B-cell lymphoma, Pyrexia, Chills, Lymphadenopathy, Asthenia, and Influenza reported a fatal outcome.

PT Haemophagocytic lymphohistiocytosis with a non-fatal outcome: 6 cases

- In this case, the patient had no comorbidities which is discussed under Analysis by presence of comorbidities below.
- In this case, a 43-year-old male patient had the medical history of metastatic stage IV back melanoma and the disease progression was observed before his COVID-19 immunization. The patient experienced macrophage activation syndrome (PTs coded to Haemophagocytic lymphohistiocytosis and Rash papular) 1 day after receiving the first vaccine dose. Co-suspect medications included ipilimumab and nivolumab for metastatic malignant melanoma. Corticosteroid therapy was administered and the clinical outcome of the relevant event was resolving at the time of the report.
- The case involved a 98-year-old male patient who experienced haemolytic anaemia thrombocytopenia, and haemophagocytic lymphohistiocytosis 2 days after receiving the second vaccine dose. The patient had the medical history of hip surgery, hypertension, myocardial ischaemia, and type 2 diabetes mellitus; while concomitant medications were not reported. The patient was hospitalized following the events and was under the treatment of corticosteroid and erythropoietin on an unspecified date and all event outcomes were not resolved at the time of this report.
- The case described a 90-year-old female patient suffering from macrophage activation syndrome after receiving COVID-19 immunization (unspecified dose number). The patient had poor general conditions with the medical history of arrhythmia, bartholinitis, breast neoplasm, depression, hypercholesterolaemia, and hypertension, which could possibly contribute to the relevant event. The patient was referred to palliative care given the severity of the clinical conditions and the clinical outcome of macrophage activation syndrome was not resolved at the time of the report.
- The case involved a 60-year-old female patient who was diagnosed with macrophage activation syndrome 5 days after receiving the first vaccine dose. The patient had the medical history of collagen disorder, hyponatraemia, liver disorder, Sjogren's syndrome, and systemic lupus erythematosus and her concomitant medications were not reported. The patient was hospitalized and received the treatment of methylprednisolone, human IgG, and antibiotics; while the outcome of the relevant event was not resolved at the time of the report.
- In this case, latency of the relevant event Haemophagocytic lymphohistiocytosis was unknown after the 80-year-old female patient received the first vaccine dose. The patient's death was possibly due to her multiple poor underlying conditions, such as breast cancer, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery stenosis, diabetes mellitus, myocardial infarction, vascular stenosis. Fatal events were coded to the PTs Acute kidney injury, Aphasia, Carotid artery occlusion, Cerebral ischaemia, Cerebral thrombosis, Coagulopathy, C-reactive protein increased, Hemiparesis, Ischaemic stroke,

Leukocytosis, Platelet count decreased, Pneumonia aspiration, Respiratory failure, and Thrombocytopenia; while the outcome of the relevant event Haemophagocytic lymphohistiocytosis was unknown.

Analysis by age group:

- Adults and Elderly (5 each);
    - A meaningful comparison between the different age groups is not possible due to the low number of cases

Analysis by presence of comorbidities:

- Number of subjects with comorbidities: 9 (90% of 10 cases, the total dataset).
- Among all 10 cases recording the relevant PT Haemophagocytic lymphohistiocytosis, one case involved a 22-year-old male patient with no comorbidities. In this case, the patient had no medical or family history and experienced lymphadenitis generalized, fever, and haemophagocytic syndrome (PT coded to Lymphadenitis, Haemophagocytic lymphohistiocytosis, Pyrexia, Malaise, Lymphadenopathy) 1 day after receiving the second vaccine dose (lot number: unknown). The patient was admitted to the hospital 9 days after the vaccination and all event outcomes were resolving on day 24. In 9 other cases, patients had various underlying conditions and relevant event outcomes in these 9 cases were fatal (4), not resolved (3), resolving and unknown (1 each). These 9 cases are detailed above.

Analysis by dose:

- Number of vaccine doses administered at the time of the event onset: 1 dose in 4 cases, 2 doses in 5 cases and number of doses was not specified in 1 case.

MAH's conclusion

Soy M, et al. indicated that haemophagocytic syndrome or haemophagocytic lymphohistiocytosis is an acute and rapidly progressive systemic inflammatory disorder characterized by cytopenia, excessive cytokine production, and hyperferritinemia. It may be triggered by genetic conditions, infections including COVID-19, malignancies, autoimmune-autoinflammatory diseases, and some drugs. Upon review of these 10 cases, most cases involved patients with poor underlying conditions, including viral infection (such as herpes zoster, mononucleosis, EBV, COVID-19), malignancies (such as B lymphoma, breast cancer), and/or other chronic diseases, which should be taken into account. No new significant safety information has emerged. Safety surveillance will continue.

Rapporteur assessment comment:

A review of cases reporting Haemophagocytic lymphohistiocytosis is provided by the MAH. A total of 10 cases were identified of which 8 were medically confirmed. Extensive medical history with underlying medical conditions, concomitant medications and/or other confounding factors (e.g., herpes zoster infection) were reported in 9 of the 10 cases. Although the remaining case did not report any comorbidities, limited information was available including information on possible concomitant viral infections and/or Covid-19 infection.

MAH's conclusion that no new safety information could be emerged based on the available information is accepted.

2.2.1.7 Serious arrhythmias

PRAC request 5th MSSR: the MAH was requested to perform a cumulative review focused on serious arrythmia, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable.

Results:

Post-marketing data:

Search criteria: PT arrhythmia (DLP: 18 June 2021)

Results:

The search identified 777 (774 from spontaneous reporting + 3 clinical trial) cases coded to PTs in the PT Arrythmia. Of these patients, there were 495 females and 263 males and 19 of unreported gender. The most frequent events occurred in the age demographic between 31-50 years (223 cases), followed by older than 75 years (189) 51-64 and 64-74 years (138 cases each), 18-30 years (40), a single case reported less than 17 years-old and 40 cases of an unreported age.

The most frequent PT reported was Arrythmia (100%). The most frequent co-reported PT was fatigue (18.3%), headache (14.6%), pyrexia (13.8), dizziness (12.5%, dyspnea (12.4%), tachycardia (11.5%) palpitations (10.7%), nausea (10.4%) and malaise (10%).

Out of the total 777 cases, 53 cases had a fatal outcome.

Out of the total 777 cases, 289 cases had a cardiovascular-related medical history and/or concomitant medications with a potential to cause irregular heartbeats as per the drug inserts of these medications. Medical histories of cardiovascular disorders included arrythmia, tachycardia, myocardial infarction, irregular heart rate, cardiac murmur and/or cardiac flutter. Concomitant medications included amlodipine, atorvastatin, and/or levothyroxine. These 289 cases of confounding medical history and/or concomitant medications were excluded from the analysis.

Analysis of cases without confounding factors

The remaining 488 cases (486 cases of spontaneous reporting and 2 cases from clinical trial data) occurred to females (343) followed by males (133) and 12 patients of unreported gender. The most frequent age group reporting arrhythmia was 31-50 years (181 cases), 51-64 years (89 cases), 65-74 years (71 cases), greater than 75 years (68 cases).

Of the total 488 cases, majority (255 cases) occurred after the first dose of vaccination, 131 occurring after the second injection, and for the rest, dose was not specified. 118 cases were reported on the same day of vaccination (dose sequence unspecified), 214 cases occurring from 1-7 days after vaccination with no significant association to dose sequence.

Of the total 488 cases, 151 cases did not resolve while 142 resolved, 8 resolved with sequalae and 96 still resolving cases. There were 18 cases with fatal outcome.

Of the 18 cases with fatal outcome, 15 were reported for subjects with an age included in the range 70-96 years and 3 were 45-57 years old. Nine of them males and the rest are females. One had history of COVID-19 infection, 11 have unreported medical history and the rest had a medical history that is not of cardiovascular nature including oncological (breast cancer), metabolic (diabetic), autoimmune (autoimmune pancreatitis). The countries with the most frequent reporting fatal outcome were the Netherland (4), Germany (3), France, Japan and Israel (2 each) followed by Australia and Italy (1 case each). No autopsy reports have been provided for any.

Out of the 488 cases, the most commonly co-reported PTs, were fatigue (88), headache (80), pyrexia (73) and dizziness (69).

In addition, the association of Arrhythmia with the following PTs of interest pertaining to the cardiovascular SOC has been analyzed in terms of frequency, dose sequence and latency and outcome.

PT: Tachycardia

Out of the 488 cases, there were 67 cases of Tachycardia. Of them 34 cases occurred after the first injection while 23 occurred after the second vaccine injection with the rest of the cases not specifying dose. Of these cases, 18 cases reported on the same day of vaccination and 34 occurred from day 1-7 post vaccination with the remaining cases of an unreported latency.

Out of the 67 cases with reported tachycardia, 26 were recovered/resolved, while 2 resolved with sequalae, 15 had not recovered and 13 are resolving and the rest of an unknown outcome. None of the tachycardia cases had a fatal outcome.

PT: Palpitations

Out of the 488 cases, there were 56 cases coded to the PT of palpitations. Of them, there were 28 after the first dose of vaccination, while 14 occurred after the second dose with the remaining cases not specifying dose. Of the 56 cases, 26 cases occurred from day 1-7 post vaccination while 11 occurred on the same day of vaccination, 9 cases between 8-30 days and the remaining were of an unknown latency. Of the 56, 22 were recovered/resolved, 13 were not resolved/not recovered while the remaining cases were of unknown outcome.

PT: Atrial fibrillation

Out of the 488 cases, there were 26 cases of Atrial Fibrillation. Of them, there were 14 after the first dose of vaccination, while 5 occurred the second dose while the rest were of unknown dose sequence. Of the 26 events, 18 occurred during the first 7 days post vaccination, 2 cases between 8-30 days and the remaining were of unknown latency. Eight cases were recovered/resolved, 8 cases were not recovered while the remaining cases are of unknown outcome.

PT: Extrasystoles

Out of 488 cases, there were 19 cases of Extrasystoles. 12 of them occurred in the first week, while 5 occurred between 8-30 days post vaccination, and the rest were of unknown latency. Of the 19, 11 cases occurred after dose 1, 4 after dose 2 while the remaining cases did not specify dose. Eight cases recovered, 4 were recovering/resolving, 7 not recovered/not resolved and 1 of unknown outcome.

PT: Bradycardia

Out of 488 cases, there were 6 cases of bradycardia. Four of them occurred in the first 2 day post vaccination and 1 cases of unknown latency. Of them, 4 occurred after the first dose, 1 after the second, and 1 of known sequence. One case recovered, 1 recovering/resolving, 1 not recovered, and 3 of unknown outcome.

PT Cardiac arrest

Out of the 488 cases, there were 8 cases of cardiac arrest aged between 43 to 91 years old. Five of them occurred after the first dose of vaccination, 3 after the second dose of vaccination. All of them occurred within the first week post vaccination except one case occurred after 35 day. Six cases had a fatal outcome (two stated that cause due to cardiac failure), 1 case that did not

recover and 1 of unknown outcome. One of these cases had history of COVID-19. No autopsy data were reported to any of these cases.

MAH's conclusion

The MAH has reviewed cases reported and conducted unadjusted O/E analyses for spontaneous reports on Arrythmia as of 18 June 2021 stratified by various risk windows. Serious arrythmias events, occurred in patients with an underlying heart-rhythm conduction disorder such as medical history of tachycardia, bradycardia, extrasystole, cardiac pacemaker insertion atrial flutter etc. and/or concomitant medication such as amlodipine, atorvastatin, levothyroxine in over one third of the cases reported (289 out of 777 cases). Arrythmia has not been identified as a signal and routine monitoring will continue.

Rapporteur assessment comment:

A review of cases reporting arrhythmia is provided by the MAH. A total of 777 cases were identified of which 289 had a cardiovascular-related medical history and/or reported concomitant medications that may contributed to arrhythmia. Within the assessment of the AESIs, the MAH has provided the O/E analysis for arrhythmia. The O/E ratios were well below 1 for the 14-day as well as the 21-day risk interval.

Based on the information provided by the MAH it is agreed that no new safety information has emerged.

2.2.1.8 Acute pancreatitis

PRAC request 5th MSSR: the MAH was requested to perform a cumulative review focused on serious acute pancreatitis, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable. The MAH should also make every effort to document such cases as the lack of information could preclude concluding on the causal relationship between the vaccine and pancreatitis.

Results:

Non-clinical data: There was no microscopic or macroscopic evidence of active or resolved pancreatitis in rats after administration of BNT162b2 (Studies 38166 and 20GR142).

Post-marketing data:

Search criteria: PT acute pancreatitis (DLP: 18 June 2021)

Results:

A total of 65 cases were retrieved. There were 35 females, 27 males, and for 3 cases gender was not reported. Age was reported as ranging from 19 to 98 years (mean: 63.6 and median: 58). A total of 30 cases were reported in adults (≥18<65), 32 cases were reported in elderly (≥ 65) and for 3 cases age was not reported. All cases were reported as serious.

Medical history was reported for 46 cases. Relevant medical history was reported for 28 cases: 3 cases reported alcohol use and 2 cases reported abstain from alcohol; 7 cases reported underlying pancreatitis; 1 case reported biliary colic and 1 reported cholelithiasis; 2 cases reported hypercholesterolaemia, 1 reported dyslipidaemia, and 1 reported hyperlipidemia; 2 cases reported HIV infection; 1 case reported intraductal papillary mucinous neoplasm, 1 reported neoplasm, and 1 reported renal neoplasm; 1 case reported suspected Covid-19 infection; and 4 cases reported

diabetes mellitus. Additionally, seven (7) cases reported pancreatitis in the context of other diagnoses: cholelithiasis (2), increased bilirubin (1), viral infection (1), Covid-19 infection (2), and hypertriglyceridaemia (1). Eight (8) cases reported the concomitant medications of estradiol, enalapril, paracetamol, and furosemide which may contribute to pancreatitis.

Forty-four (44) cases of pancreatitis occurred after dose 1, seventeen (17) cases after dose 2, and for four (4) cases dose information was not provided.

Of the remaining 19 cases that did not report any medical history: there were 9 females, 9 males, and for 1 case gender was not reported. Age ranged from 19 to 88 years (mean: 57.1 and median: 59.5). A total of 12 cases were reported in adults (≥ 18<65), 6 cases were reported in elderly (≥65) and for 1 case age was not reported. Eight (8) cases of pancreatitis occurred after dose 1, eight (8) cases after dose 2, and for three (3) cases dose information was not provided. Covid-19 test results were negative for 4 cases, 1 reported no history of Covid-19 infection, and for 1 case COVID-19 testing was not done. For the remaining 13 cases, no information was provided regarding Covid-19 testing or prior COVID-19 infection. Latency from vaccination to pancreatitis was provided in 15 reports and it ranged from day 0 to day 20. Outcome was reported as resolved/resolving in 32 cases, not resolved at time of reporting in 21 cases, fatal in 6 cases, and unknown in 6 cases.

Latency from vaccination to pancreatitis was provided in 58 reports and it ranged from day 0 to day 32.

Six (6) cases were fatal (summaries not reproduced here). Cause of death was reported in four (4) cases. It was unknown if an autopsy was performed in four (4) cases. In one (1) case, the doctor did not order an autopsy. In another case, an autopsy was requested by the family. All six patients were older with the age range of 69- to-92-year-old (mean 79.7 year / median 78.5 year) and five out of six had multiple comorbid conditions. Medical history was provided in all 6 fatal cases. Older age, relevant medical history and concurrent medical conditions are possible contributing factors to these fatal cases.

Literature search:

There were two literature articles found regarding BNT162b2 vaccine and pancreatitis.

Pancreatic Injury after COVID-19 Vaccine—A Case Report

This case report is about a healthy 29-year-old Caucasian female patient who experienced pancreatic injury symptoms 12 hours after the administration of first dose of BNT162b2. Twenty hours post vaccination, the patient developed severe abdominal pain. The mechanism responsible for vaccine-induced pancreatitis remains unclear and it was concluded "that the risk of serious complications after infection with SARS-CoV-2 outweighs the risk of potential mild pancreatic injury. As a result, the patient received a second dose of vaccine" without triggering a severe response.

Acute Pancreatitis: A Possible Side Effect of COVID-19 Vaccine

This case report is about a 96-year-old female patient with a past surgical history of cholecystectomy who presented with acute onset severe abdominal pain a few days after getting the first dose of BNT162b2. It was reported that "Although it is difficult to make conclusions about the likelihood of the vaccine being the etiologic factor of pancreatitis, it is essential to continue monitoring for possible under-reported side effects until we have extensive long-term data available in post-marketing surveillance for long-term and rare side effects."

Clinical trial data:

In the placebo-controlled portion of study C4591001 (data-lock date 13 Mar 2021), of 21,926 participants ≥ 16 years of age who received BNT162b2, there was 1 report of pancreatitis and 1 report of obstructive pancreatitis. Of the 21,921 participants in the placebo group, there were 2 reports of acute pancreatitis and 1 report of pancreatitis.

O/E analysis:

The O/E ratio was below 1 for the 14-day risk window and 21-day risk window, indicating there was not an increased risk of pancreatitis among recipients of the BNT162b2 vaccine.

Table 1. Observed versus Expected (O/E) Analyses of Select Clinical Trial and Spontaneously Reported Adverse Events of Special Interest (AESI), Cumulative Period

AESI	Background Rate per 100,000 Person Years (PY)	Observed Cases	14-Day Risk Window[a]			21-Day Risk Window[b]		
			Expected Cases	O/E Ratio	95% CI	Expected Cases	O/E Ratio	95% CI
Pancreatitis	33.74[c]	71	6.192	0.011	0.009, 0.014	8.917	0.008	0.006, 0.010

a. PY = 18,351,656
b. PY = 26,429,571
c. Xiao AY, Tan MLY, Wu LM, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1(1):45–55.

MAH's conclusion

Pancreatitis has been spontaneously reported following vaccination with BNT162b2 in the post-authorization setting. Of the total 65 cases as of 18 Jun 2021, 27 reported relevant medical history of alcoholism, pancreatitis, biliary pathologies, hypercholesterolaemia, HIV infection, intraductal papillary mucinous neoplasm, suspected COVID-19 infection, and diabetes mellitus possibly contributing to the development of pancreatitis. Additionally, seven (7) cases reported pancreatitis in the context of other diagnoses: cholelithiasis, increased bilirubin, unspecified infections, COVID-19, and hypertriglyceridaemia. Eight (8) cases reported the concomitant medications which may also contribute to pancreatitis. Four cases of pancreatitis were reported on the same day; 1 case within 5 minutes and 3 cases within few hours. Sixteen cases reported negative COVID-19 test results, three cases reported positive COVID-19 test results, while, majority of cases did not provide COVID-19 testing.

The totality of the reviewed information does not support a causal association between the vaccine and pancreatitis for the following reasons: there is not a clear mechanism of action to explain why vaccinated individuals may have an increased risk for pancreatitis and there is a distinct lack of literature linking any vaccination to the occurrence of pancreatitis, there are a relatively low number of reports of pancreatitis in the context of about 642 million of BNT162b2 doses administered in the post-authorization setting and no imbalance in reporting of pancreatitis between vaccine and placebo groups in Study C4591001. The benefit risk profile of the vaccine remains favorable. Routine signal detection activities will continue.

Rapporteur assessment comment:

As requested in the 5th MSSR, the MAH has provided a cumulative review regarding acute pancreatitis. In the clinical trial, 2 reports of (obstructive) pancreatitis were identified in the BNT162b2 arm and 3 reports of (acute) pancreatitis in the placebo arm. A total of 65 post-marketing cases were identified of the majority reported relevant medical history, were reported in the context of other diagnosis, or reported concomitant medications that may have contributed to pancreatitis.

Two literature cases were described of which one describes occurrence of pancreatitis after the first dose, without rechallenge after second dose. The other literature case describes a 96-year-old female patient with a past surgical history of cholecystectomy.

The O/E ratios were well below 1, although these were not accounted for the backlog.

Given the lack of imbalance in the clinical study, information provided on the post-marketing cases and the results of the O/E analysis, it is agreed with the MAH that the available information concerning acute pancreatitis does not suggest a safety issue for Comirnaty. The MAH should continue to monitor cases reporting acute pancreatitis as part of their routine pharmacovigilance practices.

2.2.1.9 Acquired haemophilia

PRAC request 5th MSSR: it was stated that several cases of Acquired haemophilia have been reported: 3 in France and 1 in Ireland. In the literature, 1 case has also been described at day 9 of vaccination with Comirnaty vaccine in a 69-year-old patient. Four other cases have also occurred in other countries (global data via Vigibase, as well as UK data via Vigibase). Considering that this is a very rare and serious event, and that the role of the vaccine in the occurrence of these autoantibodies to factor VIII ("acquired haemophilias") cannot be excluded, the MAH is requested to review this in the upcoming PSUR.

Results

Non-clinical data: There was no evidence of clotting or coagulation disorders identified in the non-clinical toxicity studies in rats.

Post-marketing data

Search criteria: HLT coagulation factor deficiencies (DLP: 18 June 2021)

Results:

A total of 11 cases were retrieved. 9 were spontaneous reports and 2 were from non-interventional studies, with all 11 cases assessed as serious. Gender was reported in all cases (6 males and 5 females). Ten of the 11 cases reported an age, ranging from 67 years to 90 years (mean: 78, median: 80).

All the cases were medically confirmed. Six of the 11 cases occurred after the first dose, 3 cases reported onset after the second dose while the date of vaccination was not reported in the remaining 2 cases. Case outcome was reported as follows: 5 recovering/recovered, 4 not recovered, and 2 fatal cases.

The fatal cases are described below:

- A 90-year-old female patient received the first dose of BNT162b2 on 25 February 2021. Her medical history included hypertension, aortic stenosis, heart failure, gout, and chronic renal failure. Concomitant medications included zopiclone, bisoprolol, furosemide, allopurinol and paracetamol. On 11 March 2021 the patient experienced atrial fibrillation, decreased hemoglobin, hematoma, oral mucosa bleeding, malaise, increased tendency to bruise, acquired hemophilia A and aggravated cardiac failure. Positive Anti-factor VIII antibody was reported. The patient was hospitalized due to the events. Treatment with corticosteroid (prednisolone 40 mg/l) was initiated. On 17 April 2021 the patient experienced worsening heart failure, atrial

fibrillation and kidney problem. On 24 May 2021 the patient was reported dead, with no further information expected.

- A 67-year-old male patient was reported to have received vaccine at unknown dates. His past medical history included rheumatoid arthritis, Crohn's disease, pulmonary legionellosis, and obesity. Concomitant medications include Durogesic, prednisone, Spiriva, indacaterol and Pentasa. On 18 May 2021, patient experienced a fall, with diffuse hematomas. Three days later he was brought to the emergency room due to a deteriorating general condition and vomiting and was assessed to have hemorrhagic shock associated with acute renal failure and acquired hemophilia type A (antifactor VIII reported) and was hospitalized. One day after hospitalization the patient experienced sudden deterioration with onset of coma, and the following day he died from cardiorespiratory arrest.

The remaining 9 cases are summarized below:

- A spontaneous report about a 69-years-old male patient who received 1st dose of vaccine on 28 December 2020. Medical history included prostate cancer in remission, high blood pressure, and diabetes. Concomitant medication included carvedilol, leuprorelin, abiraterone, Osteocare, metformin. The patient experienced development of autoantibody to FVIII (AHA) on 05 January 2021. Prednisolone was given as treatment. Outcome of the event was recovering.
- A spontaneous report regarding a 77-year-old male patient who received the first dose of vaccine on 30 January 2021. Medical history included hematoma, cancer, and possible urological mass. 30 days after vaccination, he experienced acquired hemophilia A with antifactor VIII. Information from the case report indicates that although the diagnosis is soon after COVID-19 vaccination, the antibody titer was very high and may suggest that this predated the vaccine. Patient was treated with blood transfusion, hemostatic treatment (FEIBA), high dose steroids and rituximab. The outcome was reported as not recovered.
- A spontaneous report about an 84-year-old female patient who received second dose of BNT162b2 on 19 March 2021. Medical history included acute coronary syndrome. Patient was hospitalized 12 days later with diagnosis and treatment of pruritus with prurigo and eosinophilia said to be evolving since January 2021. The patient experienced AHA with anti-factor VIII on an unspecified day in March 2021. The patient reported a major bleeding episode following a cut of the finger 10 days earlier. Continuation of topical corticosteroids was initiated during hospitalization. The outcome was reported as recovering.
- A non-interventional study report received about a patient who received 1st dose of vaccine at an unknown date. Medical history and concomitant medication were not reported. An attached hematological report included diagnosis of "acquired hemophilia with large hematoma of the left arm started at the time of vaccination" with the examination conducted on 16 March 2021. Outcome was not reported.
- A spontaneous report about a 78-year-old male patient who received first dose of BNT162b2 on 17 March 2021. Patient medical history included stented ischemic heart disease, hypertension with nephroangiosclerosis. Concomitant medications included atenolol, perindopril, simvastatin, tamsulosin. It was reported that patient had experienced sudden onset of lower right limb hematoma without trauma or fall, 4 days after vaccination. AHA was confirmed through laboratory diagnosis on 08 April 2021. Treatment was with Endoxan and corticoids. Outcome was reported as not recovered at time of report.
- A male patient of an unspecified age received his second dose of BNT162b2 on 03 March 2021. Medical history included gastro-oesophageal reflux disease. Concomitant medications were not reported. On 02 April 2021, the patient presented with hematuria. It was reported that on an unspecified date prior to this, patient also noted prolonged bleeding from superficial wounds, therefore he may have developed acquired hemophilia prior to presentation. The outcome of

AHA was reported as not recovered.

- An 82-year-old female patient received her first dose of BNT162b2 on 02 March 2021. Medical history included arterial hypertension, thyroid gland hypofunction. Concomitant medications included hydrochlorothiazide, telmisartan, nitrendipine, levothyroxine sodium. On 12 March 2021, the patient was diagnosed with right shoulder joint bleeding. A high titer of coagulation factor VIII inhibitor was detected. Time interval between vaccination and start of event was 10 days. After approximately three weeks since the first dose, the patient was vaccinated with the second dose, and the reaction did not reoccur. The outcome of event was reported as recovering.
- A non-interventional study report about an 84-years-old female patient who received her second dose of BNT162b2 on 08 April 2021. The patient's medical history and concomitant medications were not reported. Two days after vaccination the patient experienced acquired hemophilia A (autoantibodies anti-coagulation factor VII detected), spontaneous, superficial and deep hematomas and significant anemia. Immunosuppressive therapy was started with methylprednisolone, cyclophosphamide, Novoseven and vitamin K. Blood transfusions were performed for several episodes of acute anemia. The outcome of events was recovering.
- A spontaneous report about a 72-year-old male patient who received BNT162b2 on 15 April 2021. Medical history included radiotherapy, prostate carcinoma, hypertension and diabetes mellitus. The patient's concomitant medications were not reported. Seven days after vaccination, the patient presented to their General Practitioner with bruising, which became more extensive and was accompanied by a significant hemoglobin drop. The patient was admitted on 10 May 2021, and a diagnosis of AHA was made after lab investigation. The patient was treated with prednisolone, FEIBA, and one unit of red cell concentrate. At the time of reporting, the outcome was not recovered.

O/E analysis

Table 3. Observed versus Expected Analyses of Clinical Trial and Spontaneously Reported Adverse Events of Special Interest, Cumulative Period

			Risk Period/(Patient Years at Risk)					
			14 Days (18,351,656 PY)			21 Days (26,429,571 PY)		
	Background rate 100,000 PY	Observed cases	Expected Cases	O/E Ratio	95% CI	Expected Cases	O/E Ratio	95% CI
Acquired hemophilia	0.15	10	27.2	0.363	0.174, 0.668	39.1	0.252	0.121, 0.464

The ratio of observed to expected cases does not exceed 1 over either risk window.

MAH's conclusion

A review of Acquired hemophilia A was conducted, prompted by ANSM Update on COVID-19 vaccine monitoring published on ANSM website on 21 May 2021. This included a review of literature and post-marketing data.

Recent reports have shown rare instances of AHA following COVID-19 infections. This is thought to be due to COVID-19 induced dysregulation and formation of autoantibodies against FVIII. There is growing evidence associating COVID-19 infection with hematological and non-hematological autoimmune disease.

Although there was one report of AHA following COVID-19 vaccination, there is insufficient literature to suggest a signal or a plausible biological mechanism of AHA following vaccination, and the authors acknowledge that it is more likely to be a coincidence.

The search of the safety database identified 11 cases, all reported as serious. Seven of the 11 reports included details in the medical history regarding medical conditions and diseases under treatment that could predispose to AHA (cancer, rheumatoid arthritis, chronic kidney failure, nephroangiosclerosis, diabetes mellitus and hypothyroidism). One case reported pruritus evolving long before the administration of the vaccine, and the two cases from non-interventional studies had insufficient information on patient's medical history, background diseases, and concomitant medications. In the remaining case, it is unclear whether there was a history of prolonged bleeding prior to vaccination.

In aggregate, all the cases (except 1 case with age not reported) occurred in elderly patients greater than 65 years, who are the most predisposed to AHA, with the majority of these patients having associated comorbidities.

The ratio of observed to expected cases did not exceed 1 over either risk window for either endpoint.

Overall, the analysis does not support a causal association between vaccination and acquired hemophilia. Routine monitoring will continue.

Rapporteur assessment comment:

As requested in the 5th MSSR, the MAH has provided a cumulative review regarding acquired haemophilia. The MAH identified 11 cases reporting the PTs included in the HLT coagulation factor deficiencies. In all of the cases, medical history may have confounded the occurrence of the event, limited information was available or TTO was not supportive.

The O/E ratios were below 1, although these were not accounted for the backlog. Also, no age stratified O/E analysis were presented.

Based on the information provided on the cases, it is agreed with the MAH that the available information concerning acquired haemophilia does not suggest a safety issue for Comirnaty. Closure of this safety signal is accepted. The MAH should continue to closely monitor cases reporting acquired hemophilia as part of their routine pharmacovigilance practices.

2.2.1.10 Menstrual disorders

PRAC request 5th/7th MSSR: a number of queries have been received about menstrual disorders, especially menorrhagia. This issue merits further investigation in the upcoming PSUR which, may be a matter of concern for young women, a review is expected in the upcoming PSUR.

The preliminary PRAC AR of the 7th SMSR (01 June 2021 – 30 June 2021) included this additional request:

In accordance with the LoQ of the 5th MSSR, the MAH will provide a review on Menstrual disorders in the PSUR to be submitted in August 2021. The MAH is requested to include in this PSUR review a separate 'post-marketing cases evaluation' of the cases reporting a menstrual disorder, which should also include a sub-analysis of cases divided between post-menopausal cases and menstrual disorder cases. Causality assessment should be provided per case for at least the serious cases. SmPC and/or RMP changes with regards to menstrual disorders should also be discussed, supported with clinical data and data from literature. In addition, an O/E analysis, with sensitivity analysis to compensate for backlog cases, for Menstrual disorders, including an age-stratified analysis which separates females of childbearing age from post-menopausal aged women, should also be performed by the MAH. The MAH should use a cut-off date after the DLP of the PSUR, as

accurate as possible, in order to provide properly above requested data in the PSUR.

Rapporteur assessment comment: The current cumulative review submitted by the MAH regarding menstrual disorders was also submitted within the 8th MSSR (July 2021 data). Please refer to procedure EMEA/H/C/005735/MEA/002.7 for assessment concerning menstrual disorders in the 8th MSSR, which concluded no new safety concern.

2.2.2 Evaluation of Closed Signals During the Reporting Interval not Assessed as part of any Regulatory Procedure

Signals that were evaluated and closed as refuted during the reporting interval are updated to the end date of the PSUR reporting period and summarized below.

2.2.2.1 Signals determined to not be risks

2.2.2.1.1 Seizure

Evaluation

i) Source

Seizure was triggered as a safety signal as a result of a) a PRAC request for review of topic for the monthly SMSR, b) a request by the Saudi Arabia HA to review this topic as a safety signal, and c) request by the MHRA to review this as a safety topic. An evaluation was included in the 5th SMSR. The evaluation concluded that a causal association between the COMIRNATY vaccine and seizure could not be established, and that it would continue to be monitored.

ii) Data

Cumulatively (through 18 June 2021) there were a total of 1879 cases from the MAH safety database that reported events contained in the MedDRA SMQ (v. 24.0) "Generalised convulsive seizures following immunisation", narrow search. The most frequently reported PTs (> 9 %) were as follows:

SOC	Preferred Term	n/ (%)
Nervous system disorders	Seizure	1174/ (62.48%)
Nervous system disorders	Epilepsy	424/ (22.57%)
Nervous system disorders	Headache	318/ (16.92%)
General disorders and administration site conditions	Pyrexia	277/ (14.74%)
General disorders and administration site conditions	Fatigue	203/ (10.80%)
Nervous system disorders	Dizziness	193/ (10.27%)
Nervous system disorders	Loss of consciousness	192/ (10.22%)
Nervous system disorders	Generalised tonic-clonic seizure	175/ (9.31%)

Most cases were reported from the UK (25.7% [482)]), followed by the US (15.1% [284]), Mexico (8% [150]), France (6.5% [122]) and Japan (6.3% [119]).

There were 1107 females, 698 males and for 74 subjects the gender was not reported. Age ranged between 1 to 107 years with a mean age of 50.7 years. There were 46 subjects ≤ 17 years of age, 1144 subjects from 18 to 64 years and 519 subjects 65 years and above. In 170 subjects the age was unknown.

In 1464 cases the relevant event was reported after a single dose, as follows: after Dose 1 in 944 cases, after Dose 2 in 519 cases and after Dose 4 in 1 case. In 42 cases the relevant event was reported after both vaccine doses.

Time to onset of the relevant event was reported as follows: unspecified time following vaccination (1115 cases), ≤ 1 day (565 cases), 1 to 7 days (24 cases), >7 days to < 1 month (23 cases), > 1 month to < 6 months (14 cases) and unknown (664 cases). In 112 cases the event was reported pre-therapy.

In 337 cases a nervous system disorder was reported as a medical history including 1050 events. Most frequently reported was epilepsy (or related events) (398), a form seizure (156), a dementia type disorder (84), a cerebrovascular accident or disorder (57), and stroke-type of events (54).

The O/E analyses (cumulative through 18 June 2021) of clinical trial and spontaneously reported seizures/convulsion/seizure disorders (inc. febrile) was 0.099 (95% CI: 0.094, 0.104) for the 14-day risk window and 0.069 (95% CI: 0.065, 0.072) for the 21-day risk window.

Statistical signal detection in the safety database has not shown a signal of disproportionate reporting for Seizure.

Overall, based on review of the totality of the available information (through 18 June 2021), the conclusions of the previous in-depth evaluation of seizure remain unchanged in that there is insufficient evidence to establish association between the vaccine and seizure and related events. The event will continue to be monitored and re-evaluated as warranted. The benefit risk profile of the vaccine remains favourable.

Rapporteur assessment comment:

The signal of seizure was evaluated in the 5th MSSR (DLP: 13 March 2021) and it was concluded that the signal could be closed without further actions. Within the current PSUR, an update of the data with DLP 18 June 2021 was provided. A total of 1879 cases were identified using the SMQ Generalised convulsive seizures following immunisation. Of these, 1174 cases were related to seizure, followed by epilepsy in 424 cases, and headache in 318 cases. In 337 of the cases, medical history of a nervous system disorder was reported.

O/E analyses were well below 1 for the 14-day and 21-day risk window, although not accounted for the backlog.

Given the data previously provided and the O/E analyses being well below 1, the conclusion of the MAH is accepted that no new significant safety information has emerged.

2.2.2.1.1 Thromboembolic events

i) Source

This signal was extensively reviewed in the 4th SMSR (01 March 2021 –31 March 2021) and concluded not to be a risk caused by BNT162b2. It should be noted that the major types of thromboembolic events, such as stroke (ischemic and hemorrhagic), myocardial infarction and pulmonary embolism are AESI and are each reviewed independently.

ii) Data

The MedDRA version 24.0 search strategy used was: SMQ Embolic and Thrombotic Events (narrow).

In the placebo-controlled Phase 2/3 portion of Study C4591001 (data-lock date 13 March 2021), the table below shows subjects who reported thromboembolic events. Overall, there was no significant imbalance in these events between the vaccine and placebo groups.

Thromboembolic Preferred Term	Subjects receiving BNT162b2 (N = 21,926)	Subjects receiving Placebo (N = 21,921)
Acute myocardial infarction	3	2
Myocardial infarction	0	4
Amaurosis fugax	0	1
Retinal artery occlusion	0	1
Vascular stent occlusion	1	0
Cerebrovascular accident	3	0
Ischaemic stroke	1	1
Transient ischaemic attack	2	0
Cerebellar infarction	0	1
Cerebral infarction	0	1
Haemorrhagic stroke	0	1
Penile vein thrombosis	0	1
Pulmonary embolism	3	5
Deep vein thrombosis	5	3
Source: Data from Interim Clinical Study Report Protocol C4591001		

The safety database was searched for BNT162b2 reports using the above search strategy cumulatively through 18 June 2021. There were 9088 cases reported, 106 from clinical studies, 8966 from spontaneous sources, 13 from other solicited sources and 3 from medical literature. Two percent of the cases were non-serious and 98% were serious. Of the 9088 cases, 5874 were from sources considered medically confirmed (e.g., HCP or regulatory agencies), and 3214 were not medically confirmed.

The cases were comprised of 5162 (56.8%) females and 3723 (41.0%) males. Three of the cases were reported in very young paediatric subjects (7 days, 5 months and 15 months). These cases were individually reviewed.

1. A [redacted]-old infant report described a [redacted] born to a mother who had received vaccine approximately 1 month before [redacted] birth. The [redacted] was reported to have been diagnosed with a left sylvian stroke < 3 days after delivery, however the circumstances of the pregnancy and delivery are not reported.
2. A 5-month-old breastfeeding boy whose mother received dose 2 the day before, developed a rash, refusal to eat, fever and elevated liver enzymes and was diagnosed with TTP. The child died an unspecified time later and no further information was provided.
3. Five (5) days following vaccination of [redacted] mother with dose 1, a [redacted]-old breastfeeding [redacted] was noted to have decreased movement of [redacted] left hand and a downward turning of the left corner of [redacted] mouth. An extensive workup including brain MRI/MRA, abdominal ultrasound, echo and EEG failed to find an explanation. [redacted] was diagnosed with a TIA. Thrombocytopenia was also reported but no platelet count provided. The outcome of the hand and corner of the mouth was unknown while the other events resolved.

Excluding these 3 reports from age calculations, the remaining ages ranged from 13 to 102 years

(mean 67.8, median 72). The youngest vaccinated person was a 13-year-old girl who reported "warm spots" on various areas of her arms and legs at an unspecified time after dose 1. She also complained of forgetfulness. There were no details to support the presence of a thromboembolic event in this individual.

Countries reporting >10% of the cases were: UK (1480, 16.3%), US (1291, 14.2%) and France (1177, 13.0%). The remaining countries in decreasing order of reports were Germany, Italy, Netherlands, Spain, Sweden, Japan and Norway. Case outcomes were fatal in 986 (10.8%) cases, unknown in 1341 (14.8%), not resolved in 2607 (28.7%) and resolved/resolving/resolved with sequela in 4154 (45.7%).

The 9088 cases contained 32,543 adverse events. The thromboembolic events most commonly reported were: Pulmonary embolism (19.6% of all AEs in the 9088 cases), Cerebrovascular accident (13.4%), Deep vein thrombosis (13.3%), Thrombosis (11.4%), Myocardial infarction (7.1%), Transient ischemic attack (5.8%), Ischaemic stroke (4.7%), Cerebral infarction (4.5%), Hemiparesis (3.8%), Thrombophlebitis superficial (2.3%) and Hemiplegia (2.0%).

The table below shows the thromboembolic events with an elderly to non-elderly occurrence ≥1.

Thromboembolic event: (Preferred Term)	Number of cases with PT in Elderly	Number of cases with PT in non-Elderly
Splenic infarction	10	4
Acute myocardial infarction	189	87
Coronary artery stenosis	11	5
Intracardiac thrombus	16	7
Myocardial infarction	405	196
Amaurosis	3	1
Retinal artery thrombosis	7	1
Retinal vascular occlusion	2	1
Retinal vascular thrombosis	11	5
Intestinal ischaemia	15	3
Vascular stent thrombosis	4	1
Hepatic infarction	4	1
Portosplenomesenteric venous thrombosis	3	1
Arteriovenous fistula thrombosis	3	1
Basal ganglia infarction	4	1
Basal ganglia stroke	4	1
Basilar artery occlusion	4	1
Basilar artery thrombosis	10	3
Carotid artery occlusion	14	4
Carotid artery stenosis	9	2
Carotid artery thrombosis	12	3
Cerebellar stroke	5	2
Cerebral artery embolism	14	5
Cerebral artery occlusion	10	3
Cerebral artery thrombosis	13	3
Cerebral infarction	335	57
Cerebral ischaemia	55	15
Cerebral small vessel ischaemic disease	2	1
Cerebral thrombosis	60	27
Cerebrovascular accident	808	325
Cerebrovascular disorder	19	2
Embolic cerebral infarction	9	2
Embolic stroke	33	6
Haemorrhagic stroke	56	11
Haemorrhagic transformation stroke	8	1
Hemiplegia	114	60
Ischaemic cerebral infarction	49	9
Ischaemic stroke	356	73
Lacunar infarction	16	6
Paraplegia	6	2
Quadriplegia	5	1
Thalamic infarction	11	3
Thalamus haemorrhage	5	1
Thrombotic stroke	13	3
Transient ischaemic attack	362	142
Vertebrobasilar stroke	2	1
Renal artery thrombosis	2	1
Pulmonary artery thrombosis	10	2
Pulmonary embolism	1181	524
Thrombolysis	2	1
Arterial occlusive disease	11	6
Arterial thrombosis	16	7
Deep vein thrombosis	731	414
Embolism arterial	7	1
Haemorrhagic infarction	4	1
Infarction	21	3
Ischaemia	14	4
Obstructive shock	2	1
Pelvic venous thrombosis	14	6
Peripheral embolism	12	5
Peripheral ischaemia	16	6
Vena cava thrombosis	6	3
Venous thrombosis limb	70	32

iii) Outcome

The well controlled and randomized clinical trial did not demonstrate a signal for thrombotic events causally associated with the vaccine. As expected, the thromboembolic events that are most common in the worldwide population (e.g., PE, DVT, MI, stroke) are the events most often

reported. Likewise, many common adverse events can be expected to occur coincidental to vaccination by chance alone. Many thromboembolic events are also AESI and, as such, they are monitored closely and are subject to more specific review and evaluation (e.g., MI, Stroke, PE, DVT). Less commonly reported embolic and thrombotic events are monitored routinely and specifically when co-reported with thrombocytopenia, as part of surveillance for TTS. Based on this review, thromboembolic events are not identified as a causally associated risk for BNT162b2.

Rapporteur assessment comment:

The signal of thromboembolic events was assessed within the 4th MSSR. It was concluded that based on the data that was available at that time no new safety concern was identified. Within the current PSUR, the MAH presented a further numerical update of the review with very limited information on the cases. However, since the thromboembolic events of myocardial infarction, stroke, pulmonary embolism, and deep venous thrombosis are being closely monitored in the MSSRs and all TTS cases are under close scrutiny in the MSSRs, this is considered acceptable at the moment. Also, given that the elderly and individuals with comorbidities were given priority in the vaccination campaign, it is not unexpected that these events are being reported.

2.2.2.1.3 Delayed skin reaction

i) Source

The safety topic was identified through scientific literature and per the MHRA question on 06 March 2021: "We have become aware of some reports internationally of delayed onset skin reactions with the mRNA vaccines. Having reviewed our own data there is only a limited amount of cases with an onset 7 days or more from vaccination, however, it would be helpful to have an idea of whether there is any further data from Pfizer/BioNTech which would be relevant to this, including any spontaneous reporting of delayed onset skin reaction or relevant AEs from the clinical trials with a delayed onset."

ii) Data

Delayed skin reactions were not a safety signal identified in the controlled clinical studies for BNT162b2.

The spontaneous BNT162b2 reports were searched cumulatively through 18 June 2021 for PTs within HLT Vaccination site reactions and latency per event reported from day 4 to day 8 post any dose. There were 1283 cases retrieved.

These 1283 cases that resulted from the search were reported from day 4 to day 8 post any dose.

The most commonly co-reported PTs in these cases were reactogenicity related events (e.g., Headache, Fatigue, Myalgia, Pyrexia, etc.).

When reported, the relevant events occurred post dose 1 in 576 cases and post dose 2 in 196 cases.

The AE duration per relevant event was not reported for events in 1094 cases. When reported, the duration was: from hours to 2 days for events in 74 cases, from > 2 days to 7 days for events in 99 cases, and >7 days to 31 days (1 month) for events in 20 cases; and longer than 1 month for events in 1 case.

When reported, the most commonly reported clinical outcome per the relevant event was Resolved/Resolving in 635 cases.

Based on the data reported, considering millions of doses of the vaccine administered, the majority of delayed skin reactions that occurred from 4 to 8 days after dosing, delayed skin reactions is not a signal at this time. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

Rapporteur assessment comment:

Please refer to regarding Erythema Multiforme (EPITT 19721) to procedure EMEA/H/C/005735/SDA/034 in which erythema multiforme was added as an ADR in section 4.8 of the Comirnaty SmPC.

In the 5th MSSR (April 2021 data) MAH's conclusion was endorsed that the available information concerning delayed skin reactions does not support new safety information and that the MAH continue to monitor delayed skin reactions. Based on the presented updated data through 18 June 2021 there is no new safety information identified concerning delayed skin reactions.

2.2.2.1.4 Delayed syncope

i) Source

The signal of delayed syncope was reviewed in the 3rd SMSR based on a request from FDA CBER.

ii) Data

Clinical Trial C4591001, the Pfizer clinical database was searched for BNT162b2 adverse event reports from the safety data package (DLP 14 November 2020) used for the EUA, which is the last source of unblinded information available, containing PTs Loss of consciousness and Syncope (MedDRA v 23.1). Events that occurred on the day of vaccination (Day 1) were excluded as they are likely related to the vaccine or the blood draw procedure and do not address the question of delayed Syncope. Instead, events occurring between Day 2 and beyond after vaccination Dose 1 or 2 were identified. The data were analyzed as occurring between Day 2 to Day 7 and after day 7 for completeness.

The spontaneous BNT162b2 reports were searched cumulatively through 18 June 2021 for PTs Syncope and Loss of consciousness (LOC). There were 4930 cases retrieved. Cases with latency of 1 day and later were the focus of the review. This resulted in a total of 2390 cases. There were a total of 1430 cases reporting Syncope and 1137 cases reporting LOC (some cases reported both PTs). When reported, the relevant events occurred post dose 1 in 1176 cases and post dose 2 (with a latency of 1 day or later after dosing) in 852 cases.

The most commonly co-reported PTs in these cases were reactogenicity related events (e.g., Dizziness, Headache, Nausea, Pyrexia, etc.).

For the events of Syncope and LOC regardless of which dose of vaccine was received, the following is a breakdown on a total number of cases with Latency per the relevant event reported as 1 day and later:

- 1 day: 1465 cases;
- Days 2-5: 560 cases;
- Days 6-10: 167 cases
- Days 11-31: 174 cases;
- After day 31: remaining cases.

The largest of these datasets (latency 1 day = 1465 cases) was further analyzed for information on AE duration and AE outcome: the largest set was for unknown duration of the relevant event (in 1121 cases). The most commonly reported outcome was reported as resolved/resolving for relevant AEs in 1100 cases.

iii) Outcome

Based on the data reported, the majority of reports of syncope and loss of consciousness were reported one day following vaccination. Considering the totality of data, the signal of delayed syncope does not appear to be a risk and a causal association between the vaccine and these events cannot be confirmed. Routine PV monitoring will continue, and the signal will be re-opened if new relevant information becomes available.

Rapporteur assessment comment:

In the 3rd MSSR (February 2021 data) the signal delayed syncope was closed due to that a causal association between the vaccine and these events could be confirmed. Note that the results of the clinical trial analyses are not separately presented by the MAH. However, based on the presented data through 18 June 2021 there is no new safety information identified concerning delayed syncope.

2.2.2.1.5 Eye pain and eye swelling

i) Source

The safety topic was reviewed following a request by the PRAC in the Assessment Report of the 1st SMSR (01 December 2020 through 31 December 2020) to assess if cases of eye swelling and eye pain were reported as single AEs or in the context of hypersensitivity reactions.

ii) Data

The safety database was searched for all reports using MedDRA 24.0 for the following search criteria: PTs: Eye pain, Eye swelling through 18 June 2021. The search criteria retrieved 2564 cases. There were 2007 females and 477 males and 80 cases where gender was not reported. Age ranged between 12 years to 100 years (mean: 47.4). Medical history was reported for 1419 cases. The vast majority of cases reported eye pain and/or eye swelling in the context of allergic reaction, anaphylaxis and/or angioedema. Many cases reported were co-reported with different reactogenicity events as pyrexia, headache, pain, swelling. A few cases reported eye pain and/or eye swelling associated with high blood pressure, facial paresis and/or paralysis, dermal filler reaction or associated with conjunctivitis.

iii) Outcome

Overall, no new safety signal has been identified. Eye swelling is considered listed in the context of angioedema/allergic reaction/anaphylaxis. The analysis of this safety topic does not suggest a causal association as an independent event with BNT162b2 vaccine and no changes to the CDS are warranted.

Rapporteur assessment comment:

In the 2nd MSSR (January 2021 data) the signals eye pain and eye swelling were closed because the cases reporting eye pain and/or eye swelling did not suggest a causal association with Comirnaty.

Regarding dermal filler reactions, in the procedure EMEA/H/C/005735/SDA/023 - reaction to dermal fillers (EPITT ref. 19674) section 4.8 of the Comirnaty SmPC was updated with "Facial swelling" in the ADR table, including the footnote "Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase".

Based on the presented updated post-marketing data through 18 June 2021 there is no new safety information identified concerning cases reporting eye pain and/or eye swelling.

2.2.2.1.6 Herpes zoster (including ophthalmic HZ)

i) Source

The topic of herpes zoster including ophthalmic herpes zoster has been closely monitored through the clinical studies and in the post-authorization period. In April 2021, Swiss Medic requested a review of the topic and discussion as to whether product information needed to be adjusted.

ii) Data

The spontaneous BNT162b2 reports in the safety database were searched cumulatively through 18 June 2021 using the MedDRA version 24.0 for the following PTs: Herpes zoster; Herpes zoster infection neurological; Varicella zoster virus infection; Herpes zoster cutaneous disseminated; Herpes zoster oticus; Ophthalmic herpes zoster; Herpes zoster reactivation. There were 3450 cases retrieved.

Age ranged from 19 to 103 years (mean. 62.7 years). There were 2251 females, 1047 males and in 153 cases in which gender was not reported. Time to onset ranged between the day of vaccination up to 109 days after vaccination. Duration, when reported, ranged between 1 day up to > 3 months after vaccination.

A total of 1578 cases did not provide any medical history. Of the remaining subjects, relevant medical history was reported for 1033 cases and included various conditions that may suppress or negatively affect one's immune status: previous herpes zoster infection, varicella infection, immunodeficiency, auto-immune diseases (diabetes, rheumatoid arthritis, hypothyroidism, cancer, previous confirmed or suspected COVID-19 infection). Case outcome was reported as resolved/resolving/resolved with sequel in 1657 cases, not resolved at the time of reporting in 1204 cases, unknown in 583 cases and fatal in 6 cases. In none of the fatal cases was the cause of death attributed to HZ infection or reactivation.

A signal of disproportionality (EB_{05}>2) was not noted during the weekly routine signal detection for BNT162b2 and herpes zoster.

iii) Outcome

In most cases, the information reported was not sufficient to perform a meaningful assessment and most cases did not report any performed evaluation to confirm the diagnosis. There were no signals of disproportionality for herpes zoster in routine signal detection. The upper limit of the 95% confidence interval for the O/E ratio did not exceed 1. An estimated 642 million of doses of BNT162b2 were administered globally through 18 June 2021.

In the final AR of the 7th SMSR (01 June 2021 – 30 June 2021), the MAH was requested to provide an updated age-stratified O/E analysis of Herpes zoster, with a sensitivity analysis to account for the backlog cases. The MAH is also requested to discuss possible mechanism that could underpin Herpes zoster reactivation following vaccination (MS1/MS4).

The MAH finds that there were 3426 processed cases (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*) and 766 unprocessed cases that comprise the PTs utilized for the observed number of herpes zoster cases (Herpes zoster, Ophthalmic herpes zoster, Herpes zoster reactivation, Herpes zoster infection neurological, Herpes zoster oticus, Herpes zoster cutaneous disseminated, Varicella zoster virus infection), for a total of 4192 cases used in the sensitivity analyses. Applying a background rate of 414.21/100,000 PY (Study C4591004), and assuming PY= 26,429,571, the O/E during a 21-day risk window remains less than <1 (O/E = 0.038, 95% CI [0.037, 0.039]). Age-specific O/E are not provided for this PSUR because age-specific background rates are not available in ACCESS. The MAH will look for other sources with this detail and will provide age-specific O/E in next monthly report as background rates allow.

Varicella zoster virus reactivation has been reported coincident with cases of COVID-19. It is theorized that lymphopenia associated with the infection may induce a reactivation (of herpes zoster) by affecting the T-cells' ability to mobilize a response to control varicella zoster virus. Following immunization for COVID-19, it could be hypothesized that the humoral and cell-mediated immune responses stimulated by BNT162b2 vaccination, result in an alteration of the balance of T-cells with the end result being an inability to keep the infection in check and therefore, reactivation occurs. 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. Routine signal detection activities will continue.

Rapporteur assessment comment:

Through 18 June 2021, the MAH retrieved 3,426 processed cases reporting herpes zoster. The O/E ratios were all below 1 (14-day risk window: O/E ratio 0.045; 95% CI 0.044, 0.047 and 21-day risk window: O/E ratio 0.031; 95% CI 0.030, 0.032). In the O/E analysis that included the 766 unprocessed cases (total of 4,192 cases) the O/E ratio was below 1 (21-day risk window: O/E ratio 0.038; 95% CI 0.037, 0.039).

In the 9th MSSR (Aug data; EMEA/H/C/005735/MEA/002.8) and in the 10th MSSR (Sept data; EMEA/H/C/005735/MEA/002.8) the MAH provided for cases reporting herpes zoster age-specific O/E analyses resulting in all O/E ratios below 1.

No new safety issue could be identified concerning cases reporting herpes zoster. MAH's conclusion is accepted that no changes in the risk minimization measures or updates to the product information label are warranted.

2.2.2.1.7 Appendicitis

i) Source

The safety topic was followed closely in C4591001 and reviewed in the post-authorization setting following a request by a regulatory agency following a reported assessment by the WHO Uppsala Monitoring Center dated April 2021.

ii) Data

The safety database was searched cumulatively through 18 June 2021 for all BNT162b2 vaccine spontaneous and literature reports and serious clinical trial reports reporting the PT Appendicitis (MedDRA version 24.0).

A total of 145 cases have been retrieved using the criteria mentioned above. There were 94 females, 45 males and for 6 cases gender was not reported. Age was reported as ranging from 13

to 89 years (mean: 45.8). A total of 6 cases were reported in paediatric subjects less than or equal to 17 years of age, 104 cases were reported in adults (≥ 18 to <65), 25 cases were reported by elderly (≥ 65) and for 10 cases age was not reported. Latency from vaccination to onset of appendicitis was provided in 126 cases and ranged from day of vaccination to 225 days after vaccination. Ninety-three (93) cases occurred within one week after vaccination whereby in eleven (11) of these cases appendicitis occurred on the same day as vaccination; (1 case within 15 minutes and 2 cases within 5 hours and 12 hours).

Medical history was reported for 74 cases. A relevant medical history was reported for 44 cases: 7 cases reported appendicitis/appendix disorder; 8 cases reported Covid-19 infection; 6 cases reported Type 1 and 2 diabetes mellitus diabetes; 1 case reported mixed connective tissue disease / Sjogren's syndrome; 1 case reported cutaneous lupus erythematosus and Sjogren's syndrome; 4 cases reported cancer; 1 case reported diverticulitis; 1 case reported Hodgkin's disease and sarcoidosis; 2 case of endometriosis; 2 reported diarrhea/gastrointestinal disorder; 2 reported constipation; 4 reported infections; 2 reported unspecified surgery; and 3 reported abdominal pain.

Of the 145 cases, 4 cases reported positive SARS-COV-2 test results, 53 cases reported negative COVID-19 test results, 1 reported pending COVID-19 test result, and 87 cases did not provide COVID-19 testing information.

Case outcome was reported as resolved in 41 cases, resolving in 66 cases, resolved with sequelae in 9 cases, not resolved at time of reporting in 10 and unknown in 19 cases.

A signal of disproportionality (EB05>2) for term indicative of appendicitis was not noted on 18 June 2021 for BNT162b2 during routine PV monitoring activities. A literature review did not identify a specific signal for BNT162b2 vaccine associated appendicitis. The O/E ratio was below 1 for both the 21-day risk window and no risk window.

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.

iii) Outcome

Appendicitis has been spontaneously reported following vaccination with BNT162b2 vaccine. Most reports are in adult patients, consistent with the age populations targeted for vaccination in most regions. Forty-four (44) cases reported relevant medical conditions that may have predisposed to GI inflammation and/or appendicitis. Review of the literature review did not identify a significant safety information for vaccine associated appendicitis. The O/E ratio was below 1 in the epidemiology signal detection analyses.

The totality of the reviewed information does not indicate a causal association between the vaccine and appendicitis for the following reasons: there is not a clear mechanism to explain why vaccinated individuals may have an increased risk for appendicitis, there was no indication identified from the literature linking vaccination to the occurrence of appendicitis, and given the relatively low number of reports of appendicitis in the context of more than half a billion BNT162b2 vaccine doses administered. The benefit risk profile of the vaccine remains favorable. Routine signal detection activities will continue.

Rapporteur assessment comment:

In the 6th MSSR (May 2021 data) the signal appendicitis was closed due to that a causal association between the vaccine and the event could be confirmed. Within the current PSUR, the MAH has provided an update of the review. No signal of disproportionality was observed and the O/E ratios were well below 1. It is therefore agreed with the MAH that, based on the presented updated post-marketing data through 18 June 2021, there is no new safety information identified concerning cases reporting appendicitis.

In the 10th MSSR (Sept data; EMEA/H/C/005735/MEA/002.8) the MAH provided for cases reporting appendicitis age-specific O/E analyses resulting in all O/E ratios below 1.

2.2.2.1.8 Hearing loss and tinnitus

The MAH submitted a cumulative review of cases reporting hearing loss (n=980) and tinnitus (n=2,499) through 18 June 2021.

Rapporteur assessment comment:

The current cumulative review submitted by the MAH regarding hearing loss/tinnitus was also submitted within the 8th MSSR. Please refer to procedure EMEA/H/C/005735/MEA/002.7 for assessment concerning hearing loss/tinnitus in the 8th MSSR, in which a causal association with Comirnaty exposure was not suggested based on the data through 18 June 2021.

2.3. Evaluation of risks and new information

Follow-up Questionnaires

As per the coreRMP19 guideline, for those events for which follow-up questionnaires are implemented (e.g. anaphylaxis, VAED/VAERD) the MAH should provide process data (e.g. response rate, need for corrective actions) and reassess the need for continuing this routine pharmacovigilance activity in the PSURs.

Two Data Capture Aids (DCAs) and a Follow-up Questionnaire (FUQ) have been created for COVID-19 vaccine:

- The first DCA is intended to capture the available clinical details about the nature and severity of COVID 19 illness experienced in a vaccinated individual, particularly in relation to potential cases of vaccine lack of effect or VAED (vaccine-associated enhanced disease). The DCA was implemented on 07 December 2020 based on MHRA, EMA and FDA commitments and remains in use.
- The second DCA is intended to enable the retrieval of clinical details about potential anaphylactic reactions experienced by an individual following administration of BNT162b2. The DCA was implemented on 23 December 2020 and based on MHRA, and EMA commitments and remains in use.
- Additionally, a Pfizer BioNTech COVID-19 Vaccine FUQ is used for all other reports and, is intended to capture more specific information about vaccine administration details, facility where vaccine was provided, any prior vaccinations received, medical and family history, adverse events and relevant medical tests (e.g., Platelet Factor IV antibody in cases of thromboembolic events with thrombocytopenia). This FUQ was implemented on 15 February 2021 and to be used for all reports not meeting the DCA criteria above.

Follow-up for COVID-19 vaccine cases received through EudraVigilance

For cases received through Eudravigilance, the Drug Safety Unit (DSU) case reviewer requests follow-up information from the owner of the case (e.g., National Competent Authority [NCA]), when applicable and for all cases with a suspect COVID-19 vaccine as follows:

Table 1. Follow-up for COVID-19 Vaccine Cases Received through Eudravigilance

Case type	As per process implemented on 10 March 2021	As per process implemented on 17 May 2021
All serious cases meeting DCA criteria	1st follow-up performed within 10 calendar days from SRD applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No second attempt performed.	No change
Non-serious cases identified by SSRM and meeting DCA criteria	1st follow-up performed within 10 calendar days from notification applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No second attempt performed.	No change
Any other non-serious case not identified by SSRM and meeting DCA criteria	1st follow-up performed within 10 calendar days from notification applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No follow-up attempts are performed	1st follow-up performed within a maximum of 60 calendar days from SRD applying only the appropriate Pfizer-BioNTech COVID-19 DCA No second attempt performed.
All other serious and non-serious cases not meeting DCA criteria	No follow-up attempts are performed	No change
ICH Invalid	1st follow-up attempt within 10 calendar days from book-in. No second attempt performed.	No change

Abbreviations: International Conference on Harmonisation (ICH); Safety Receipt Date (SRD); Safety Surveillance Risk Management (SSRM).

In compliance with the criteria mentioned above, the local DSU case reviewer or case reviewer acting on their behalf (e.g., a DSU case reviewer from one of the Platforms) is responsible for evaluation of follow-up requirements and setting appropriate action items within the global safety database. Execution of action items is performed by the DSU case reviewers within the relevant local DSU.

For those NCAs that either prohibit the request of follow up information from Pfizer or that have communicated to Pfizer that they automatically request follow-up from the original reporter, the DSU case reviewer enters a contact log entry in the case to document how follow-up activities are managed by the NCA.

Follow-up for COVID-19 vaccine cases received outside of the EudraVigilance process

For all COVID-19 vaccine cases that are not received through Eudravigilance, the DSU case reviewer requests follow-up information directly from the HCP reporter, if possible, as follows:

Table 2. Follow-up for COVID-19 Vaccine Cases Received Outside of the Eudravigilance Process

Case type	As per process implemented on 10 March 2021	As per process implemented on 17 May 2021
All serious cases	1st follow-up performed within 10 calendar days from SRD applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.	No change
Non-serious cases identified by SSRM	1st follow-up performed within 10 calendar days from notification applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.	No change
Any other non-serious case not identified by SSRM	No follow-up attempts are performed.	1st follow-up performed within a maximum of 60 calendar days from SRD applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.
ICH Invalid	1st follow-up attempt within 10 calendar days from book-in. No second attempt performed.	No change

Abbreviations: International Conference on Harmonisation (ICH); Safety Receipt Date (SRD); Safety Surveillance Risk Management (SSRM).

In compliance with the criteria mentioned above, the local DSU case reviewer or case reviewer acting on their behalf (e.g., a DSU case reviewer from one of the Platform) is responsible for evaluation of follow-up requirements and setting appropriate action items within the global safety database. Execution of action items is performed by the DSU case reviewers within the relevant local DSU.

For consumer cases, the DSU case reviewer sends the Pfizer BioNTech COVID-19 Vaccine Follow-up Questionnaire to the consumer and requests to provide it to his/her HCP for appropriate completion. The consumer is requested to complete the questionnaire to the best of his/her knowledge if unable to provide it to the HCP. Only one attempt is performed with the consumer; an additional attempt is performed with the HCP if the contact details are provided.

Follow-up via Emergency Phone Calls

The DSU case reviewer performs emergency phone calls requesting follow-up only for HCP reporters, if the phone number of the HCP is available and contact can be made. The phone call is performed only for the following events:

Serious allergic reactions – events of anaphylaxis, anaphylactoid reaction, or anaphylactic shock.

The DSU case reviewer pursues follow up information of all available clinical details immediately with HCP reporters, applying the Pfizer BioNTech COVID-19 DCA on vaccine anaphylactic reactions.

- If no response is received via the phone contact, the DSU case reviewer sends the Pfizer BioNTech COVID-19 DCA.

- If response is received via the phone contact, there is no need to send the DCA unless specifically requested by the reporter.

DSU case reviewers perform follow-up activities with reporter(s), as described above and document in the contact log when the follow-up activities are not possible.

Product Safety Surveillance and Reporting Individual Case Safety Reports case reviewers confirm that follow-up activities have been initiated or closed before completing the cases under their process. If follow-up activities have not been appropriately tracked, they notify the relevant DSU. No additional queries are asked during case assessment, as follow-up is being conducted by use of the applicable COVID DCAs or Pfizer BioNTech COVID 19 Vaccine FUQ.

Follow-up Questionnaires – Analysis of data during the reporting interval: Anaphylaxis

During the PSUR interval there were 3,830 initial cases of anaphylaxis; of these cases there were 1,695 (44.3%) that received a significant FU; and 1,764 cases (46.1%) with no FU received.

Of note, in certain circumstances: 1) follow-up with the reporter is not permitted by local regulatory authorities and/or by local regulations; 2) follow-up with the reporter is not possible because cases are received via a Regulatory Authority (RA) and the RA does not accept requests for follow-up from a pharmaceutical company; or 3) where follow-up must be discontinued, i.e., where the reporter states "no additional information will be available" or the reporter refuses further contact or wants to remain anonymous.

Based on the above note, the MAH performed the same calculation by selecting case reports received by RA only and to verify especially the percentage of cases that did not receive FU information; accordingly, there were: 1,458 cases (38.1%) with no FU from Regulatory Authority, and 1,764 cases (46.1%) with no FU from all case report types. Therefore, removing the RA cases with no FU from the total count, the number of remaining cases with no FU received during the period decreases to 306 (8.0%), thus confirming the RA circumstances described above.

MAH's conclusion: The percentage of significant follow-up information received from all case report types for anaphylaxis-related PTs is around 30%; this relatively low percentage is due, in part, to the fact that many reports are from Regulatory Authorities.

Rapporteur assessment comment: In contrast to MAH's conclusion, it should be noted that of the total 3,830 initial cases of anaphylaxis reported during the interval period, there were 1,695 (44.3%) that received a significant FU, of which 1,139 cases (29.7% of 3,830 initial cases) were RA reports. The percentage of significant FU is therefore 44.3% instead of around 30%.

Direct follow-up by MAH is severely limited due to the vast number of reports under mass vaccination processes that are provided directly by regulatory authorities. The MAH consider the use of the DCA a useful source when the reporters choose to respond and no corrective actions are warranted at this time; the MAH will re-evaluate the efficiency of these tools at the next PBRER.

Follow-up Questionnaires – Analysis of data during the reporting interval: VAED/VAERD

During the PSUR interval there were 631 initial cases of VAED/VAERD; of these cases, 336 (53.2%) received a significant FU and 212 (33.6%) with no FU received.

Considering the number of cases received from RA, that usually prevent any FU information, the number of cases that did not receive FU information was 182, therefore removing them from the total count (212) the percentage of no FU decreased to 30 (4.8%).

MAH's conclusion: Direct follow-up by MAH is severely limited due to the vast number of reports under mass vaccination processes that are provided directly by regulatory authorities. Based on the percentage of significant follow-up information received (53.2%) for VAED/VAERD-related PTs the MAH consider the DCA a useful source of information when reporters choose to respond; no corrective actions are warranted at this time. The MAH will reevaluate the use of these tools at the next PBRER.

Rapporteur assessment comment:

As per the coreRMP guideline, the MAH provided the processes of follow-up as part of case processing of COVID-19 reports, in particular the use of two COVID-19 Data Capture Aids (DCAs) and a COVID-19 vaccine Follow-up Questionnaire (FUQ).

One DCA has been developed to capture clinical details about the nature and severity of COVID-19 illness, particularly in relation to potential cases of vaccine lack of effect of VAED.

The other DCA captures clinical details about potential anaphylactic reactions following vaccination with BNT162b2.

Both DCAs are based on, amongst others, EMA commitments and will remain in use, which is accepted.

The COVID-19 Vaccine FUQ is used by the MAH for all other reports not meeting the DCA criteria. This FUQ was implemented on 15 February 2021 and captures more specific information about vaccine administration details, facility where vaccine was provided, any prior vaccinations received, medical and family history, adverse events and relevant medical tests (e.g., Platelet Factor IV antibody in cases of thromboembolic events with thrombocytopenia).

Different FU processes are in place for cases received by the MAH through EudraVigilance and for cases that are received outside of the EudraVigilance process. Follow-up requirements and setting appropriate action items within the global safety database are evaluated by the MAH, for which the results on 10 March 2021 and 17 May 2021 have been presented in the tables above.

The response rate of significant follow-up information received from all case report types for anaphylaxis-related PTs is 44.3% and 53.2% for VAED/VAERD-related PTs. The MAH considers the DCAs useful sources of information when reporters choose to respond and no corrective actions are warranted at this time, which is accepted.

At the moment, there are no comments on the presented processes, the response rate and MAH's evaluation (results) thereof. The MAH should continue to reassess the need for continuing this routine PhV activity and provide process data (e.g., response rate, need for corrective action) as above in the next PSUR. **Request for next PSUR**

2.3.1.1. Evaluation of Important Identified Risks

2.3.1.1.1. Anaphylaxis

Search criteria*: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock*

Clinical trial data

N=1

Post-marketing data

From 19 December 2020 until 18 June 2021 there were **3,829 anaphylaxis cases** received by the MAH, comprising of:

- Reported relevant PTs (n=3,919): Anaphylactic reaction (3418), Anaphylactic shock (421), Anaphylactoid reaction (75), Anaphylactoid shock (5).
- Serious: 3873, non-serious: 46.
- Time to event onset (n = 3288), range:<24 hours to 180 days, median 0 days.
- Duration of relevant events (n = 891 out of 2246 occurrences with outcome of resolved/resolved with sequelae), range: 10 seconds to 114 days, median 0 day.
- Relevant event outcome: fatal (28), resolved/resolving (2,961), resolved with sequelae (56), not resolved (173), unknown (704).
- **Paediatric** (23), Adults (3021), **Elderly** (395) and Unknown (388). No significant difference observed in the reporting proportion of anaphylaxis relevant PTs between adult and elderly population. However, a higher reporting proportion of event coded to the PTs Anaphylactic shock was observed in paediatric population when compared to adult or elderly population (48.8.% in paediatrics vs 11.0% in adults vs 11.9% in elderly).
- Number of subjects with **comorbidities**: 1055. The reporting proportion of anaphylaxis related events with fatal outcome (1.7%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.3% of events with fatal outcome), but this is expected considering that underlying comorbidities are likely to be contributory to individual's death and delayed recovery. The reporting proportion of anaphylaxis related events with outcome not resolved (4.5%) is comparable in individuals with comorbid conditions when compared to the reporting proportion (4.3%) observed in the individuals without comorbidities.

Data from literature: during the reporting interval, there were no new significant data received from literature sources according to the MAH.

Rapporteur assessment comment:

Anaphylaxis is an adverse drug reaction in Section 4.8 of the Comirnaty EU SmPC, and appropriate action to be taken is included in SmPC section 4.4.: "Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty."

During the reporting period, the topic of anaphylaxis following vaccination with Comirnaty was assessed in the post-authorisation measure LEG-022.1 for the 'cumulative review anaphylaxis' (EMA/PRAC/181346/2021). It was concluded that no amendment of the Product Information is warranted.

No new safety information concerning anaphylaxis could be identified from the data in this PSUR. The current risk minimisation measures described in the product information are considered adequate. Anaphylaxis is closely monitored through the MSSRs for Comirnaty.

2.3.1.2. Evaluation of Important Potential Risks

2.3.1.2.1. 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

No cases.

Post-marketing data

From 19 December 2020 until 18 June 2021, the MAH has received **584 VAED cases**, comprising of:

- Female: 298, male: 268, and unknown gender: 18.
- Patients' age in years (n = 553), range: 17 – 103, mean 70.3, median 77.
- Reported relevant PTs by organ system:
    - *Respiratory system PTs (500)*: Dyspnoea (180), COVID-19 pneumonia (179), Respiratory failure (52), Pulmonary embolism (33), Hypoxia (24), Tachypnoea (17), and Acute respiratory distress syndrome (15).
    - *Gastrointestinal (188):* Diarrhoea (111), Vomiting (50), Abdominal pain (27); Cardiovascular system (60): Cardiac failure (25), Arrhythmia (13), Myocarditis (7), Acute myocardial infarction (5), Deep vein thrombosis (4), Cardiogenic shock, Vasculitis (2 each), Peripheral ischaemia, and Shock (1 each);
    - *Nervous system (29)*: Cerebrovascular accident (12), Seizure (10), Altered state of consciousness (6), and Encephalopathy (1);
    - *Renal and urinary system (33):* Acute kidney injury (20), and Renal failure (13);
    - *Blood and lymphatic system (16):* Thrombocytopenia (16);
    - *Other PTs (17):* Multiple organ dysfunction syndrome (15), and Meningitis (2).
- Case outcome: fatal (160), not resolved (169), resolved/resolving (182), resolved with sequelae (7), unknown (66).
- **COVID-19 positivity and severity of events (n=584)**
    - Suspected COVID-19 infection: 159 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (154 cases) or to Vaccination failure (5 cases)];

- Confirmed COVID-19 infection: 425 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (240 cases) or Vaccination failure (185 cases)]. 290 of the 425 cases were severe, resulting in hospitalisation, disability, life threatening consequences or death. None of the 290 cases could be definitively considered as having VAED/VAERD.

Data from literature: during the reporting interval, there were no new significant data received from literature sources according to the MAH.

Rapporteur assessment comment: No new safety concern is identified regarding VAED/VAERD. VAED/VAERD is closely monitored through the MSSRs for Comirnaty.

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

2.3.1.3.1. Adverse events of special interest (AESIs)

Anaphylactic AESIs

Rapporteur assessment comment: Please refer to the assessment above (section 2.3.1.1).

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: 33 (4.7% of 702 cases, the total CT dataset; 20 were blinded therapy, 10 BNT162b2, 3 were placebo).
- Subjects' gender: female (4), and male (29).
- Subjects' age in years (n = 33), range: 36-79, mean 62.7, median 63.0.
- Medical history (n = 30): the reported relevant medical conditions included hypertension (20), hypercholesterolaemia (10), obesity, type 2 diabetes mellitus (9 each), coronary artery disease (8), cardiac disorder, hyperlipidaemia (5 each), coronary artery bypass, tobacco user (4 each), blood cholesterol increased, dyslipidaemia (3 each), angina pectoris, diastolic dysfunction, myocardial infarction, tobacco abuse, transient ischaemic attack (2 each), acute myocardial infarction, angiopathy, aortic arteriosclerosis, aortic valve repair, blood pressure increased, cardiovascular disorder, chest pain, coronary arterial stent insertion, diabetes mellitus, ex-tobacco user, hypertriglyceridaemia, mitral valve prolapse, myocardial ischaemia, overweight, peripheral arterial occlusive disease, and ventricular extrasystoles (1 each).
- There were no cases that reported medical history of COVID-19.
- There were no cases that reported co-suspect medications.

- Reported relevant PTs: Acute myocardial infarction (15), Myocardial infarction (11), and Coronary artery disease (7).
- BNT162b2 related event coded to the PT: Myocardial infarction (1). Time to onset of event 2 months 8 days and the event outcome is reported as resolved. None of the events were related to blinded therapy

Post-authorization data

- Number of cases: 8,398 (2.6% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (6,451), Non-medically confirmed cases (1,947).
- Country of incidence: Mexico (2,078), Italy (1,063), France (952), UK (797), US (677), Germany (505), Japan (386), Spain (248), Netherlands (215), Greece (127); the remaining 1350 cases were distributed among 50 countries.
- Subjects' gender: female (6,221), male (2,018) and unknown (159).
- Subjects' age in years (n = 8,000), range: 12 – 104, mean 50.9, median 47.
- Medical history (n = 4,138): the most frequently (≥2%) reported relevant medical conditions included hypertension (900), atrial fibrillation (282), diabetes mellitus (197), cardiac failure (184), hypothyroidism (183), type 2 diabetes mellitus (170), obesity (129), arrhythmia (122), myocardial infarction (120), myocardial ischaemia (102), dyslipidaemia (95), coronary artery disease (86), anxiety (81).
- COVID-19 Medical history (n = 449): the most frequently (≥2%) reported medical conditions included COVID-19 (309), Suspected COVID-19 (89), SARS-CoV-2 test positive (13).
- Co-suspects (n = 79 cases). Frequently (>5 occurrences) reported relevant co-suspect was adalimumab (6).
- Number of relevant events: 8616.
- Relevant event seriousness: serious (4,195), non-serious (4,422).
- Most frequently reported relevant PTs (≥2%): Tachycardia (6,238), Arrhythmia (775), Myocardial infarction (635), Cardiac failure (489), Acute myocardial infarction (265).
- Time to event onset (n = 7,087), range: <24 hours to 118 days, median <24 hours.
- Duration of relevant events (n = 1,176 out of 3,672 occurrences with outcome of resolved/resolved with sequelae), range: 1 second to 63 days, median 1 day.
- Relevant event outcome: fatal (638), resolved/resolving (4,699), resolved with sequelae (123), not resolved (890), unknown (2,276).
    - In the 593 cases (reporting 638 relevant events with a fatal outcome), the reported cause of death (>20 occurrence) were coded to PTs Myocardial infarction (186), Cardiac failure (182), Acute myocardial infarction (79), Cardiac arrest, Dyspnoea (43 each), Cardiac failure acute, Cardiogenic shock (39 each), Arrhythmia (38), Tachycardia (32), Pyrexia (24), and Cardio-respiratory arrest (23). Of note, in 12 cases limited information regarding the cause of death was provided (PT Death [5], Unknown [7]). Most (511 of 593 cases) of the fatal cases involved elderly subjects. When the medical history was provided (496 cases), significant medical conditions included hypertension, atrial fibrillation, cardiac failure, myocardial ischaemia, type 2 diabetes

mellitus, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, renal failure, myocardial infarction, and coronary artery disease.

Analysis by age group

Clinical trials: Adults (19), and Elderly (14).

- A meaningful comparison between the different age groups is not possible due to the low number of cases.

Post-marketing: Paediatric (19), Adults (6,100), Elderly (1,961) and Unknown (317).

- Higher reporting proportion of events coded to the PTs Acute myocardial infarction, Arrhythmia, Cardiac failure, and Cardiac failure acute was reported in elderly population when compared to adult and paediatric population (Acute myocardial infarction [1.4% in adults vs 0% in paediatrics vs 9.2% in elderly], Arrhythmia [6.7% in adults vs 5.3% in paediatrics vs 16.6% in elderly], Cardiac failure [0.6% in adults vs 0% in paediatrics vs 22.6% in elderly], Cardiac failure acute [0.05% in adults vs 0% in paediatrics vs 3.2% in elderly], and Myocardial infarction [3.1% in adults vs 5.3% in paediatrics vs 20.3% in elderly]). Higher reporting proportion of events coded to the PTs Tachycardia was reported in the adult and paediatric population when compared to the elderly population ([88.9% in adults vs 84.2% in paediatrics vs 29.6% in elderly]). Higher reporting proportion of event coded to the PT Postural orthostatic tachycardia syndrome was reported in the paediatric population when compared to the adult and elderly population ([0.5% in adults vs 10.5% in paediatrics vs 0.1% in elderly]).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1,832 (0.6% of 327,827 cases, the total dataset).
- The reporting proportion of cardiovascular AESIs with fatal outcome (8.9%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (2.9% of events with fatal outcome).

O/E analysis

O/E analysis was performed for Acute myocardial infarction; Arrhythmia; Heart failure (PTs: Cardiac failure; Cardiac failure acute); Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy

Conclusion

No cardiovascular signals have emerged from the review of post-authorisation data. The review of cases and O/E analysis does not raise new concerns. Safety surveillance will continue.

Rapporteur assessment comment:

In line with what would be expected, a higher proportion of cardiovascular AESIs was reported in the elderly population as compared to the adult and paediatric population and the proportion of fatal cases was higher among those with comorbid conditions.

Overall O/E ratios were below 1 and, when available, age stratified O/E ratios were also <1.

No new safety issue could be identified for cardiovascular AESIs. Cardiovascular AESIs continue to be monitored in the MSSRs for Comirnaty.

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: 18 (2.6% of 702 cases, the total CT dataset; 15 were blinded therapy, 2 BNT162b2, and 1 placebo).
- Country of incidence: US (12), Argentina (2), Brazil, Germany, South Africa, and Turkey (1 each).
- Subjects' gender: female (9), and male (9).
- Subjects' age in years (n = 18), range: 32 - 81, mean 57.9, median 59.5.
- Medical history (n = 15 cases): the reported relevant medical conditions included Hypertension (9), Obesity (4), Asthma, Type 2 diabetes mellitus (2 each), Chronic obstructive pulmonary disease, Diabetes mellitus, HIV infection, Hypoxia, Lung neoplasm malignant, Pulmonary fibrosis, Asthma exercise induced (1 each).
- COVID-19 Medical history: None.
- There were no cases that reported co-suspect.
- Reported relevant PTs: COVID-19 (14), COVID-19 pneumonia (4). None of the events were related to BNT162b2 or blinded therapy.

Post-authorization data

- Number of relevant cases: 12,058 (3.7% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (6915); Non-medically confirmed cases (5143).
- Country of incidence: US (4,332), UK (1,702), France (897), Italy (840), Germany (812), Portugal, Spain (272 each), Mexico (267), Austria (247), Romania (236); the remaining 2181 cases were distributed among 62 countries.
- Subjects' gender: female (6,876), male (3,692) and unknown (1,490).
- Subjects' age in years (n = 8,127), range: 3 - 104, mean 57.8, median 56.0.
- Medical history (n = 4,237): the most frequently (≥2%) reported relevant medical conditions included Hypertension (955), Diabetes mellitus (295), Asthma (290), Type 2 diabetes mellitus (217), Obesity (174), Chronic obstructive pulmonary diseases (144).
- COVID-19 Medical history (n = 1,001): the most frequently (≥2%) reported medical conditions included COVID-19 (452), Suspected COVID-19 (291), Exposure to SARS-CoV-2 (151), Occupational exposure to SARS-CoV-2 (33), SARS-CoV-2 test positive (29).
- Co-suspects (n = 83 cases). Frequently (>5 occurrences) reported relevant co-suspect was COVID-19 AstraZeneca (11)
- Number of events: 13,209.
- Relevant event seriousness: serious (8,633), non-serious (4,576).

- Most frequently reported relevant PTs (≥2%): COVID-19 (8,154), Ageusia (1,135), Anosmia (924), Suspected COVID-19 (910), SARS-CoV-2 test positive (677), Asymptomatic COVID-19 (567), COVID-19 pneumonia (324).
- Time to event onset (n = 8,692), range: <24 hours to 132 days, median 8 days.
- Duration of relevant events (n = 894 out of 2,221 occurrences with outcome of resolved/resolved with sequelae), range: 1 hour to 68 days, median 9 days
- Relevant event outcome: fatal (658), resolved/resolving (3,312), resolved with sequelae (70), not resolved (2,001), unknown (7,174).
    - In 595 cases (reporting 658 relevant events with a fatal outcome), the reported cause of death (>20 occurrence) were coded to PTs COVID-19 (458), Drug ineffective (169), COVID-19 pneumonia (111), Vaccination failure (87), Respiratory failure (33), Pyrexia (28), Dyspnoea (25), Pneumonia, and SARS-CoV-2 test positive (24 each). Of note, in 13 cases limited information regarding the cause of death was provided (PT Death [8], Unknown [5]). Most (439 of 595 cases) of the fatal cases involved elderly subjects. When the medical history was provided (462 cases), significant medical conditions included hypertension, type 2 diabetes mellitus, COVID-19, chronic obstructive pulmonary disease, and diabetes mellitus.

Analysis by age group

- Clinical trial: Adults (10), and Elderly (8)
    - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (33), Adults (5179), Elderly (3143).
    - No significant difference observed in the reporting proportion of frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2,086 (0.6% of 327,827 cases, the total dataset).
- The reporting proportion of COVID-19 AESIs with fatal outcome (13.1%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (2.9% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Ageusia and Anosmia.

Conclusion

No safety signals have emerged based on the review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment: O/E analyses including those that were age-stratified showed O/E ratios <1. No new safety issue 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: 178 (0.05% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (112), Non-medically confirmed cases (66).
- Country of incidence: UK (69), France (24), US (22), Japan (16), Italy (14), Netherlands (6), Poland (4), Finland (3); the remaining 20 cases were distributed among 14 countries.
- Subjects' gender: female (119), male (54) and unknown (5).
- Subjects' age in years (n = 163), range: 16-92, mean 53.1, median 53.
- Medical history (n = 92): the most frequently (≥2%) reported medical conditions included Hypothyroidism (11), Chillblains, Food allergy (7 each), Drug hypersensitivity (6), Erythema multiforme (2).
- COVID-19 Medical history (n = 16): the medical conditions included COVID-19 (8), Suspected COVID-19 (7), and SARS-CoV-2 antibody test positive (1).
- Co-suspects (n = 2). COVID-19 AstraZeneca vaccine, zonisamide (1 each).
- Number of events: 178.
- Relevant event seriousness: serious (99), non-serious (79).
- Most frequently reported relevant PTs Chillblains (98); Erythema multiforme (80).
- Time to event onset (n = 139), range: <24 hours to 41 days, median 4 days.
- Duration of relevant events (n = 16 out of 33 occurrences with outcome of resolved/resolved with sequelae), range: 3 days to 1 month, median 10 days.
- Relevant event outcome: fatal (1), resolved/resolving (74), resolved with sequelae (4), not resolved (68), unknown (32).
    - There was 1 case reporting 1 relevant PT Erythema multiforme with a fatal outcome. The cause of death was reported as abdominal pain lower; anuria; arteriosclerosis; cervical spinal stenosis; contusion; cyanosis; erythema multiforme; hypotonia; intervertebral disc protrusion; metabolic acidosis; paralysis; paraparesis; respiratory failure; spinal cord compression; swelling.

Analysis by age group

Post-marketing: Paediatric (1), Adults (112), Elderly (52) and Unknown (13).

- 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. Higher reporting proportion of event erythema multiforme was reported in elderly population (5.8%) compared to adult population (0.9%).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 42 (23.6% of the cases reporting dermatological AESIs)
- Due to low volume of cases with fatal outcome, a meaningful comparison between subjects with and without comorbidities is not possible.

O/E analysis

O/E analysis was performed for Chillblains and Erythema multiforme.

Conclusion

No safety signals have emerged based on the review of these cases, or of the Observed versus Expected analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Within the signal procedure (EMEA/H/C/005735/SDA/034, EPITT ref. 19721), it was concluded that erythema multiforme should be included as ADR in the product information of Comirnaty.

No new other safety issue 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.

Post-authorization data

- Number of relevant cases: 2,392 (0.7% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (1,386), Non-medically confirmed cases (1,006).
- Country of incidence: UK (511), US (495), France (197), Italy (183), Germany (155), Spain (93), Japan (64), Hong Kong (48), Sweden (45), Israel (44), Mexico (41), Ireland (40); the remaining 476 cases were distributed among 42 countries.
- Subjects' gender: female (1,458), male (831), and unknown (103).
- Subjects' age in years (n = 2,124), range: 16 – 100, mean 57.5, median 52.
- Medical history (n = 1,166 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (298), Diabetes mellitus (102), Bell's palsy (77), Type 2 diabetes mellitus (68), Hypothyroidism (60), Obesity (38), Cerebrovascular accident (31), Blood cholesterol increased (27), and Facial paralysis (26). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n = 81 cases): Reported medical conditions include COVID-19 (50), Suspected COVID-19 (23), COVID-19 pneumonia (5), SARS-CoV-2 test positive (3), Asymptomatic COVID-19 (2), and Coronavirus infection (1). Of note, more than 1 medical history was reported in some cases.

- Co-suspects: 5 cases. Relevant co-suspects were botulinum toxin type A and lithium (1 each).
- Number of relevant events: 2,392.
- Relevant event seriousness: serious (2,268) and non-serious (131).
- Reported relevant PTs: Bell's palsy (998), Facial paralysis (1,054), Facial paresis (337), and Oculofacial paralysis (3).
- Time to event onset (n = 1,908 events), range: <24 hours to 109 days, median 3 days.
- Duration of relevant events (n = 239 out of 481 occurrences with outcome of resolved/resolved with sequelae), range: 15 seconds to 72 days, median 2 days.
- Relevant event outcome: fatal (1), resolved/resolving (979), resolved with sequelae (31), not resolved at the time of reporting (884), and unknown (504).
    - In the single fatal case, the cause of death was coded to the PTs Asthenia, Facial paralysis, Hypothermia, Septic shock, and Slow speech. The case involved a 98-year-old subject with a medical history of atrial fibrillation, hypertension, and colon neoplasm.
- Lot/Batch Number: The lot/batch numbers which reported ≥2% of cases reporting facial paralysis are: #EL1484 (55 cases) and #EM0477 (51 cases). No quality issues identified during investigations of the impacted lot/batch numbers.

Analysis by age group

- Post-marketing: Paediatric (5), Adults (1516), Elderly (616) and Unknown (255).
    - 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: 570 (23.8% 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)

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 (eg, C4591008, C4591010) and secondary data collection studies (eg, C4591009, C4591011, C4591012, C4591021).

Rapporteur assessment comment: Overall O/E ratios were below 1, although no age stratified analysis were performed.

No new safety information could be identified for facial paralysis.

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: 19 (2.7% of 702 cases, the total CT dataset; 7 cases involved BNT162b2, 11 cases involved blinded therapy, and 1 case involved placebo).
- Country of incidence: US (14), Brazil (2), Germany (2), and Argentina (1).
- Subjects' gender: female (5) and male (14).
- Subjects' age in years (n = 19 cases), range: 24-78, mean 59.8, median 64.
- Medical history (n = 19 cases): the relevant subjects' medical conditions reported more than twice were coded to the PTs Hypertension (7), Type 2 diabetes mellitus and Hyperlipidaemia (4 each).
- There were no cases that reported medical history of COVID-19.
- There were no cases that reported co-suspect.
- Number of relevant events: 19.
- Reported relevant PTs (≥2 occurrences): Gastrointestinal haemorrhage (4), Lower gastrointestinal haemorrhage and Subdural haematoma (2 each). None of the SAEs were assessed as related to BNT162b2 or blinded therapy or placebo

Post-authorization data

- Number of relevant cases: 9,430 (2.9% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (4,109), Non-medically confirmed cases (5,321).
- Country of incidence: UK (3,054), US (1,845), Netherlands (696), France (671), Italy (552), Japan (348), Germany (293), Spain (267), Mexico (210), Sweden (161), Norway (129), Canada (119), Australia (104); the remaining 981 cases were distributed among 48 countries.
- Subjects' gender: female (7,112), male (2069), and unknown (249).
- Subjects' age in years (n = 8427 cases), range: 164-115, mean 56.5, median 51.
- Medical history (n = 5,652 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (879), Disease risk factor (472), Diabetes mellitus (229), Atrial fibrillation, Hypothyroidism (219 each), and Type 2 diabetes mellitus (155). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n = 627 cases): Medical conditions reported more than once were coded to the PTs COVID-19 (308), Suspected COVID-19 (307), SARS-CoV-2 test positive (13), COVID-19 pneumonia (9), Exposure to SARS-CoV-2 and SARS-CoV-2 antibody test positive (4 each). Of note, more than 1 medical history was reported in some cases.
- Co-suspects: 248 cases. Frequently (≥10 occurrences) reported relevant co-suspects were apixaban (47), acetylsalicylic acid (27), clopidogrel (13), rivaroxaban and warfarin (10 each).
- Number of relevant events: 10,935.

- Relevant event seriousness: serious (5,816) and non-serious (5119).
- Most frequently reported relevant PTs (≥2%): Epistaxis (1267), Contusion (1251), Heavy menstrual bleeding (881), Vaccination site haematoma (699), Thrombocytopenia (537), Haemorrhage (509), Vaccination site bruising (472), Vaginal haemorrhage (414), Petechiae (382), Haematoma (354), Intermenstrual bleeding (292), Haematochezia (221), Vaccination site haemorrhage (219), Immune thrombocytopenia (201), and Purpura (195).
- Time to event onset (n = 7,719 events), range: <24 hours to 125 days, median 2 days.
- Duration of relevant events (n = 1,342 out of 2,909 occurrences with outcome of resolved/resolved with sequelae), range: 30 seconds to 88 days, median 3 days.
- Relevant event outcome: fatal (241), resolved/resolving (4,780), resolved with sequelae (104), not resolved (2,596), and unknown (3286).
    - In 189 cases (reporting 241 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Thrombocytopenia (30), Gastrointestinal haemorrhage (18), Haematemesis (15), Dyspnoea (14), Cardiac arrest (13), Contusion (11), and Vomiting (10). Of note, in 21 cases limited information regarding the cause of death was provided (PT Death) or not reported the cause of death. Most (127 of 189 cases) of these fatal cases involved subjects who were ≥75 years of age. When the medical history was provided (150 cases), significant medical conditions included atrial fibrillation, cardiac failure, cerebral infarction, cerebrovascular accident, chronic kidney disease, chronic obstructive pulmonary disease, haemorrhagic stroke, renal failure and various malignancies. Of note, few patients received anticoagulants or nonsteroidal anti-inflammatory agents as concomitant medications.
- The lot/batch number which reported ≥2% of cases reporting immune mediated/autoimmune AESIs is: #EJ6795 (211 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- Clinical trial: Adults (10) and Elderly (9).
    - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- Post-marketing: Paediatric (61), Adults (5,870), Elderly (2,600) and Unknown (899).
    - A significantly higher reporting proportion of events coded to the PTs Vaginal haemorrhage and Intermenstrual bleeding was observed in adult population when compared to elderly population (Vaginal haemorrhage [5.7% in adults vs 0.8% in elderly] and Intermenstrual bleeding [4.1% in adults vs 0.2% in elderly]. It is expected that the women of reproductive age will have more bleeding than the elderly population. In paediatric population, vaginal haemorrhage and intermenstrual bleeding was reported in 1 case each. While the reporting proportion of PT Vaccination site haemorrhage was significantly higher in paediatric population (9.8%) when compared to adults and elderly population (1.8% and 2.3% in adults and elderly population, respectively).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3,136 (33.2% of the CT and PM cases reporting haematological AESIs).

- The reporting proportion of haematological AESIs with fatal outcome (3.8%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.0%).

O/E analysis

O/E analysis was performed for Haemorrhage, Immune thrombocytopenia, and Thrombocytopenia.

Conclusion

No signals for the hematological AESIs have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Please refer concerning immune thrombocytopenia to the assessment of the cumulative review of cases following vaccination in section 2.2 Signal evaluation. Note that a relative large number of reports included the PTs Vaginal haemorrhage and Intermenstrual bleeding, which could be considered Menstrual disorders (please refer to section 2.2 Signal evaluation of this AR).

All presented O/E ratios were below 1.

No new safety issue is identified for haematological AESIs.

Hepatic AESIs

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

Clinical trial data

Number of cases: 1 (0.1% of 702 cases, the total CT dataset; the case involved BNT162b2). A 62-year-old male subject in [redacted] received BNT162b2 and reported relevant events coded to the PTs Alanine aminotransferase increased and Aspartate aminotransferase increased (1 each). Time to onset of events was recorded as 74 days. The events were assessed as unrelated to BNT162b2 by the investigator and the Sponsor.

Post-authorization data

Number of cases: 551. Upon review, 1 case was determined to be non-contributory and is not included in the discussion since this case involved a baby who was indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 550 (0.2% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (391), Non-medically confirmed cases (159).
- Country of incidence: US (113), UK (94), France (66), Japan (62), Germany (30), Italy (24), Netherlands, Spain (18 each), Austria, Israel, Sweden (10 each), Belgium, Canada, Denmark, Greece, Hungary (7 each), Czech Republic (6); the remaining 54 cases were distributed among 22 countries.
- Subjects' gender: female (335), male (199), and unknown (16).
- Subjects' age in years (n=483), range: 16 – 104, mean 57.2, median 59.
- Medical history (n=368 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Type 2 diabetes mellitus (21), Diabetes mellitus,

Hypothyroidism (17 each), Hyperlipidaemia, Obesity (12 each), Cholecystectomy (10), Dyslipidaemia (9), Alcohol use and Hypercholesterolaemia (8 each). Of note, more than 1 medical history was reported in some cases.

- COVID-19 Medical history (n=42 cases). Medical conditions reported more than once were coded to the PTs COVID-19 (24), Suspected COVID-19 (14), COVID-19 pneumonia (3), Asymptomatic COVID-19 and SARS-CoV-2 antibody test positive (2 each). Of note, more than 1 medical history was reported in some cases.
- Co-suspects: 25 cases. Relevant co-suspects reported more than once were paracetamol, atorvastatin (3 each), adalimumab, amoxicillin-clavulanic acid, apixaban, and palbociclib (2 each).
- Number of relevant events: 714.
- Relevant event seriousness: serious (359) and non-serious (355).
- Most frequently reported relevant PTs (≥2%): Alanine aminotransferase increased (99), Hepatic enzyme increased (66), Aspartate aminotransferase increased (62), Hepatic function abnormal (60), Liver function test abnormal (52), Transaminases increased (49), Hepatic pain (47), Gamma-glutamyltransferase increased (46), Liver function test increased (41), Blood bilirubin increased (37), Blood alkaline phosphatase increased (29), Liver injury (23), Hepatic enzyme abnormal and Hepatomegaly (16 each).
- Time to event onset (n=438 events), range: <24 hours to 83 days, median 5 days.
- Duration of relevant events (n = 44 out of 109 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 37 days, with a median of 7 days.
- Relevant event outcome: fatal (12), resolved/resolving (203), resolved with sequelae (8), not resolved at the time of reporting (119), and unknown (372).
    - In 12 cases (reporting 12 relevant events with a fatal outcome), the cause of death (≥3 occurrences) were coded to the PTs General physical health deterioration (4), Liver function test abnormal and Renal failure (3 each). When the medical history was provided (11 cases), the subject's medical condition included alcoholism, breast cancer, cholecystitis, ischaemic cardiomyopathy, liver disorder, renal failure. Eight (8) of the 12 cases involved subjects who were ≥80 years of age.
- The lot/batch number which reported ≥2% of cases reporting hepatic events is: #EM0477 (14 cases), #ET3674 (13 cases), and #EJ6788 (11 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

Clinical Trials: Adult (1)

Post-Marketing: Paediatric (3), Adults (284), Elderly (201) and Unknown (62).

- Among the frequently (≥2%) reported relevant hepatic events, PT Hepatic pain was reported significantly higher in adult population when compared to elderly population (13% in adult vs 3% in elderly). No cases reported events coded to the PT Hepatic pain in the paediatric population. Upon further review, the majority of the events (hepatic pain) was assessed as non-serious in adult population (25 of 37 events).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 202 (36.7% of the CT and PM cases reporting hepatic AESIs).
- The reporting proportion of hepatic AESIs with fatal outcome (2.1%) is slightly higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.1%)

O/E Analysis

- O/E analysis was performed for Acute liver injury/Liver injury.

Conclusion

Hepatic events were a safety topic determined not to be validated signals. 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:

The presented O/E ratios were (far) below 1, however the O/E analyses were based on observed case count of 23 events of liver injury out of total 714 reported hepatic events (no cases of acute liver injury were reported).

In 368 (67%) of the 550 cases reporting hepatic AESIs, relevant medical history was reported and the reporting proportion of hepatic AESIs with fatal outcome was slightly higher in cases with comorbid conditions compared to cases without comorbidities.

No new safety issue 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 Cytokine release syndrome; Cytokine storm; Hypersensitivity.*

Clinical Trial Data

- Number of cases: 15 (2.1% of 702 cases, the total CT dataset; 7 cases involved BNT162b2/BNT162b1 and 8 cases involved blinded therapy).
- Country of incidence: US (14) and China (1).
- Subjects' gender: female (9) and male (6).
- Subjects' age in years (n=15), range: 33 – 82, mean 53.5, median 51.
- Medical history (n=13 cases): the relevant subjects' medical conditions reported more than once were coded to the PTs Type 2 diabetes mellitus (4), Hypothyroidism (3), and Seasonal allergy (2). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history: None.
- Co-suspects: 4. The co-suspects reported were calcium folinate, fluorouracil, irinotecan, and oxaliplatin (1 each).
- Reported relevant PTs (15): Diabetic ketoacidosis (4), Pancreatitis (3), Colitis, Enterocolitis, Eosinophilic oesophagitis, Hypersensitivity, Hyperthyroidism, Myasthenia gravis, Pericarditis,

and Polymyalgia rheumatica (1 each). Of the above SAEs, Polymyalgia rheumatica (time to onset of event: 58 days; with event outcome resolving) and Hyperthyroidism (time to onset of event: 218 days; with event outcome resolving) were assessed as related to BNT162b2 and BNT162b1, respectively. All the other SAEs were assessed as not related to blinded therapy.

Post-Authorization Data

Number of cases: 6,906. Upon review, 4 cases were determined to be non-contributory and are not included in the discussion since these 4 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 6,902 (2.1% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (3,898), Non-medically confirmed cases (3,004).
- Country of incidence: US (1,587), UK (1461), France (532), Italy (459), Germany (420), Japan (349), Israel (229), Spain (186), Sweden (117), Mexico (115), Netherlands (114); the remaining 1,333 cases were distributed among 50 countries.
- Subjects' gender: female (4,735), male (1,863), and unknown (304).
- Subjects' age in years (n=6,057), range: 12 – 100, mean 68.1, median 51.
- Medical history (n=4,134 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Asthma (406), Drug hypersensitivity (390), Hypersensitivity (311), Food allergy (275), Seasonal allergy (240), Diabetes mellitus (192), Hypothyroidism (180), Psoriasis (132), Type 2 diabetes mellitus (114), Immunodeficiency (110), Colitis ulcerative (103), and Rheumatoid arthritis (102). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n=370 cases): Medical conditions reported more than twice were coded to the PTs COVID-19 (205), Suspected COVID-19 (139), SARS-CoV-2 test positive (11), Exposure to SARS-CoV-2 (7), COVID-19 pneumonia, Occupational exposure to SARS-CoV-2 (5 each), Coronavirus infection and Post-acute COVID-19 syndrome (3 each). Of note, more than 1 medical history was reported in some cases.
- Co-suspects: 151 cases. Frequently (>5 occurrences) reported relevant co-suspects were adalimumab (14) and paracetamol (6)
- Number of relevant events: 7,152
- Relevant event seriousness: serious (4,669) and non-serious (2,483).
- Most frequently reported relevant PTs (≥2%): Hypersensitivity (3,177), Myocarditis (502), Pericarditis (364), Dermatitis (207), and Psoriasis (172).
- Time to event onset (n=4,703), range: <24 hours to 151 days, median 1 day.
    - <24 hours: 1,857 events (5 of which had a fatal outcome);
    - 1 day: 740 events (7 of which had a fatal outcome);
    - 2-7 days: 1,192 events (18 of which had a fatal outcome);
    - 8-14 days: 445 events (9 of which had a fatal outcome);
    - 15-30 days: 313 events (9 of which had a fatal outcome);
    - 31-181 days: 156 events (1 of which had a fatal outcome).

- Duration of relevant events (n = 765 out of 1,822 occurrences with outcome of resolved/resolved with sequelae), range: 5 minutes to 99 days, median 1 day.
- Relevant event outcome: fatal (82), resolved/resolving (3,069), resolved with sequelae (116), not resolved at the time of reporting (1,524), and unknown (2,386).
    - In 77 cases (reporting 82 relevant events with a fatal outcome), the reported cause of death (≥4 occurrences) were coded to the PTs Myocarditis (15), Dyspnoea (7), Interstitial lung disease (6), Acute respiratory failure, Diabetes mellitus, Encephalitis (5 each), Condition aggravated, Diabetic ketoacidosis, Haemophagocytic lymphohistiocytosis, Hypersensitivity, and Toxic epidermal necrolysis (4 each). Of note, in 3 cases limited information regarding the cause of death was provided (PT Death). Most (61 of 77 cases) of the fatal cases involved elderly subjects. When the medical history was provided (53 cases), significant medical conditions included cardiac failure, chronic obstructive pulmonary disease, COVID-19, dermatitis atopic, general physical health deterioration, hypersensitivity idiopathic pulmonary fibrosis, interstitial lung disease, type 1 and 2 diabetes mellitus, and various malignancies.
- The lot/batch number which reported ≥2% of cases reporting immune mediated/autoimmune AESIs is: #EM0477 (192 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- Clinical Trials: Adults (13) and Elderly (2).
- Post-Marketing: Paediatric (92), Adults (4437), Elderly (1594) and Unknown (779).
    - Among the frequently (≥2%) reported immune mediated/autoimmune AESIs, a higher reporting proportion of events coded to the PTs Myocarditis and Pericarditis were observed in paediatric population when compared to adult or elderly population (Myocarditis [53.3.% in paediatrics vs 8.6% in adults vs 3.1% in elderly] and Pericarditis [14.1% in paediatrics vs 4.9% in adults vs 6.5% in elderly]).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2,392 (34.6% of the CT and PM cases reporting immune mediated/autoimmune AESIs).
- The reporting proportion of immune mediated/autoimmune AESIs with a fatal outcome (1.6%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.8% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Autoimmune thyroiditis, Encephalitis, Myasthenia gravis, Myelitis, Myocarditis, Pericarditis, Polymyalgia rheumatica, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Type 1 diabetes mellitus, and Urticarial vasculitis.

Conclusion

- Myocarditis and Pericarditis is an ongoing signal.
  The O/E analysis for myocarditis, is >1 in some age-stratified analyses in the 14-and 21-day risk windows. A warning about myocarditis has been added to product information. It should

be noted that O/E may be influenced by factors including an increased awareness and diagnosis by HCPs.

- The O/E analysis for Myasthenia gravis is >1 in the 14-day risk window. Of note, on case review over half of the observed cases occurred in patients with underlying myasthenia gravis.
- The O/E analysis for Transverse myelitis is above 1, however, the observed cases include both transverse myelitis and myelitis while the expected case count is based on a background rate for transverse myelitis only, which may be appropriate for signal detection. The O/E ratio would be lower if only transverse myelitis reports were included. Future O/E of transverse myelitis will include a narrower inclusion criteria for the observed cases.

Cases of myasthenia gravis, polyneuropathy, and transverse myelitis will continue to be reviewed and monitored.

No new safety signals have emerged based on a review of the remaining events and on O/E analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Please refer regarding the evaluation of the signal of **myocarditis and pericarditis** to the separate procedure EMEA/H/C/005735/SDA/032, EPITT ref. 19712.

Cumulative review of **myasthenia gravis** (MG) up to 15 August 2021 was assessed in MSSR#9 (procedure EMEA/H/C/005735/MEA/002.8), in which the background rates of MG were updated. Using these updated background rates, all O/E ratios were well below 1. It was concluded that the data do not support a safety issue and the safety signal was closed.

Due to an update of ACCESS background rates, the estimated O/E ratios for **transverse myelitis** were lower in MSSR#9 compared to those in the O/E analyses of the 8th MSSR. Cumulatively the O/E ratios presented in the PSUR were below 1 for both 14-day and 21-day risk windows.

Regarding **Thrombocytopenic purpura** and **Thrombotic thrombocytopenic purpura**, please refer to Section 2.2 Signal evaluation "Immune thrombocytopenia" as these PTs are categorized under HLT Thrombocytopenias, and included in the O/E analysis for 'Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia'.

Autoimmune thyroiditis, Encephalitis, Polymyalgia rheumatica, Type 1 diabetes mellitus and Urticarial vasculitis showed O/E ratios <1.

No other new safety issue could be identified for immune-mediated/autoimmune AESIs. Immune-mediated/autoimmune AESIs continue to be monitored in the MSSRs for Comirnaty.

Musculoskeletal AESIs

Search Criteria: *PTs Arthralgia; Arthritis; Chronic fatigue syndrome; Polyarthritis; Post viral fatigue syndrome; Rheumatoid arthritis.*

Clinical Trial Data

- Number of cases: 2 (0.28% of 702 cases, the total CT dataset; 1 case involved BNT162b2; and other case involved blinded therapy).
- Country of incidence: [redacted](2).
- Subjects' gender: female (2).

- Subjects' age: 58 years in both cases.
- Number of subjects' reporting medical history: 2 cases.
- Relevant subjects' medical histories reported coded to the PTs Arthritis, Hip fracture, Joint injury, Obesity, Osteoarthritis (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PT (2): Arthritis (2), not related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of relevant cases: 36,146 (11.05% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (21,105), Non-medically confirmed cases (15,041).
- Country of incidence(≥100 occurrences): Italy (8,097), UK (6,472), Mexico (4,782),US (4,273), Netherlands (3,496), Spain (1,063), Austria (1,053), France (948), Japan (583), Czech Republic (579), Germany (525), Australia (478), Belgium (452), Portugal (423), Sweden (304), Norway (303), Ireland (253), Denmark (240), Finland (171), Greece (159), Poland (151), Canada (139), Romania (114), Estonia (110), Lithuania (107), Hungary (102); the remaining 769 cases were distributed among 41 countries.
- Subjects' gender: female (27,973), male (7,456), and no data (717).
- Subjects' age in years (n = 33,839), range: 12 – 101, mean 46.9, median 47.
- Number of subjects' reporting medical history: 15,463 cases.
- Relevant subjects' medical histories most frequently (≥20 occurrences) reported coded to the PTs Hypothyroidism (517), Rheumatoid arthritis (492), Arthritis (445), Osteoarthritis (304), Obesity (176), Spinal osteoarthritis (32), Joint injury (28), Alcohol use (26), Autoimmune hypothyroidism (20). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 medical history: (n = 3,253 cases). Medical conditions reported were coded to the PTs COVID-19 (1,780), Suspected COVID-19 (1,274), SARS-CoV-2 test positive (101), COVID-19 pneumonia (30), SARS-CoV-2 antibody test positive (25), Exposure to SARS-CoV-2 (13), Asymptomatic COVID-19 (9), SARS-CoV-2 test (8), SARS-CoV-2 antibody test (6), Occupational exposure to SARS-CoV-2, Post-acute COVID-19 syndrome (3 each), COVID-19 prophylaxis (1). Of note, more than 1 relevant medical history was reported in some cases.
- Co-suspects: 207 cases. Reported relevant co-suspects were atorvastatin calcium (3), leflunomide (2), amitriptyline, furosemide, olanzapine, pitavastatin (1 each).
- Number of relevant events: 36,454
- Relevant event seriousness: serious (6,685), non-serious (29,776)
- Most frequently reported relevant PTs (≥50 occurrences): Arthralgia (35,410), Arthritis (568), Rheumatoid arthritis (251), Chronic fatigue syndrome (65), Post viral fatigue syndrome (61), Rhabdomyolysis (55), Polyarthritis (44).
- Time to relevant event onset (n = 30,107), range: <24 hours to 117 days, median 1 day.

- Duration of relevant events was reported in 6,135 out of 15,249 occurrences with outcome of resolved/resolved with sequelae; it ranged from 5 minutes to 109 days.
- Relevant event outcome (36,708): fatal (19), resolved or resolving (21,958), resolved with sequelae (293), not resolved at the time of reporting (7,020), and unknown (7,418).
    - In 19 cases, the reported cause of death (≥2 occurrences) was coded to the PTs Arthralgia (16), Rhabdomyolysis (2). Most (17 of 19 cases) of the fatal cases involved elderly subjects. When the medical history was provided (13 cases), significant medical conditions included Rheumatoid arthritis, Osteoarthritis (3 each), Arthralgia, Hypothyroidism, Alcohol use (2 each), Arthritis (1).
- The lot/batch number which reported > 5% of cases involving musculoskeletal related ADRs is EL1484 (2,283 cases) and EJ6797 (2,196 cases). No quality issues were identified during investigations of the impacted lot.

Analysis by age group

- Clinical Trials: Adult (2).
- Post-Marketing: Paediatric (65), Adult (29,744), Elderly (4,240), Unknown (2,096).
    - No significant difference observed in the reporting proportion of frequently reported musculoskeletal AEs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 4,930 (13.6% of the cases reporting musculoskeletal AESIs)
- A higher reporting proportion of musculoskeletal AESIs was reported in patients without significant comorbidities (86.4%) when compared to patients with significant comorbidities.
- The reporting proportion of musculoskeletal AESIs with resolved (42.9%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (29.2% of events with resolved).

O/E Analysis

O/E analysis was performed for Rheumatoid arthritis, Polyarthritis, Chronic fatigue syndrome, and Post viral fatigue syndrome.

Conclusion

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:

The most frequently reported PT is **arthralgia** (n = 35,410), which is listed in the product information.

Please refer to the cumulative review of **Rheumatoid arthritis** (RA), relapse and new onset (DLP of 13 August 2021) in the 9th MSSR (procedure EMEA/H/C/005735/MEA/002.8). For new onset RA the data do not support a new safety issue, however the MAH did not provide sufficient information regarding RA flares. Causality assessment of RA flare-up cases is requested for the 10th MSSR.

Rhabdomyolysis is being evaluated in the MSSRs, an updated review is provided in the 11th MSSR.

No other new safety issue is 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: 8 (1.14% 702 cases, the total CT dataset; 4 cases involved BNT162b2, 1 case involved placebo and 3 cases involved blinded therapy).
- Country of incidence: US (7), Argentina (1).
- Subjects' gender: female (1), male (7).
- Subjects' age in years (n = 8), range: 34 – 73, mean 51.1, median 49.
- Number of subjects' reporting medical history: 7 cases.
- Relevant subjects' medical histories reported coded to the PT Seizure (1).
- COVID-19 medical history: 1 case (COVID-19).
- Co-suspect: None.
- Reported relevant PTs: Seizure (3), Encephalopathy, Guillain-Barre syndrome, Hypergammaglobulinaemia benign monoclonal, Neuropathy peripheral, Optic neuritis (1 each). However, none of the SAE were assessed as related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of relevant cases: 3,471 (1.1% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (2,174), Non-medically confirmed cases (1,297).
- Country of incidence (≥50 occurrences): UK (862), US (631), Japan (281), France (226), Italy (224), Mexico (187), Germany (172), Netherlands (118), Spain (113), Australia, Poland (52 each); the remaining 88 cases were distributed among 27 countries.
- Subjects' gender: female (2,290), male (1,064), and unknown (117).
- Subjects' age in years (n = 3,155), range: 12 – 107, mean 51.6, median 50.
- Number of subjects' reporting medical history: 2,234 cases.
- Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Epilepsy (381), Seizure (133), Multiple sclerosis (114), Headache (36), Dementia Alzheimer's type (29), Trigeminal neuralgia (27), Generalised tonic-clonic seizure, Partial seizures, Polyneuropathy (20 each), Parkinson's disease (16), Ischaemic stroke (15), Petit mal epilepsy (13) and Relapsing-remitting multiple sclerosis (10). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 223 cases). Medical conditions reported were coded to the PTs COVID-19 (124), Suspected COVID-19 (80), COVID-19 pneumonia (6), SARS-CoV-2 test positive, Occupational exposure to SARS-CoV-2 (4 each), Asymptomatic COVID-19, Exposure

to SARS-CoV-2, Post-acute COVID-19 syndrome, SARS-CoV-2 antibody test positive, SARS-CoV-2 test (1 each). Of note, more than 1 relevant medical history was reported in some cases.

- Co-suspects: 55 cases. Reported relevant co-suspect drug were carbamazepine, etanercept, tramadol, tacrolimus (1 each).
- Number of relevant events: 3,809.
- Relevant event seriousness: serious (3,446), non-serious (363).
- Most frequently reported relevant PTs (≥50 occurrences): Seizure (1,165), Epilepsy (420), Neuropathy peripheral (398), Guillain-Barre syndrome (226), Generalised tonic-clonic seizure (175), Fibromyalgia (137), Trigeminal neuralgia (125), Febrile convulsion (107), Multiple sclerosis (99), Status epilepticus (86), Ataxia, Optic neuritis (66 each), Multiple sclerosis relapse (65), Myelitis transverse (55), Petit mal epilepsy (54).
- Time to relevant event onset (n = 2,780), range: <24 hours to 111 days, median 1 day.
    - <24 hours: 1,016 events (5 of which had a fatal outcome);
    - 1 day: 588 events (8 of which had a fatal outcome);
    - 2-7 days: 663 events (16 of which had a fatal outcome);
    - 8-14 days: 262 events (15 of which had a fatal outcome);
    - 15-30 days: 180 events (9 of which had a fatal outcome);
    - 31-180 days: 71 events (8 of which had a fatal outcome).
- Duration of relevant events (n = 501 out of 1289 occurrences with outcome of resolved/ resolved with sequelae), range: from 1 minute to 99 days.
- Relevant event outcome: fatal (82), resolved or resolving (1,793), resolved with sequelae (102), not resolved at the time of reporting (765), and unknown (1082).
    - In 82 cases, the reported cause of death (≥5 occurrences) was coded to the PTs Seizure (31), Epilepsy (18), Guillain-Barre syndrome (6), Generalised tonic-clonic seizure, Status epilepticus (5 each). Most (57 of 82 cases) of the fatal cases involved elderly subjects. When the medical history was provided (26 cases), significant medical conditions included epilepsy (9), Dementia Alzheimer's type, Parkinson's disease (4 each), Seizure, Headache (2 each).

Analysis by age group

- Clinical Trials: Adult (6) and Elderly (2).
- Post-Marketing: Adolescent (49), Adult (2247), Elderly (895), unknown (280).
    - No significant difference observed in the reporting proportion of frequently reported neurological AEs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1,078 (31.5% of the cases reporting neurological AESIs). A higher reporting proportion of neurological AESIs was reported in patients without significant comorbidities (87.1%) when compared to patients with significant comorbidities.

- The reporting proportion of neurological AESIs with fatal outcome (3.5%) is higher in individuals with co morbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute disseminated encephalomyelitis (ADEM), Fibromyalgia, Guillain-Barre syndrome, Meningitis, Meningitis aseptic, Multiple sclerosis, Multiple sclerosis relapse, Myelitis transverse, Neuropathy peripheral, Optic neuritis, Polyneuropathy and Seizure/Seizure disorders.

Conclusion

- Seizure was a signal evaluated and determined not to be a risk. Optic neuritis and Polyneuropathy/Neuropathy peripheral were reviewed as safety topics and determined not to be validated signals.
- ADEM and Myelitis transverse are not validated signals.
  The O/E analysis for cases reporting ADEM narrow definition is slightly above 1. The number of cases reported are 21 nevertheless, 4 cases were meeting the BC definition of level 5, i.e., not an ADEM case. If we would consider only ADEM cases meeting the BC level 1 to 4 (17 cases) the O/E analysis would be lower.

No new safety signals have emerged based on a review of these cases or of the Observed versus Expected analysis. Safety surveillance will continue.

Rapporteur assessment comment:

Febrile convulsion, Generalised tonic-clonic seizure, Fibromyalgia, Meningitis, Meningitis aseptic, Multiple sclerosis, Multiple sclerosis relapse, Optic neuritis showed all O/E ratios below 1.

Please refer to Section 2.2 Signal Evaluation for the assessment of the signal of **Seizure**. Within the current PSUR, an update of the data with DLP 18 June 2021 (following previous DLP of 13 March 2021) was provided. No new significant safety information has emerged from the data.

Regarding **polyneuropathy/neuropathy peripheral**, the upper level of the 95% CI exceeds 1 for the 14-Day risk window in the PSUR period. However all O/E ratios are below 1.

Please refer to the cumulative reviews of **ADEM** and **Guillain-Barré Syndrome** with DLP 31 August 2021 in the 9th MSSR (procedure EMEA/H/C/005735/MEA/002.8). For both it was concluded that the data do not support a safety issue.

Due to an update of ACCESS background rates, the estimated O/E ratios for **transverse myelitis** were lower in MSSR#9 compared to those in the O/E analyses of the 8th MSSR. Cumulatively the O/E rates presented in the PSUR were below 1 for both 14-day and 21-day risk windows.

No new safety signal 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; Multiple organ dysfunction syndrome; 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; Systemic inflammatory response syndrome.

Clinical Trial Data

- Number of cases: 3 (0.43% of 702 cases, the total CT dataset; 1 case involved BNT162b2/placebo and 2 cases involved blinded therapy).
- Country of incidence: US (2), Brazil (1).
- Subjects' gender: male (3).
- Subjects' age in years (n = 3), range: 48 - 73 years, mean 62, median 65.
- Number of subjects' reporting medical history: 3 cases. Relevant subjects' medical histories reported coded to the PT Neoplasm malignant (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (3): Herpes zoster oticus, Multiple organ dysfunction syndrome, Pyrexia (1 each). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of cases: 70,105 (21.4% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (43,119), Non-medically confirmed cases (26,986).
- Country of incidence (≥100 occurrences): Italy (15,166), UK (10,209), US (9,397), Mexico (5,253), Spain (5,081), Netherlands (4,108), France (2,853), Germany (2,115), Austria (1,982), Japan (1,970), Portugal (1,012), Czech Republic (997), Belgium (993), Sweden (932), Norway (883), Australia (728), Denmark (678), Ireland (662), Greece (456), Finland (448), Estonia (406), Poland (401), Romania (354), Hungary (352), Lithuania (324), Israel (264), Canada (244), Croatia (195), Switzerland (175), Slovakia (156), Serbia (140), Latvia (123), Hong Kong (120), Luxembourg(113); the remaining 815 cases were distributed among 44 countries.
- Subjects' gender: female (53,099), male (15,284), and unknown (1,722).
- Subjects' age in years (n = 64,584), range: 12 – 120, mean 46.9, median 46.
- Medical history (n = 27,409). Relevant subjects' medical histories most frequently (≥50 occurrences) reported coded to the PTs Herpes zoster (450), Immunodeficiency (293), Breast cancer (277), Neoplasm malignant (110), Prostate cancer (90), Oral herpes (79), Herpes simplex (58), Thyroid cancer (49), Lung neoplasm malignant (45). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 7,480 cases). Medical conditions (≥50 occurrences) reported were coded to the PTs COVID-19 (4,517), Suspected COVID-19 (2,243), SARS-CoV-2 test positive (236), COVID-19 pneumonia (114), Coronavirus infection (80), Exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (52 each), Asymptomatic COVID-19 (51).
- Co-suspects: 339 cases. Reported relevant co-suspects were apixaban (8), etanercept (7), adalimumab (6), methotrexate sodium (5), aflibercept, infliximab, rituximab (1 each).

- Number of relevant events: 71,230.
- Relevant event seriousness: serious (13,136), non-serious (58,112).
- Most frequently reported relevant PTs (≥ 25 occurrences): Pyrexia (64,212), Herpes zoster (3,215), Inflammation (2,040), Oral herpes (780), Ophthalmic herpes zoster (130), Herpes simplex (124), Herpes virus infection (105), Multiple organ dysfunction syndrome (79), Product supply issue (76), Genital herpes (69), Herpes zoster reactivation (46), Herpes ophthalmic (43), Herpes zoster oticus (41), Nasal herpes, Systemic inflammatory response syndrome, Varicella (32 each), and Herpes simplex reactivation (26).
- Time to relevant event onset (n = 60,334), range: <24 hours to 151 days, median 1 day:
    - <24 hours: 23,640 events (41 of which had a fatal outcome);
    - 1 day: 27,211 events (82 of which had a fatal outcome);
    - 2-7 days: 6,380 events (99 of which had a fatal outcome);
    - 8-14 days: 1,460 events (25 of which had a fatal outcome);
    - 15-30 days: 1,178 events (25 of which had a fatal outcome);
    - 31-180 days: 465 events (11 of which had a fatal outcome).
- Duration of relevant events (n = 16,677 out of 36,255 occurrences with outcome of resolved/ resolved with sequelae), range: from 1 second to 116 days.
- Relevant event outcome: fatal (351), resolved or resolving (48,722), resolved with sequelae (610), not resolved at the time of reporting (8,995), and unknown/no data (12,925).
- In 351 cases, the reported cause of death (≥50 occurrences) was coded to the PTs Multiple organ dysfunction syndrome (57). Most (310 of 351 cases) of the fatal cases involved elderly subjects.
- The lot/batch number which reported > 5% of cases involving other AESI related ADRs is EJ6797, EK9788, and EJ6136. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

Clinical Trials: Adult (1) and Elderly (2).

- A meaningful comparison between the different age groups is not possible due to the low number of cases.

Post-Marketing: Paediatric (245), Adult (56,190), Elderly (8,941), and Unknown (4,729).

- No significant difference observed in the reporting proportion of frequently reported other AESIs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities

Number of subjects reporting comorbidities: 9,022 (12.9% of the cases reporting other AESIs). A higher reporting proportion of other AESIs was reported in patients without significant comorbidities (87.1%) when compared to patients with significant comorbidities.

The reporting proportion of other AESIs with fatal outcome (2.2%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.2% of events with fatal outcome).

O/E Analysis

O/E analysis was performed on Herpes zoster, Herpes ophthalmic, Herpes zoster oticus, Multiple organ dysfunction syndrome, Systemic inflammatory response syndrome.

Conclusion

- Herpes zoster, including Ophthalmic herpes zoster, was a signal evaluated and determined not to be a risk.
- O/E analysis for Multisystem inflammatory syndrome is >1 in some age-stratified analyses in the 14- and 21-day risk windows. This may be influenced by factors including its association with COVID-19 and an increased awareness of this condition by HCPs.

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

Rapporteur assessment comment:

Please refer regarding cases reporting **Multisystem inflammatory syndrome** to the separate signal procedure (EPITT ref. No. 19732) - Multisystem inflammatory syndrome.

Reported O/E ratios of cases reporting **herpes zoster** are all below 1. The MAH has committed to provide updates of the reviews of the cases reporting herpes zoster in the 10th MSSR (Sept 2021 data).

No new safety concern could be identified.

Pregnancy related AESIs

Rapporteur assessment comment:

Please refer to the Section 2.3.5.3 *Use in Pregnant/Lactating Women.*

Renal AESIs

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

Clinical Trial Data

- Number of cases: 3 (0.43% of 702 cases, the total CT dataset; 2 cases involved BNT162b2 and 1 case involved blinded therapy).
- Country of incidence: [redacted](3).
- Subjects' gender: female (1), male (2).
- Subjects' age in years (n = 3), range: 32 – 81, mean 60.7, median 69.
- Medical history (n = 3 cases). Relevant subjects' medical histories reported coded to the PTs Renal artery stenosis, and Type 2 diabetes mellitus (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (3): Acute kidney injury (3). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of cases: 387 (0.12% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (309), Non-medically confirmed cases (78).
- Country of incidence: France (66), UK (57), Germany (44), US (43), Italy (25), Spain (21), Netherlands (14), Sweden (12), Belgium, Denmark, Japan (11 each); the remaining 72 cases were distributed among 20 countries.
- Subjects' gender: female (203), male (178), and Unknown (6).
- Subjects' age in years (n = 367), range: 18 – 103, mean 76.5, median 81.
- Medical history (n = 316 cases). Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Chronic kidney disease (53), Type 2 diabetes mellitus (50), Diabetes mellitus (28), Obesity (24), Renal failure (22), Acute kidney injury (12). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 19 cases). Medical conditions reported were coded to the PTs COVID-19 (11), Suspected COVID-19 (3), Asymptomatic COVID-19, COVID-19 pneumonia, COVID-19 immunisation, COVID-19 prophylaxis, Exposure to SARS-CoV-2(1 each).
- Co-suspects: 27 cases. Reported relevant co-suspects were methotrexate sodium, tacrolimus, valaciclovir hydrochloride, zoledronic acid monohydrate.
- Number of relevant events: 391.
- Relevant event seriousness: serious (389), non-serious (2).
- Most frequently reported relevant PTs: Acute kidney injury (224), Renal failure (167).
- Time to relevant event onset (n = 229), range: <24 hours to 71 days, median 5 days.
- Duration of relevant events (n = 17 out of 44 occurrences with outcome of resolved/resolved with sequelae), range: 1 - 47 days.
- Relevant event outcome: fatal (106), resolved or resolving (88), resolved with sequelae (4), not resolved at the time of reporting (60), and unknown (133).
    - In 106 cases, the reported cause of death was coded to the PTs Acute kidney injury (52), Renal failure (54). Most (95 of 106 cases) of the fatal cases involved elderly subjects. When the medical history was provided (73 cases), significant medical conditions included Chronic kidney disease (22), Type 2 diabetes mellitus (13), Diabetes mellitus (15), Obesity (8), Renal failure (12), Acute kidney injury (3).
- The lot/batch number which reported >3% of cases involving renal related ADRs is EM0477 and EJ6788. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

Clinical Trials: Adult (1) and Elderly (2).

Post-Marketing: Adult (64), Elderly (307) and Unknown (16).

- No significant difference observed in the reporting proportion of the PTs Acute kidney injury and Renal failure 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 [24.7% in adults vs 37.5% in elderly]).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 259 (66.9% of the cases reporting renal AESIs).
- The reporting proportion of renal AESIs with fatal outcome (30.5%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (19% of events with fatal outcome).

O/E Analysis

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

Conclusion

No new safety signals have emerged based on a review of these cases. Safety surveillance will continue.

Rapporteur assessment comment: Of note, the signal of Glomerulonephritis and nephrotic syndrome has been assessed in the separate procedure (EPITT ref. 19722); EMEA/H/C/005735/SDA/035. No new safety concern could be identified.

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; Pulmonary haemorrhage; Respiratory disorder.*

Clinical Trial Data

- Number of cases: 28 (4% of 702 cases, the total CT dataset; 15 cases involved BNT162b2, 12 cases involved blinded therapy and 1 case involved placebo).
- Country of incidence: US (20), Argentina (5), Brazil (2), Japan (1).
- Subjects' gender: female (12), male (16).
- Subjects' age in years (n = 28), range: 22 – 84, mean 62.4, median 68.
- Medical history (n = 22 cases). Relevant subjects' medical histories reported coded to the PTs Asthma, Chronic obstructive pulmonary disease (3 each), Asthma exercise induced, Interstitial lung disease, Lung neoplasm malignant, Nicotine dependence, Seasonal allergy, Tobacco user (1 each).
- COVID-19 medical history (n = 1 case). The subjects' medical history was significant for COVID-19.
- Co-suspects: None.
- Reported relevant PTs (30): Pneumonia (15), Acute respiratory failure (8), Respiratory failure (3), Cardio-respiratory arrest (2), Lower respiratory tract infection, Respiratory syncytial virus bronchiolitis (1 each). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of cases: 2,263 (0.7% of 327,125 cases, the total PM dataset).

- Medically confirmed cases (1,534), Non-medically confirmed cases (729).
- Country of incidence: US (359), UK (286), France (236), Japan (218), Italy (149), Germany (121), Spain (119), Belgium (104), Netherlands (87), Mexico (61), Norway (55), Australia (50); the remaining 418 cases were distributed among 45 countries.
- Subjects' gender: female (1,258), male (959), and unknown (46).
- Subjects' age in years (n = 2,066), range: 12 – 102, mean 69.1, median 74.
- Medical history (n = 1,613 cases). Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Chronic obstructive pulmonary disease (175), Asthma (169), Pneumonia (78), Lower respiratory tract infection (38), Pulmonary embolism (32), Seasonal allergy (27), Bronchitis (24), Lung disorder (18), Chronic respiratory failure, Respiratory failure (17 each), Lung neoplasm malignant (16), Bronchitis chronic (14), Respiratory tract infection (12), Pleural effusion, Pneumonia aspiration (11 each), Pulmonary fibrosis (10). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 189 cases). The subjects' medical history was significant for COVID-19 or suspected COVID-19. The most frequently reported medical conditions (≥5 occurrences) were coded to the PTs COVID-19 (99), Suspected COVID-19 (52), COVID-19 pneumonia (13), Exposure to SARS-CoV-2 (7). Of note, more than 1 relevant medical history was reported in some cases.
- Co-suspects: 56 cases. Reported relevant co-suspects were adalimumab, atorvastatin (2 each), amiodarone hydrochloride, cyclophosphamide, etanercept, methotrexate sodium, phenytoin sodium, rituximab (1 each).
- Number of relevant events: 2,468.
- Relevant event seriousness: serious (2,216), non-serious (253).
- Most frequently reported relevant PTs (≥ 50 occurrences): Pneumonia (831), Respiratory disorder (329), Respiratory failure (280), Cardio-respiratory arrest (227), Hypoxia (210), Lower respiratory tract infection (184), Bronchitis (151), Acute respiratory failure (96) and Acute respiratory distress syndrome (60).
- Time to relevant event onset (n = 1,673), range: <24 hours to 124 days, median 0 day.
- Duration of relevant events (n = 139 out of 371 occurrences with outcome of resolved/resolved with sequelae), range: from 20 minutes to 61 days.
- Relevant event outcome: fatal (667), resolved or resolving (704), resolved with sequelae (22), not resolved at the time of reporting (341), and unknown (736).
    - In 667 cases, the reported cause of death (≥10 occurrences) was coded to the PTs Pneumonia (185), Cardio-respiratory arrest (180), Respiratory failure (124), Acute respiratory failure (43), Hypoxia (33), Acute respiratory distress syndrome (27), Cardiopulmonary failure (24), Respiratory disorder (14), Lower respiratory tract infection (11). Most (536 of 667 cases) of the fatal cases involved elderly subjects. When the medical history was provided (496 cases), significant medical conditions included Chronic obstructive pulmonary disease (71), Asthma (169), Pneumonia (28), Lower respiratory tract infection (5), Pulmonary embolism (15), Lung neoplasm malignant (13), Bronchitis, Lung disorder, Respiratory tract infection Respiratory failure, Pleural effusion, Pulmonary fibrosis (7 each), Seasonal allergy (5), Pneumonia aspiration (4).

- The lot/batch number which reported >2% of cases involving respiratory related ADRs is EM0477, EJ6796, EK9788 and EJ6795. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

Clinical Trials: Adult (13) and Elderly (15).

Post-Marketing: Paediatric (5), Adult (746), Elderly (1,335) and Unknown (177).

- 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 Respiratory disorder and Lower respiratory tract infection was observed in adult population when compared to elderly population (Respiratory disorder [15.3% vs 5.6%], Lower respiratory tract infection [18.2% vs 4.8%].

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1,108 (48.4% of the cases reporting respiratory AESIs).
- A higher reporting proportion of respiratory AESIs was reported in patients without significant comorbidities (51.6 %) when compared to patients with significant comorbidities.
- The reporting proportion of respiratory events with fatal outcome (35.8%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (16.1%).

O/E Analysis

O/E analysis was performed for Acute respiratory distress syndrome.

Conclusion

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

Rapporteur assessment comment: No new safety information could be identified concerning Respiratory AESIs. Respiratory AESIs continue to be monitored in the MSSRs for Comirnaty.

Thromboembolic AESIs

Search Criteria: *HLGT (All path) Embolism and thrombosis, excluding PTs reviewed as Stroke AESIs.*

Clinical Trial Data

- Number of cases: 23 (3.3% of 702 cases, the total CT dataset; 15 cases involved BNT162b2, 5 cases involved blinded therapy, and 3 cases involved placebo).
- Country of incidence: US (14), Brazil (4), Argentina (3), South Africa and Turkey (1 each).
- Subjects' gender: female (9) and male (14).
- Subjects' age in years (n=23 cases), range: 16 – 74, mean 52.2, median 55.
- Medical history (n=22 cases): the frequently (≥3 cases) reported relevant medical conditions included Hypertension (7), Deep vein thrombosis (5), Nephrolithiasis, Pulmonary embolism (4

each), and Hypercholesterolaemia (3). Of note, more than 1 medical history was reported in some cases.

- COVID-19 medical history (n=2 cases): COVID-19 (2).
- Co-suspects: The co-suspects reported were drospirenone/ethinylestradiol, ethinylestradiol/levonorgestrel, and naproxen (1 each)
- Reported relevant PTs (27): Pulmonary embolism (13), Deep vein thrombosis (8), Embolism, Portal vein thrombosis, Portosplenomesteric venous thrombosis, Renal vein thrombosis, Thrombosis, and Venous thrombosis limb (1 each). Of the above SAEs, Portal vein thrombosis was assessed as related to BNT162b2 (time to onset of event was recorded as 60 days and the event outcome was reported as resolved). None of other SAEs were related to blinded therapy or placebo.

Post-Authorization Data

- Number of relevant cases: 4,725 (1.4% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (3,117), Non-medically confirmed cases (1,608).
- Country of incidence: UK (755), US (700), France (623), Germany (445), Italy (323), Spain (270), Sweden (228), Netherlands (226), Norway (127), Denmark (106); the remaining 922 cases were distributed among 50 countries.
- Subjects' gender: female (2,653), male (1,956) and unknown (116).
- Subjects' age in years (n=4,370), range: 13 – 102, mean 58, median 70.
- Medical history (n=3,175 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (918), Type 2 diabetes mellitus (193), Deep vein thrombosis (177), Pulmonary embolism (167), Diabetes mellitus (164), Obesity (159), Hypothyroidism (152), Hypercholesterolaemia (127), Atrial fibrillation, Chronic obstructive pulmonary disease (121 each), Dyslipidaemia (116), Osteoarthritis (92), Tobacco user (90), Chronic kidney disease (89), Rheumatoid arthritis (86), Thrombosis (83), Cerebrovascular accident (79), Breast cancer (78), Varicose vein (71), and Ex-tobacco user (63). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n=229 cases). Medical conditions reported more than twice were coded to the PTs COVID-19 (148), Suspected COVID-19 (58), COVID-19 pneumonia (12), SARS-CoV-2 test positive (9), Asymptomatic COVID-19 (4), and Exposure to SARS-CoV-2 (3). Of note, more than 1 medical history was reported in some cases.
- Co-suspects: 119 cases. Frequently (≥3 occurrences) reported relevant co-suspects were COVID-19 AstraZeneca vaccine (8), ethinylestradiol/levonorgestrel (5), cisplatin, methotrexate, and prednisone (3 each).
- Number of relevant events: 5,517.
- Relevant event seriousness: serious (5,297), non-serious (221).
- Most frequently reported relevant PTs (≥2%): Pulmonary embolism (1,758), Deep vein thrombosis (1,197), Thrombosis (1,030), Thrombophlebitis superficial (207), Thrombophlebitis (152), Pulmonary thrombosis (114), Coagulopathy (113), Venous thrombosis limb (108), and Embolism (107).
- Time to event onset (n=4,196), range: <24 hours to 140 days, median 8 days.

- Duration of relevant events (n = 230 out of 718 occurrences with outcome of resolved/resolved with sequelae), range: 8 minutes to 94 days, median 7 days.
- Relevant event outcome: fatal (325), resolved/resolving (2,344), resolved with sequelae (158), not resolved at the time of reporting (1,447), and unknown (1,266).
    - In 275 cases (reporting 325 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Pulmonary embolism (166), Thrombosis (33), Cardiac arrest (24), Dyspnoea (21), Deep vein thrombosis (18), Pyrexia, Thrombocytopenia (12 each), Coagulopathy and Myocardial infarction (11 each), and Sudden death (10). Of note, in 10 cases limited information regarding the cause of death was provided (PT Death) or not reported the cause of death. Most (204 of 275 cases) of these fatal cases involved elderly subjects. When the medical history was provided (213 cases), significant medical conditions included aortic thrombosis, cardiac failure, cerebral artery embolism, chronic obstructive pulmonary disease, coronary artery stenosis, deep vein thrombosis, fall, general physical health deterioration, hospitalisation, major surgeries, Parkinson's disease, pulmonary embolism, and various malignancies.
- The lot/batch number which reported ≥2% of cases reporting thromboembolic events is: #ER9470 (100 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

Clinical Trial: Paediatric (1), Adults (16), and Elderly (6).

Post-Marketing: Paediatric (10), Adults (1,747), Elderly (2,647) and Unknown (321).

- There was no significant difference observed in the reporting proportion of thromboembolic events between age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1,743 (36.7% of the CT and PM cases reporting thromboembolic events).
- The reporting proportion of thromboembolic events with fatal outcome (7.7%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (3.7%).

O/E Analysis

O/E analysis was performed for Deep vein thrombosis, Disseminated intravascular coagulation, and Pulmonary embolism.

Conclusion

Thromboembolic events, has emerged as a concern for some COVID-19 vaccines; it has been evaluated by the MAH as a signal and closed as no risk. No additional safety signals have emerged based on a review of these cases and of the O/E analysis performed. Surveillance will continue.

Rapporteur assessment comment: Please refer to Section 2.2 Signal evaluation in which the numerical update of the review of the signal of thromboembolic events (in 4th MSSR) was assessed. All presented O/E ratios were below 1.

Based on the data that was available no new safety concern was identified.

Stroke

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

Clinical Trial Data

- Number of cases: 20 (2.85% of 702 cases, the total CT dataset; 13 cases involved BNT162b2, 5 cases involved blinded therapy and 2 cases involved placebo).
- Country of incidence: US (14), Argentina, China, Germany (2 each).
- Subjects' gender: female (10), male (10).
- Subjects' age in years (n = 20), range: 44 – 82, mean 64.2, median 65.5.
- Medical history (n = 18 cases). Relevant subjects' medical histories reported coded to the PTs Coronary artery disease, Hypercholesterolaemia, Hyperlipidaemia (4 each), Obesity (3), Atrial fibrillation, Sleep apnoea syndrome, and Tobacco user (2 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (20): Cerebrovascular accident (14), Cerebral infarction, Ischaemic stroke (2 each), Haemorrhagic stroke, Subarachnoid haemorrhage (1 each). Of the above SAEs, cerebrovascular event was assessed as related to BNT162b2 (duration of event was 1 day and the event outcome was reported as resolved). All the other SAEs were assessed as not related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of cases: 2,930 (0.9% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (1010), Non-medically confirmed cases (1,920).
- Country of incidence: UK (443), France (393), US (359), Japan (271), Germany (220), Netherlands (216), Italy (177), Sweden (112), Spain (104), Norway (81), Denmark (67); the remaining 489 cases were distributed among 40 countries.
- Subjects' gender: female (1,664), male (1,200), and unknown (66).
- Subjects' age in years (n = 2,754), range: 16 – 102, mean 72.3, median 76.
- Medical history (n = 2,053 cases). Relevant subjects' medical histories most frequently (≥50 occurrences) reported coded to the PTs Atrial fibrillation (278), Diabetes mellitus (150), Type 2 diabetes mellitus (149), Dyslipidaemia (141), Hypercholesterolaemia (119), Obesity (79), Transient ischaemic attack (68), Tobacco user (65), Myocardial ischaemia (64), Cerebral infarction (62), Cardiac failure (57), Ischaemic stroke (52), Myocardial infarction (51). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 medical history (n = 108 cases). The subjects' medical history was significant for COVID-19 or suspected COVID-19. Medical conditions reported more than twice were coded to the PTs COVID-19 (77), Suspected COVID-19 (24). Of note, more than 1 relevant medical history was reported in some cases.

- Number of subjects' reporting co-suspects: 82 cases. Reported relevant co-suspect was methotrexate sodium (2).
- Number of relevant events: 3,365.
- Relevant event seriousness: serious (3,349), non-serious (16).
- Most frequently reported relevant PTs (≥20 occurrences): Cerebrovascular accident (1,199), Ischaemic stroke (424), Cerebral infarction (403), Cerebral haemorrhage (312), Cerebral venous sinus thrombosis (106), Subarachnoid haemorrhage (101), Cerebral thrombosis (95), Haemorrhagic stroke (69), Cerebral ischaemia (68), Ischaemic cerebral infarction (56), Embolic stroke (39), Cerebral venous thrombosis (34), Cerebral haematoma (30), Haemorrhage intracranial (29), Lacunar infarction(23), Cerebral artery embolism (20).
- Time to relevant event onset (n = 2,679), range: <24 hours to 127 days, median 4 days.
- Duration of relevant events (n = 129 out of 560 occurrences with outcome of resolved/resolved with sequelae), range: 30 minutes to 74 days.
- Relevant event outcome: fatal (545), resolved or resolving (986), resolved with sequelae (245), not resolved at the time of reporting (753), and unknown (843).
    - Of the 545 fatal events, the most commonly reported cause of death (≥10 occurrences) were coded to the PTs Cerebrovascular accident (152), Cerebral haemorrhage (136), Ischaemic stroke (49), Cerebral infarction (45), Haemorrhagic stroke (33), Subarachnoid haemorrhage (27) and Cerebral thrombosis (12). Most (409 of 545 cases) of the fatal cases involved elderly subjects. When the medical history was provided (316 cases), significant medical conditions included atrial fibrillation (88), Type 2 diabetes mellitus (30), Diabetes mellitus (29), Cardiac failure, Cardiac failure (23 each), Dyslipidaemia (21), Myocardial ischaemia (20), Transient ischaemic attack (18), Hypercholesterolaemia (17), Cerebral infarction (15), Obesity (12), Myocardial infarction, Tobacco user (10 each).

Analysis by age group

Clinical Trials: Adult (10) and Elderly (10)

Post-marketing: Paediatric (6), Adult (729), Elderly (2,052), Unknown (143).

- No significant difference observed in the reporting proportion of stroke AEs (≥2%) between adult and elderly population. However, a higher reporting proportion of events coded to the Ischaemic stroke and Cerebral infarction was observed in elderly population when compared to adult population and paediatric (Ischaemic stroke [4.4% vs 8.8% vs 0%; Cerebral infarction [3.3% in adults vs 8.3% in elderly vs 5% in paediatric].

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1,148 (38.9% of the cases reporting stroke AESIs). A higher reporting proportion of stroke AESIs was reported in patients without significant comorbidities (61.9 %) when compared to patients with significant comorbidities.
- The reporting proportion of stroke AESIs with fatal outcome (18.9%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (13% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Ischemic strokes and Hemorrhagic strokes.

Conclusion

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

Rapporteur assessment comment:

In the age stratified O/E analyses, the upper level of the 95% CI exceeds 1 in age group ≤ 17 years for the 14-day risk window in the cumulative period.

	≤17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Ischemic stroke	0.510	0.166, 1.190	0.103	0.047, 0.195	0.096	0.080, 0.114	0.045	0.038, 0.053	0.040	0.035, 0.045	0.040	0.038, 0.043

This was based on 5 paediatric cases of ischemic stroke, which is of concern considering the seriousness and rareness of the condition in the younger age group. However, the O/E ratios of the age-stratified O/E analyses are below 1, and cases are confounded by risk factors and underlying conditions.

No new safety issue could be identified.

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.

Post-Authorization Data

- Number of cases: 360 (0.1% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (267), Non-medically confirmed cases (93).
- Country of incidence: UK (91), France (55), Italy (40), US (31), Germany (23), Spain (20), Netherlands (17), Japan (15), Portugal, Sweden (10 each), Norway (5); the remaining 43 cases were distributed among 21 countries.
- Subjects' gender: female (239), male (117), and unknown (4).
- Subjects' age in years (n=326 cases), range: 13 – 99, mean 58.9, median 68.
- Medical history (n=230 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (69), Type 2 diabetes mellitus (14), Dyslipidaemia (12), Diabetes mellitus, Ex-tobacco user, Obesity (9 each), Drug hypersensitivity, Hypersensitivity, Rheumatoid arthritis, Vasculitis (8 each), Behcet's syndrome (7), Hypercholesterolaemia (6), Aortic aneurysm and Myocardial ischaemia (5 each). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n=22 cases). The medical conditions were coded to the PTs COVID-19 (15), Suspected COVID-19 (5), and Exposure to SARS-CoV-2 (2).
- Co-suspects: Relevant co-suspects are acenocoumarol, acetylsalicylic acid, and enoxaparin (1 each).

- Number of events: 380.
- Relevant event seriousness: serious (269) and non-serious (111).
- Most frequently reported relevant PTs (≥2%): Vasculitis (124), Peripheral ischaemia (56), Cutaneous vasculitis (43), Giant cell arteritis (38), Vasculitic rash (25), Henoch-Schonlein purpura (23), and Hypersensitivity vasculitis (17).
- Time to event onset (n = 269), range: <24 hours to 75 days, median 3 days.
- Duration of relevant events (n = 28 out of 69 occurrences with outcome of resolved/resolved with sequelae); range: 10 minutes to 44 days, with a median of 7 days.
- Relevant event outcome: fatal (11), resolved/resolving (166), resolved with sequelae (5), not resolved at the time of reporting (101), and unknown (97).
    - In 10 cases (reporting 11 relevant events with a fatal outcome), the reported cause of death (≥2 occurrences) were coded to the PTs Peripheral ischaemia (6), Coagulopathy, Pulmonary vasculitis, and Renal vasculitis (2 each). Most (8 of 10 cases) of these fatal cases involved subjects who were ≥75 years of age. When the medical history was provided (8 cases), medical conditions included arterial disorder, cardiac ventricular thrombosis, chronic kidney disease, chronic obstructive pulmonary disease, and peripheral arterial occlusive disease.
- Lot/Batch Number: The lot/batch number which reported ≥3% of cases reporting vasculitic events is: #EM0477 (14 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

Post-Marketing: Paediatric (3), Adults (146), Elderly (180) and Unknown (31).

- Among the frequently (≥2%) reported relevant PTs, the reporting proportion of PT Giant cell arteritis was significantly higher in elderly population when compared to adult population (16.7% in elderly vs 4.8% in adult). No paediatric cases reported PT Giant cell arteritis. This is not surprising because giant cell arteritis is the most common vasculitis of the elderly.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 147 (40.8% of the PM cases reporting vasculitic events).
- The reporting proportion of vasculitic AESIs with a fatal outcome (4.5%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.5% for fatal outcome).

O/E Analysis

O/E analysis was performed for Behcet's syndrome, Cutaneous vasculitis, Giant cell arteritis, Peripheral ischaemia, Vasculitic rash, and Vasculitis.

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:

Observed/Expected analysis was performed for Giant cell arteritis, Cutaneous vasculitis, Peripheral ischaemia, Behcet's syndrome, Vasculitic rash and Vasculitis: all O/E ratios are below 1.

No new safety concern could identified concerning Vasculitic events during the reporting period.

Sudden Death

Rapporteur assessment comment:

Please refer to Section 2.3.4.1 Death.

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: 3 (0.4% of 702 cases, the total CT dataset; 3 were blinded therapy).
- Country of incidence: US (2), South Africa (1).
- Subjects' gender: female (2), and male (1).
- Subjects' age in years (n = 3), range: 55 – 75, mean 64, median 62.
- Medical history = HIV infection (3).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported PTs (4): COVID-19 pneumonia, Pneumonia, Road traffic accident, and Type 2 diabetes mellitus (1 each). None of the events were related to BNT162b2 or blinded therapy.

Post-Authorization Data

- Number of cases: 294 (0.09% of 327,125 cases, the total PM dataset).

Patients with pre-existing HIV Infection: 114 (0.03% of 327,125 cases, the total PM dataset).

- Medically confirmed cases (49), Non-medically confirmed cases (65).
- Country of incidence: US (33), UK (29), France (19), Italy (11), Switzerland (3), Belgium, Germany, Netherlands, Norway, Portugal, Spain (2 each). The remaining 7 cases were distributed among 7 countries.
- Subjects' gender: female (28), male (84) and unknown (2).
- Subjects' age in years (n = 107), range: 20 – 89, mean 50.6, median 52.
- COVID-19 Medical history (n = 11): COVID-19, Suspected COVID-19 (5 each), and Exposure to SARS-CoV-2 (1).
- Co-suspects: Acyclovir, etravirine, emtricitabine, tenofovir alafenamide (1 each).
- Of the 114 cases reporting a pre-existing HIV condition, 9 subjects reported cardiac disorders. The events in these cases were coded to PTs Arrhythmia (3), Tachycardia (2), Acute myocardial infarction, Cardiac arrest, Cardio-respiratory arrest, Extrasystoles, Hypertensive heart disease, Myocardial infarction, Palpitations, Ventricular extrasystoles, Ventricular fibrillation (1 each). Of the 14 events 12 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (6), and unknown (4).
- Of the 114 cases, 44 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (21), Dizziness (7), Generalised tonic-clonic seizure, Lethargy, Somnolence (3 each), Ageusia, Anosmia, Dysgeusia, Loss of consciousness, Sciatica, Taste disorder (2 each), Cerebrovascular accident, Disturbance in attention, Dysaesthesia, Dysgraphia, Dyslexia, Dysstasia, Facial paralysis, Guillain-Barre syndrome, Hypersomnia, Hypoaesthesia, Hypokinesia, Hypotonia, Migraine, Paraesthesia, Paresis, Presyncope, Sinus headache, Speech disorder, Status epilepticus, Syncope, Tremor, Vocal cord paralysis (1 each). Twenty-six (26) were assessed as serious and 46 were non-serious. Outcome of the events was reported as resolved/resolving (30), not resolved (25), and unknown (17).
- Of the 114 cases, 8 subjects reported infectious events. The events in these cases were coded to PTs COVID-19, Herpes zoster, Suspected COVID-19 (2 each), Asymptomatic COVID-19, Conjunctivitis, Influenza (1 each). Of the 9 events 7 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as resolved/resolving (4), not resolved (2), and unknown (3).
  - 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 114 cases, 92 cases involved adults, 15 cases involved elderly and in 7 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: 85 (0.02% of 327,125 cases, the total PM dataset).

- Medically confirmed cases (62), Non-medically confirmed cases (23).

- Country of incidence: France (30), UK (18), US (12), Spain (5), Ireland, Italy (4 each), Germany, and Japan (3 each). The remaining 6 cases were distributed among 6 countries.
- Subjects' gender: female (57), male (28).
- Subjects' age in years (n = 85), range: 18 – 97, mean 61.6, median 66.
- COVID-19 Medical history (n = 7): COVID-19 (4), and Suspected COVID-19 (3).
- Co-suspects: None.
- Of the 85 cases reporting a pre-existing tuberculosis, 15 subjects reported cardiac disorders. The events in these cases were coded to PTs Tachycardia (5), Atrial fibrillation, Palpitations (3 each), Acute myocardial infarction, Arrhythmia, Cardiac failure, Cardiac failure chronic, Cardiac flutter, Cardio-respiratory arrest, Coronary artery disease, Left ventricular hypertrophy, Myocardial ischaemia, Myocarditis, Pericardial effusion, Sinus bradycardia, and Ventricular tachycardia (1 each). Of the 24 events, 22 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (8), not resolved (9), and unknown (3).
- Of the 85 cases, 32 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (13), Dizziness (4), Paraesthesia (3), Facial paralysis, Guillain-Barre syndrome, Hemiplegia, Somnolence, Syncope (2 each), Ageusia, Amnesia, Aphasia, Circadian rhythm sleep disorder, Coma, Dysarthria, Hemianopia homonymous, Hypoaesthesia, Incoherent, Ischaemic stroke, Lethargy, Monoparesis, Motor dysfunction, Paresis, Petit mal epilepsy, Sensory loss, Tension headache, Transient ischaemic attack, Tremor, Unresponsive to stimuli (1 each). Of the 50 events, 33 were assessed as serious and 17 events were non-serious. Outcome of the events was reported as resolved/resolving (20), not resolved (15), resolved with sequelae (3), and unknown (12).
- Of the 85 cases, 9 subjects reported infectious events. The events in these cases were coded to PTs COVID-19, Pneumonia (3 each), Influenza, Nasopharyngitis, Pyelonephritis, Staphylococcal bacteraemia, Tonsillitis, Urinary tract infection, and Urosepsis (1 each). Of the 13 events, 11 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (5), resolved (6), and unknown (2).
  - 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 85 cases, 42 cases involved adults, and 43 cases involved elderly. The reporting proportion of cardiac events was higher in elderly (41.9%) compared to the adult population (14.3%). No significant difference was observed in the reporting proportion of infections (16.3% in elderly vs 14.3% in adults), and nervous system disorders (79.1% in elderly vs 38.1% in adults) between the elderly and adult population.

Patients with pre-existing malnutrition: 91 (0.03% of 327,125 cases, the total PM dataset).

Patients with pre-existing malnutrition: There were 91 cases that reported a medical history of malnutrition. However, 72 cases were determined to be non-contributory and are not included in the discussion as limited information was available regarding weight and/or height of subjects, and precise aetiology of the underlying malnutrition.

- Number of cases: 19 (0.01% of 327,125 cases, the total PM dataset).
- Medically confirmed cases (17), Non-medically confirmed cases (2).

- Country of incidence: France (9), Norway (4), Switzerland (2), Czech Republic, Sweden, UK, US (1 each).
- Subjects' gender: female (17), male (2).
- Subjects' age in years (n = 19), range: 23 – 103, mean 79.2, median 85.
- COVID-19 Medical history (n = 3): COVID 19 (2), and Suspected COVID-19 (1).
- Co-suspects: None.
- In 19 these cases, the most frequently reported events (>1 occurrence) were Death, Decreased appetite, Drug ineffective, Fall (3 each), Acute respiratory failure, Dyspnoea, Fatigue, General physical health deterioration, Pyrexia, Thrombocytopenia, Urinary incontinence (2 each).
- Of the 19 cases reporting pre-existing malnutrition, 5 subjects reported PTs Decreased appetite (3), General physical health deterioration (2), Condition aggravated, and Weight decreased (1 each). Four (4) events were assessed as serious and 3 events were non-serious. Outcome of the events was reported as fatal (2), resolving (1), and unknown (4).
- Of the 19 cases, 17 were reported in elderly and 2 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.

Conclusion

No safety signals have emerged based on the review of these cases. Safety surveillance will continue.

Rapporteur assessment comment:

There were no reports from Low- and Middle-Income Countries (WHO request).

Based on the data available concerning 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, no new safety concern could be identified.

AESIs in subjects with malnutrition, tuberculosis, HIV infection and other high prevalent infectious diseases continue to be monitored in the PSURs for Comirnaty.

2.3.1.4. 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:
No clinical relevant differences between the SARS-CoV-2 positive subgroup and the negative subgroup were reported, although it is noted that the baseline SARS-CoV-2 positive subgroup included far fewer participants than the baseline negative subgroup.

2.3.1.5. Local adverse reactions

Search Criteria: PTs Erythema; Injection site erythema; Injection site pain; Injection site swelling; Swelling

Clinical Trial Data (CT)

- There were no serious clinical trial cases of local reactions reported during the reporting interval.

Post-Authorization Data (PM)

- Number of cases: 21,806 (6.7% of 327,125 cases, the total PM dataset). MC 14,816 cases.
- Country of incidence (≥2%): Italy (9021), UK (3657), US (3369), Mexico (1208), Japan (985), France (673).
- Subjects' gender: female (17,150), male (4174) and unknown (482).
- Subjects' age in years (n = 20,417), range: 0.04 - 109, mean 48, median 47.
- Number of events: 105,498 (of which 23,518 were PTs of interest).
- Relevant event seriousness: serious (3048), non-serious (20,475).
- Most frequently reported relevant PTs (≥2%): Injection site pain (10,105), Erythema (7884), Swelling (3737), Injection site erythema (1170), Injection site swelling (622).
- Time to event onset (n = 19,140), range: < 24 hours – 131 days, median < 24 hours.
    - <24 hours: 11,106 events;
    - 1 day: 5186 events;
    - 2-7 days: 2090 events;
    - 8-14 days: 506 events;
    - > 14 days: 252 events.
- Duration of event :

- <24 hours: 1226 events;
- 1 day: 2422 events;
- 2-7 days: 4526 events;
- 8-14 days: 361 events;
- > 14 days: 542 events.

- Relevant event outcome: fatal (7), resolved/resolving (15,470), resolved with sequelae (138), not resolved (3015), unknown (4984).
- Analysis by age group:
  - PM - 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:
  - PM: Number of subjects with comorbidities: 2920 (0.9% of 327,125 cases, the total PM dataset). Subjects with comorbidities were reported in 13.4% 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:
  - PM: The majority of post-authorization events reported across doses were similar with the exception of erythema being reported more frequently after the 1st dose and Injection site erythema and Injection site pain being more frequently reported in the unspecified dose group. The majority of events (87%) were non-serious.

MAH's conclusion: Local adverse reactions were reported in 21,806 cases representing 6.7% of the cases in the reporting period. The majority of events (87%) were non-serious events with 66.1% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 7 fatal cases describing local adverse reactions; all were in elderly patients. 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 patients. 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:

MAH's conclusion is accepted that the evaluation of the reported local adverse reaction cases did not reveal any significant new safety information. Local adverse reactions are stated in the ADR table of section 4.8 of the Comirnaty SmPC (last updated 24/09/2021):

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia;[e] Injection site swelling	Injection site redness	Asthenia; Malaise; Injection site pruritus		Extensive swelling of vaccinated limb;[c] Facial swelling[f]

a. The frequency category for urticaria and angioedema was Rare.
b. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
c. Adverse reaction determined post-authorisation.
d. Refers to vaccinated arm.
e. A higher frequency of pyrexia was observed after the second dose.
f. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

2.3.1.6. Systemic adverse reactions

Search Criteria: PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia.

Clinical Trial Data (CT)

- Number of cases: 3 (0.4% of 702 cases, the total CT dataset; BNT162b2 [2], and blinded therapy [1]).
- Relevant PTs: Fatigue, Myalgia, and Pyrexia (1 each). Of these SAEs, no SAEs were assessed as related to BNT162b2 or blinded therapy by the Sponsor.

Post-Authorization Data (PM)

- Number of cases: 157,857 (48.3% of 327,125 cases in the total PM dataset). MC cases (87,004).
- Country of incidence (≥2%): UK (31,636), Italy (27,998), US (23,668), Mexico (11,793), Netherlands (11,564), Spain (7638), France (6056), Germany (5091), Austria (3967), and Japan (3163).
- Subjects' gender: female (120,768), male (32,995) and unknown (4094).
- Subjects' age in years (n = 144,347), range: 12 – 120, mean 47.2; median 46.
- Number of events: 782,639 (of which 328,517 were PTs of interest).
- Relevant event seriousness: 62 serious (56,426), non-serious (272,148).
- Relevant PTs: Headache (83,668), Pyrexia (64,190), Fatigue (54,664), Myalgia (49,373), Chills (41,220), and Arthralgia (35,402).
- Time to event onset (n = 274,746), range <24 hours to 151 days, median 1 day.
    - <24 hours: 121,702 events (64 of which had a fatal outcome);

- 1 day: 118,623 events (144 of which had a fatal outcome);
- 2-7 days: 26,571 events (136 of which had a fatal outcome);
- 8-14 days: 3924 events (37 of which had a fatal outcome);
- 15-30 days: 2907 events (14 of which had a fatal outcome);
- 31-181 days: 1019 events (7 of which had a fatal outcome).

- Duration of event (n = 71,710), range: <24 hours to 109 days, median 2 days.
  - <24 hours: 5092 events;
  - 1 day: 25,916 events;
  - 2-7 days: 37,589 events;
  - 8-14 days: 1927 events;
  - 15-30 days: 903 events;
  - 31-181 days: 283 events.
- Relevant event outcome: fatal (483), not resolved (52,475), resolved/resolving (214,179), resolved with sequelae (2494), and unknown (60,508).

Analysis by age group

- CT: Adults (2 PTs [Fatigue, Myalgia]), Elderly (1 PT [Pyrexia]). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: The most frequent systemic adverse reactions in participants 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, the paediatric population had the highest proportion of the PTs Fatigue, Headache and Pyrexia; the adult population had the highest proportion of the PT Myalgia; the elderly population had the highest proportion of the PT Arthralgia; and the PT Chills was evenly distributed across populations. In general, relevant events were more likely to be assessed as serious and/or associated with a worse outcome (i.e., fatal or not resolved) with increasing age. Of note, none of the relevant events were fatal in the paediatric population.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 21,863 (6.7% of 327,827 cases in the total dataset and 13.8% of 157,860 [3 CT and 157,857 PM] cases reporting systemic adverse reactions).
- CT: None of the CT cases reported selected comorbidities.
- PM: 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 serious and/or associated with a worse outcome (i.e., fatal or not resolved). 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 49,212 cases, 2 doses in 48,264 cases; and in 60,386 cases the dose was either not specified or reported as other.
- CT: Vaccination dose number: 2 doses (2) and 3 doses (1). A meaningful comparison by dose is not possible due to the low number of CT cases.
- PM: In general, the total proportion of relevant events, event seriousness, and event outcome were evenly distributed by dose and no significant differences were noted.

MAH's conclusion: Systemic adverse reactions were reported in 157,860 (3 CT and 157,857 PM) cases representing 48.2% of the cases in the total dataset for the reporting period. The majority of events (82.8%) were non-serious events with 65.6% of the events resolved, resolved with sequelae or resolving at the time of reporting. When reported, the majority onset of events occurred within 48 hours with a median duration of 2 days. 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:

MAH's conclusion is accepted that the evaluation of the reported 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 stated in the ADR table of section 4.8 of the Comirnaty SmPC (last updated 24/09/2021):

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity[d]		
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia;[e] Injection site swelling	Injection site redness	Asthenia; Malaise; Injection site pruritus		Extensive swelling of vaccinated limb;[c] Facial swelling[f]

a. The frequency category for urticaria and angioedema was Rare.
b. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
c. Adverse reaction determined post-authorisation.
d. Refers to vaccinated arm.
e. A higher frequency of pyrexia was observed after the second dose.
f. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

2.3.1.7. Severe reactogenicity

Search Criteria: PT Extensive swelling of vaccinated limb.

Clinical Trial Data (CT)

- During the current reporting interval, there were no serious CT cases indicative of extensive swelling of vaccinated limb.

Post-Authorization Data (PM)

- Number of cases: 427 (0.13% of 327,125 cases, the total PM dataset). MEDICALLY CONFIRMED cases (90).
- Country of incidence (≥2%): Netherlands (295), Belgium (45), Croatia (26), France (15), UK (12), Australia (9); the remaining 25 cases were distributed among 13 countries.
- Subjects' gender: female (383), male (42), unknown (2).
- Subjects' age in years (n = 409), range: 18.0 - 95.0, mean 46, median 46.
- Number of events: 3608 (of which 427 were PTs of interest).
- Relevant event seriousness: serious (85), non-serious (342).
- Most frequently reported relevant PTs: 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 = 384) , range: <24 hours to 91 days, median 0 day.
    - <24 hours: 155 cases;
    - 1 day: 158 cases;
    - 2-7 days: 56 cases;
    - 8-14 days: 12 cases (1 case had a fatal outcome);
    - 15 -91 days: 3 cases.
- Duration of relevant events was reported in 57 out of 115 occurrences with outcome of resolved; it ranged from 1 hour to 15 days.
    - <24 hours: 3 cases;
    - 1 day: 6 cases;
    - 2-7 days: 42 cases;
    - 8-15 days: 6 cases.

- Relevant event outcome: fatal (1), resolved/resolving (274), resolved with sequelae (1), not resolved (133), unknown (18).
- Analysis by age group:
    - PM: Adult (377), Elderly (43), Unknown (7). A higher reporting proportion of events coded to the PTs Extensive swelling of vaccinated limb was observed in elderly versus adult population (Extensive swelling of vaccinated limb [17.2% in adults vs 21.7% in elderly]
- Analysis by presence of comorbidities:
    - PM: Number of subjects reporting comorbidities: 41 (9.6% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (90.4%) when compared to patients with significant comorbidities.

      The reporting proportion of event severe reactogenicity with fatal outcome (none) and resolving (38.6%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (26.8% of events with resolving).

MAH's conclusion: There was a total of 427 cases, in the safety database reporting the Preferred Term Extensive swelling of vaccinated limb with the use of BNT162b2, and were mostly reported from the Netherlands (295, 69.1%) and Belgium (45, 10.5%). Majority of cases involved females (383, 89.7%) and were reported in patients aged 31-64 years (377, 88.2%). Eighty-five (19.9; 19.3%) of the cases were assessed as serious due to meeting medically significant criteria (there were no hospitalizations due to reported events). There was 1 case reporting a fatal outcome. There was limited information provided in the case for a meaningful assessment. Three hundred and thirteen (313) cases reported time to onset of the event as the same day or the day following vaccination. 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 ADR 'Extensive swelling of vaccinated limb' was added to section 4.8 of the Comirnaty SmPC after the assessment of the 4th MSSR (EMEA/H/C/005735/MEA/002.3).

No new safety information could be identified based on the data presented by the MAH concerning severe reactogenicity.

2.3.1.8. Age-related adverse reactions

Clinical Trial Data (CT)

- Number of cases: 702
- Time to event onset (n = 704), range <24 hours to 181 days, median 74 days:
    - <24 hours: 15 events;
    - 1 day: 8 events;
    - 2-7 days: 36 events;

- 8-14 days: 41 events;
- 15-30 days: 91 events;
- 31-181 days: 513 events.

- Relevant event outcome34: fatal (59), resolved/resolving (684), resolved with sequelae (51), not resolved (79), unknown (11).

Post-Authorization Data (PM)

- Number of cases: 327,125
- Time to event onset (n = 898,933), range <24 hours to 151 days, median 1 day.
  - <24 hours: 410,018 events;
  - 1 day: 291,576 events;
  - 2-7 days: 135,212 events;
  - 8-14 days: 31,086 events;
  - 15-30 days: 20,494 events;
  - 31-151 days: 10,547 events.
- Relevant event outcome: fatal (11,112), resolved/resolving (630,717), resolved with sequelae (10,706), not resolved (201,052), unknown (323,571).

Analysis by age group

- CT: Paediatric (27), Adults (412), Elderly (255) and Unknown (2).

  The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 28, Table 29, and Table 30 of the PSUR (not shown here). The Cardiac disorders and Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOCs was included in the top 5 SOCs for the adult and elderly age group, however, was not seen in the paediatric age group.

  There were 84 cases reporting 94 events in the Cardiac disorders SOC for the adult and elderly age group. Sixty-six (66) cases reported relevant medical history (e.g., hypertension, coronary artery disease, myocardial infarction, cardiac disorder) 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 Acute myocardial infarction, Atrial fibrillation (15 each), Myocardial infarction (11), Coronary artery disease (7) and Cardiac failure congestive (5). It is not unexpected for events of cardiac disorders to be reported more frequently in adult and elderly patients compared to paediatric patients.

  There were 86 cases reporting 92 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Thirty (30) cases reported pre-existing medical history of cancer (e.g., breast cancer, uterine leiomyoma, prostate cancer, colon cancer, leukaemia). The most frequently reported events (>3 occurrences) in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group were Breast cancer (11), Uterine leiomyoma (5), Invasive ductal breast carcinoma and Prostate cancer (4 each). When reported, latency ranged from <24 hours to 203 days with a median of 87 days.

There were 13 cases reporting 15 events in the Psychiatric disorders SOC for the paediatric age group. Twelve (12) cases reported relevant medical history (e.g., anxiety, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder) that may have contributed to the relevant events. The 15 events reported were Depression, Suicidal ideation (5 each), Major depression (2), Anxiety, Bipolar I disorder, Conversion disorder (1 each).

- PM: Paediatric (1605), Adults (220,883), Elderly (61,781) and Unknown (42,429).

  The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 31, Table 32, and Table 33 of the PSUR (not shown here). The top 5 SOCs were generally comparable for all age groups except Injury, poisoning and procedural complications in the paediatric age group and Skin and subcutaneous tissue disorders in the adult and elderly age group.

  The most commonly reported PTs (>30) in Injury, poisoning and procedural complications for the paediatric age group were Off label use (126), Poor quality product administered, Product administered to patient inappropriate age (94 each), Product use issue (70), and Overdose (43) reported in 347 cases. Of note, some cases more reported more than 1 PT. Off label use, Product administered to patient inappropriate age and Product use issue cases are reviewed in Section Off-Label Use. Poor quality product administered and Overdose are reviewed in Section Medication Errors and Section Overdose, respectively. Of the 347 cases, there were no clinical events co-reported in 258 cases. The most commonly co-reported PTs (>10 occurrences) in the remaining 84 cases were Pyrexia (19), Pain in extremity (16), and Headache (13). These events are considered listed or consistent with listed AEs in current RSI.

  In the Skin and subcutaneous tissue disorders SOC for the adult and elderly age group, event seriousness was assessed as serious (16,160) and non-serious (44,265). Event outcome was reported as resolved/resolving (31,583), not resolved (11,855), resolved with sequel (485), unknown (16,827) and fatal (80). The fatal cases are reviewed in Section Death. The most commonly reported PTs (>800) in Skin and subcutaneous tissue disorders for the adult and elderly age group were Pruritis (10,456), Rash (9553), Sensitive skin (7402), Erythema (7367), Urticaria (5043), Hyperhidrosis (4634), Rash pruritic (1690), Rash erythematous (1462), Cold sweat (1095), Rash macular (878). Most of these events are listed or consistent with listed events as per the current RSI.

MAH's conclusion: Overall, the highest number of events was reported in the adult group, compared to the elderly group; this is partially reflected in the overall European exposure data (assuming the European data well represent the worldwide picture). 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:

MAH's conclusion is accepted that the age-related AEs did not identify any new safety information. However, it is noted that here reports of myocarditis and pericarditis in younger males were not discussed by the MAH. Please refer regarding the evaluation of the signal of myocarditis and pericarditis to the separate procedure EMEA/H/C/005735/SDA/032, EPITT ref. 19712.

2.3.1.9. 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 (CT)

- Number of cases: 16 (2.3% of 702 cases in the total CT dataset; blinded therapy [8], BNT162b2 [7], placebo [1]).
- Reported relevant PTs (16): Syncope (6), Dyspnoea (5), Anxiety (2), Blood pressure increased, Dizziness, Palpitations (1 each). None of the events were assessed as related to BNT162b2/blinded therapy by the investigators.

Post-Authorization Data (PM)

- Number of relevant cases: 57,806 (18% of 327,125 cases, the total PM dataset). MC cases (33,739).
- Country of incidence (≥2%): UK (13,367), US (10,632), Mexico (6610), Italy (5457), France (2830), Japan (2553), Germany (1997), Spain (1679), Netherlands (1423).
- Subjects' gender: female (44,721), male (11,639) and unknown (1446).
- Subjects' age in years (n = 52,861), range: 5 - 107, mean 48.6, median 47.
- Number of events: 328,287 (of which 73,819 were relevant PTs for this topic).
- Relevant event seriousness: serious (27,975), non-serious (45,871).
- Most frequently reported relevant PTs (≥2%): Dizziness (23,935), Dyspnoea (11,041), Paraesthesia (9532), Tachycardia (6238), Hyperhidrosis (5023), Palpitations (4405), Syncope (3213), Blood pressure increased (3176), Paraesthesia oral (2659), Loss of consciousness (2086), and Anxiety (1683).
- Time to event onset (n = 58,529) , range < 24 hours to 122 days, median < 24 hours:
    - <24 hours: 34,591 events (94 of which had a fatal outcome);
    - 1 day: 12,544 events (94 of which had a fatal outcome);
    - 2-7 days: 8416 events (153 of which had a fatal outcome);
    - 8-14 days: 1586 events (40 of which had a fatal outcome);
    - 15-30 days: 1024 events (22 of which had a fatal outcome);
    - 31-181 days: 368 events (3 of which had a fatal outcome).
- Duration of event (n = 11,617 of 73,819 relevant events with outcome of resolved/resolved with sequelae) :
    - <24 hours: 2856 events;
    - 1 day: 4643 events;
    - 2-7 days: 3414 events;
    - 8-14 days: 388 events;
    - 15-30 days: 217 events;

- 31-181 days: 95 events.

- Relevant event outcome: fatal (529), resolved/resolving (41,237), resolved with sequelae (951), not resolved (11,577), unknown (20,032).

Analysis by age groups

- CT: Paediatric (1), Adults (9) and Elderly (6). A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (289), Adults (42,718), Elderly (9990) and Unknown (4809). 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 PTs, Loss of consciousness and Syncope was observed in the paediatric population when compared to the adult or elderly population (Loss of consciousness [12.8% in paediatrics vs 3.0% in adults vs 6.5% in elderly], Syncope [16.3.% in paediatrics vs 5.1% in adults vs 6.7% in elderly]. This is consistent with expectations based on age-related event reports from other vaccines.

Analysis by presence of comorbidities

- PM: Number of subjects with comorbidities: 11,256 (19.5% of the cases reporting stress/anxiety ADRs). The reporting proportion of cases with fatal outcome is higher in individuals with comorbid conditions (0.9%) when compared to the reporting proportion observed in individuals without comorbidities (0.2%). In these cases, underlying comorbidities or events not related to stress/anxiety, are likely to be contributory to individual'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 described in section 4.4 and 4.8 of the Comirnaty SmPC. MAH's conclusion is accepted that no new significant safety information could be identified based on the review of cases reporting vaccination stress/anxiety related AEs.

2.3.1.10. Evaluation of special situations

2.3.1.10.1. 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 filed 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 (CT)

- Number of cases: 46 (6.6% of 702 cases, the total CT dataset; 41 cases involved blinded therapy [22]/BNT162b2 [19]). In the remaining 5 cases subjects received placebo.

- Country of incidence: US (32), Argentina (5), Brazil (3) and South Africa (1).
- Subjects' gender: female (15) and male (26).
- Subjects' age in years (n = 41), range: 29 – 87, mean 62.4, median 64.
- The most frequently reported PTs (≥3 occurrences): Acute respiratory failure, Cardiac arrest (4 each), Completed suicide, COVID-19, COVID-19 pneumonia, Myocardial infarction (3 each). None of these events are considered related to blinded therapy/BNT162b2.

Post-Authorization Data (PM)

- Number of Number of cases: 5042 (1.5% of 327,125 cases, the total PM dataset). MC cases (3961).
- Country of incidence (≥2%): Germany (721), France (632), UK (443), Japan (377), Netherlands (322), US (321), Italy (240), Sweden (220), Spain (178), Norway (171), Australia (168), Hungary (144), Belgium (119), Romania (110), Austria (103), and Poland (102).
- Subjects' gender: female (2455), male (2316), unknown (271).
- Subjects' age in years (n = 4614), range: 2 - 105, mean 80.3, median 83.
- The most frequently reported (≥2%) events coded to the PTs: Death (1268), COVID-19 (485), Sudden death (332), Cardiac arrest (325), Dyspnoea (291), Pyrexia (263), Drug ineffective (229), Cardiac failure (194), Myocardial infarction (192), Pneumonia (185), General physical health deterioration (181), Cardio-respiratory arrest (180), Pulmonary embolism (170), Malaise (166), Cerebrovascular accident (152), Vomiting (140), Cerebral haemorrhage (136), Respiratory failure (124), Vaccination failure (122), COVID-19 pneumonia (120), Asthenia (114), Oxygen saturation decreased (105), and Fatigue (101).
- Time to fatal event onset (n = 8127), range: <24 hours to 133 days, median 1 day.
    - Same day: 1059 events;
    - 1 day: 1575 events;
    - 2-7 days: 3061 events;
    - 8-14 days: 1126 events;
    - 15-30 days: 908 events;
    - 31-181 days: 400 events.

Analysis by age groups

- CT: Adults (22), and Elderly (19). A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.
- PM: Paediatric (4), Adults (542), Elderly (4138) and Unknown (358).

  There is a significant difference observed in the reporting proportion of most 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 (82.1% vs 10.7%, respectively). There is no meaningful comparison between elderly vs paediatric population is possible due to the low number of paediatric fatal cases reported (0.1% vs 82.1%, respectively).

Most of the cases reporting a fatal outcome (68.6%) 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

- PM: Number of subjects with comorbidities: 2760 (0.8% of 327,827 cases, the total dataset). Upon review, there were no significant differences observed in the patterns of fatal events reported between the group with comorbidities and the one without comorbidities.

Analysis by dose

- PM: Number of vaccine doses administered at the time of the subjects' death:
    - First dose (2264)
    - Second dose (1437). Of the 1437 cases, 781 cases (54.3%) reported a latency of same day to 3 days after vaccination. There were 3374 fatal events. The most frequently reported (>50 occurrences) fatal events were coded to PTs Death (355), COVID-19 (155), Vaccination failure (121), Cardiac arrest (105), Sudden death (88), Dyspnoea, Pyrexia (87 each), Drug ineffective (66), Myocardial infarction (61), Cardiac failure (55), Pneumonia (52), and Cardio-respiratory arrest (51).
    - Third dose (1). There was 1 case that reported a 57-year-old male subject who had a fatal outcome after receiving a third dose of BNT162b2 in an outpatient setting with "no effect or specific complaint immediately after". One (1) day after he "spoke a little inconsistently" and was not feeling well. He was found deceased in his home 2 days later. Medical history included bi-pulmonary and hepatic transplant with COPD and non-alcoholic liver cirrhosis and concomitant medications were not reported. It was unknown if an autopsy was completed, however, the physician reported that there was no cardiovascular antecedent, no hypertension, normal coronary angiography and ultrasound, no kidney damage. The subject was hospitalized a few days before for suspected acute rejection and was given a corticosteroid bolus (as reported).
    - In the remaining cases (1340), it was not specified if the subjects received the first or the second vaccine dose at the time of the subject's death.

Literature - Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

O/E Analysis - O/E analysis was performed for events with a fatal outcome (Appendix 6C of the PSUR): all O/E ratios were below 1.

MAH's conclusion: No new risks were identified following review of fatal cases, particularly in the comorbid elderly population.

Rapporteur assessment comment: Among the cases reporting fatal outcome, no specific pattern regarding underlying conditions or cause of death could be identified. All O/E ratios for death were far below 1 (using 14-day and 21-day risk windows, Cumulative). MAH's conclusion is accepted that no new safety risks could be identified based on assessment of the fatal cases.

2.3.1.10.2. Overdose

Search Criteria: HLT Overdoses NEC OR PT Accidental overdose.

Clinical Trial Data (CT)

- Number of cases: 2 (0.3% of 702 cases, the total CT dataset; one case involved blinded therapy and one case involved BNT162b2).
- Country of incidence: [redacted] (both cases).
- Subjects' gender: female (1) and male (1).
- Subjects' age (n = 2): 17 years, and 39 years.
- Medical history (n = 2): the reported medical conditions included: Anxiety (2), Attention deficit hyperactivity disorder, Depression, Hot flush, Insomnia, Invasive ductal breast carcinoma, Metastases to lymph nodes and Migraine (1 each).
- Co suspects: alprazolam, cyclobenzaprine, escitalopram and sertraline (1 each).
- Number of events: 3 (of which 2 were events of interest).
- Relevant PTs: Overdose [2, both assessed as unrelated to BNT162b2 (1) and blinded therapy (1)].
- Relevant event outcome: resolved (1), resolved with sequelae (1).
- Co-reported PT: Suicide attempt (1), assessed as unrelated to blinded therapy.

Post-Authorization Data (PM)

- Number of cases: 1498 (0.5% of 327,125 cases, the total PM dataset). MC cases (1300).
- Country of incidence (≥2%): US (1089), Portugal (115), Italy (73), UK (64) and France (31).
- Subjects' gender: female (442), male (223) and unknown (833).
- Subjects' age in years (n = 607), range: 12 – 100, mean 49.1, median 49.
- Medical history (n = 167): the most frequently (≥2%) reported medical conditions included: Hypertension (104), COVID-19 (60), Asthma (36), Migraine (26), Drug hypersensitivity (25), Food allergy (23) and Seasonal allergy (20).
- Co suspects: COVID-19 Moderna (mRNA-1273) vaccine, COVID-19 vaccine AstraZeneca vaccine (2 each), amoxicillin, clarithromycin, diazepam, ergocalciferol, hepatitis B vaccine, metronidazole, sodium chloride, topiramate, varicella zoster vaccine rgE (CHO) (1 each).
- Number of events: 3647 (of which 1500 were events of interest).
- Relevant event seriousness: serious (42), non-serious (1458).
- Relevant PTs: Overdose (1368), Accidental overdose (126), Intentional overdose (5) and Prescribed overdose (1).
- Relevant event outcome: resolved/resolving (55), not resolved (7), unknown (1438).
- Most frequently co-reported PTs (≥2%): Product preparation issue (572), Product preparation error (172), Headache (100), Pyrexia (77), Pain in extremity (60), Arthralgia (57), Vaccination site pain (55), Myalgia (53), Pain (49) and Fatigue (45).
- Clusters of cases:

- a physician reported 15 subjects (age and gender unknown) who received the vaccine from vials reconstituted with 1.3 mL instead of 1.8 mL of saline;
- a healthcare professional reported 304 subjects (age and sex unknown) who received the vaccine from vials diluted with 1.3 ml instead of 1.8 ml of saline;
- a pharmacist reported that 9 staff members accidentally received 0.5 ml of vaccine instead of 0.3 ml for their second dose;
- a physician stated that 64 subjects received 0.5 ml of vaccine instead of 0.3 ml;
- a nurse reported that 77 subjects inadvertently received a full undiluted vial (all vials from batch PAA165969);
- a nurse administered both doses of vaccine in a single shot (one syringe) to 17 inmates (unknown gender and age).

Analysis by age group

- CT: Paediatric (1) and Adults (1). A meaningful comparison between the different age groups is not possible due to the low number of CT cases.
- PM: Paediatric (48), Adults (415), Elderly (158) and Unknown (877). Upon review, events indicative of overdose occurred more in adult subjects, but no significant differences in the reporting proportion of the most frequently co-reported AEs was noted between the different age groups. In addition, more adults than paediatric subjects were vaccinated during the reporting period.

Analysis by presence of comorbidities

- PM: Number of subjects with comorbidities: 74 (4.9% of the total cases reporting overdose and 0.02% of 327,827 cases, the total dataset). 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 commonly reported reasons (≥ 2%) for overdose were:

- dilution with a volume of sodium chloride different from the recommended 1.8 ml (532; 35.5% of the total cases reporting overdose);
- administration of incorrect dose of diluted vaccine, different from the recommended 0.3 ml (361; 24.1% of the total cases reporting overdose);
- administration of undiluted vaccine (268; 17.9% of the total cases reporting overdose);
- administration of a double dose of vaccine (118; 7.9% of the total cases reporting overdose);
- third dose of vaccine was administered (35; 2.3% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 181 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 commonly 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:

MAH's conclusion is accepted that no new significant safety information could be identified based on the review of cases reporting overdose.

2.3.1.10.3. 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.

Clinical Trial Data

- There were no serious clinical trial cases of abuse or misuse of the vaccine reported during the reporting period.

Post-Authorization Data (PM)

- Number of cases: 65 (0.01% of 327,125 cases, the total PM dataset). MC cases (16).
- Country of incidence (≥2%): US (38), UK (13), Italy, Mexico, Spain (2 each).
- Subjects' gender: female (38), male (20) and unknown (7).
- Subjects' age in years (n = 38), range: 24 - 90, mean 59.2, median 62.
- Medical history (n = 24): the most frequently (≥2%) reported medical conditions included Supressed lactation (4), Depression, Drug hypersensitivity (3 each), Asthma, Epilepsy, Fatigue, Hypersensitivity, Hypertension, Hypoaesthesia, Paraesthesia (2 each).
- COVID-19 Medical history (n = 2): COVID-19, Suspected COVID-19 (1 each).
- Co suspects: COVID-19 Moderna (mRNA 1273) vaccine, ipilimumab, levothyroxine, medroxyprogesterone, methotrexate, nivolumab, ocrelizumab, zonisamide (1 each).
- Number of events: 276 (of which 66 were events of interest).
- Relevant event seriousness: serious (12), non-serious (54).
- Most frequently reported relevant PTs (≥2%): Intentional dose omission (19), Intentional product misuse (17), Withdrawal syndrome (9), Intentional product use issue, Toxicity to various agents (6 each), Disturbance in social behaviour (3).
- Time to event onset (n = 8), range: 0 - 2 days, median 0 days:
    - >24 hours: 5 cases;

- 1 day: 1 case;
- 2-7 days: 2 cases.

- Relevant event outcome: fatal (1), resolved/resolving (5), not resolved (5), unknown (55).
- Analysis by age group:
- PM: Adults (20), Elderly (18) and Unknown (27). There was no meaningful difference between different age groups.
- Analysis by dose:
  - PM: Number of vaccine doses administered at the time of the event onset: 1 dose in 29 cases, 2 doses in 23 cases; in 18 cases the dose was either not specified or reported as other. There are no differences between the AEs that occurred after the 1st and 2nd 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 65 cases representing 0.01% of the overall post-marketing dataset, that reported events indicative of misuse. The majority of the cases involved subjects who intentionally did not receive their second BNT162b2 dose or the second dose was received after the recommended time frame per the RSI. In general, the most frequently reported events observed in the cases reporting abuse or misuse 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:
MAH's conclusion is accepted that no new safety signals could be identified based on the review of cases reporting abuse or misuse.

2.3.1.10.4. Occupational exposure

Search criteria: PTs Exposure to contaminated device; Occupational exposure to product; Occupational exposure to radiation; Occupational exposure to toxic agent.

Clinical Trial Data

- There were no serious clinical trial cases indicative of occupational exposure during the reporting period.

Post-Authorization Data (PM)

- Number of cases: 32 (0.01% of 327,125 cases, the total PM dataset). MC cases (27).
- Country of incidence: US (17), France (4), UK (3), Italy, Japan (2 each), Belgium, Germany, Greece Netherlands (1 each).
- Subjects' gender: female (20), male (7) and unknown (5).
- Subjects' age in years (n = 8), range: 26 - 47, mean 36.9, median 38.5.
- Medical history (n = 1): Allergy to animal, Food allergy, Seasonal allergy (1 each).
- COVID-19 Medical history: None.

- Co suspects: None.
- Number of events: 67 (of which 32 were events of interest).
- Relevant event seriousness: all non-serious (32).
- Reported relevant PT: Occupational exposure to product (32).
- Co-reported AEs (≥2 occurrences): Eye irritation (4), Exposure via eye contact (3), Exposure via skin contact, Injury associated with a devise (2 each).
- Time to event onset (n = 7): < 24 hours.
- Relevant event outcome: resolved (2), not resolved (1), unknown (29).
- Analysis by age group
    - PM: Adults (8), Unknown (24). 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 32 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: MAH's conclusion is accepted that the review of the cases did not identify any significant new safety information regarding Comirnaty usage and occupational exposure.

2.3.1.10.5. Lack of therapeutic efficacy

Search Criteria: PTs Drug ineffective; Vaccination failure.

The summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date is as follows:

1st dose (day 1-13)	From day 14 post 1st dose to day 6 post 2nd dose	Day 7 post 2nd dose
Code only the events describing the SARS-CoV-2 infection	Code "Drug ineffective"	Code "Vaccination failure"
Scenario Not considered LOE	Scenario considered LOE as "Drug ineffective"	Scenario considered LOE as "Vaccination failure"

Clinical Trial Data

- There were no lack of efficacy cases in the clinical trial dataset.

Post-Authorization Data

- Number of cases: 6376 (1.9% of 327,125 cases, the total PM dataset). MC cases (4024).
- Number of lack of efficacy events : 6376 (Drug ineffective [4767] and Vaccination failure [1609]).

- Country of incidence (≥2%): the US (2091), the UK (728), France (645), Italy (600), Germany (387), Austria (204), Portugal (149), Croatia (144), Belgium (141) and Spain (127).
- Subjects' gender: female (3404), male (1904) and unknown (1060).
- Subjects' age in years (n = 3958), range: 15 – 104, mean 61.8, median 61.0.
- Relevant event seriousness: all serious.

Confirmed vaccination failure (1492 cases)

- Vaccination failure was reported in 1492 cases where the COVID-19 infection was confirmed by laboratory test (ie, COVID-19 PCR positive test or antigen test).
- Age groups: Adolescent (1), Adults (662), Elderly (724) and Unknown (105).
- Time to event onset was known for 1431 cases; in the remaining 61 cases, it was implied that vaccination failure was reported on or after day 7 post second dose but detailed information was not provided:
    - day 7 to ≤30 days: 477 subjects;
    - ≥ 31 days to ≤ 60 days: 548 subjects;
    - ≥ 61 days to ≤ 90 days: 340 subjects;
    - ≥ 91 days to ≤ 120 days: 66 subjects.
- Reported vaccine preventable infections : COVID-19 (1090), Asymptomatic COVID-19 (299), SARS-CoV-2 test positive (86), COVID-19 pneumonia (72), Suspected COVID 19 (3) .
- Vaccination failure outcome: fatal (116), resolved/resolving (494), resolved with sequelae (8), not resolved (271), unknown (603).

Not confirmed vaccination failure (119 cases)

- Vaccination failure was reported in 119 cases where subjects received 2 doses of the vaccine at the appropriate interval and developed a COVID-19 infection, clinically diagnosed but not laboratory confirmed (i.e., COVID-19 PCR positive test or antigen test), at least 7 days after the 2nd dose.
- Age groups: Adults (51), Elderly (56) and Unknown (12).
- Time to event onset was known for 107 cases; in the remaining 12 cases, it was implied that vaccination failure was reported on or after day 7 post second dose but detailed information was not provided:
    - day 7 to ≤30 days: 33 subjects;
    - ≥ 31 days to ≤ 60 days: 42 subjects;
    - ≥ 61 days to ≤ 90 days: 24 subjects;
    - ≥ 91 days to ≤ 120 days: 8 subjects.
- Reported vaccine preventable infections : COVID-19 (96), Asymptomatic COVID-19 (10), COVID-19 pneumonia (3), and Suspected COVID-19 (3).
- Vaccination failure outcome: fatal (5), resolved/resolving (45), not resolved (29), unknown (40).

Not a vaccination failure cases

- There were 4757 cases reporting Drug ineffective, indicative of occurrence of the disease:
    - in patients who have not received the full dose schedule;
    - during the incubation period;
    - in patients for which it was possible to determine whether they received the appropriate series of 2 doses at the appropriate interval;
    - in patients for which it was not possible to determine how many days have passed since the last dose administration.
- Lack of efficacy term was reported:
    - after the 1st dose in 2450 cases;
    - after the 2nd dose in 1199 cases;
    - in 1108 cases it was unknown after which dose the lack of efficacy occurred.
- Time to event onset reported after the 1st dose was known for 851 cases:
    - day 14 to ≤ 30 days: 727 subjects
    - ≥ 31 days to ≤ 60 days: 99 subjects;
    - ≥ 61 days to ≤ 90 days: 19 subjects;
    - ≥ 91 days to ≤ 112 days: 6 subjects.
- Time to event onset reported after the 2nd dose was known for 571 cases:
    - before day 7: 263 subjects;
    - day 7 to ≤ 30 days: 122 subjects;
    - ≥ 31 days to ≤ 60 days: 103 subjects;
    - ≥ 61 days to ≤ 90 days: 61 subjects;
    - ≥ 91 days to ≤ 124 days: 22 subjects.

COVID-19 variant (287 cases)

- *Alpha (UK) variant (219 cases)*
    - In 219 of the 6376 cases, COVID-19 infection with British variant was reported. Country of incidence: France (105), Italy (63), Austria (32), Germany, Spain (5 each), Switzerland (2); the remaining 7 cases originated from 7 different countries.
    - Lack of efficacy events: Vaccination failure (124) and Drug ineffective (95).
    - The outcome of COVID-19 infection related events reported in these 219 cases were: fatal (34), resolved or resolving (61), not resolved (51), and unknown (72).
- *Beta/Gamma (South African or South African/Brazilian) variant (55 cases)*
    - In 55 of the 6376 cases, COVID-19 infection with South African variant (33) or South African or Brazilian variant (22) was reported. Country of incidence: France (54), Finland (1).

- Lack of efficacy events: Vaccination failure (36) and Drug ineffective (18).
- The outcome of COVID-19 infection related events reported in these 55 cases were: fatal (5), resolved or resolving (17), not resolved (8), and unknown (25).

- *Gamma (Brazilian) variant (7 cases)*
  - In 7 of the 6376 cases, COVID-19 infection with Brazilian variant was reported. Country of incidence: Italy (5) and France (2).
  - Lack of efficacy events: Vaccination failure (4) and Drug ineffective (3).
  - The outcome of COVID-19 infection related events reported in these 7 cases were: fatal (1), resolved (2), resolved with sequelae (1) and unknown (2).
- *Delta (Indian) variant (5 cases)*
  - In 5 of the 6376 cases, COVID-19 infection with Brazilian variant was reported. Country of incidence: Germany (2), Belgium, India and the US (1 each).
  - Lack of efficacy events: Vaccination failure (1) and Drug ineffective (4).
  - The outcome of COVID-19 infection related events reported in these 5 cases were: fatal (1), resolved (1), not resolved (1), and unknown (2).
- In 1 additional case it was reported that the patient had a "new variant" (not further specified).

Literature - Review of the literature did not identify any significant new information with regards the use of BNT162b2 and lack of therapeutic efficacy.

MAH's conclusion: According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 4757 cases where lack of efficacy was reported after the first dose or the second dose, 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. No new safety signals have emerged based on a review of these cases.

Rapporteur assessment comment:

During the reporting period (since launch of the product), the proportion of lack of efficacy cases reported in the subsequent 7 MSSRs (till 30 June 2021) is varying between 1.8% and 7.2% of the total post-marketing dataset [3.7%, 7.2%, 3.6%, 3.1%, 4.4%, 3.3%, and 1.8% as reported in MSSRs 1 to 7, respectively], and does not show a particular trend. 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.

MAH's conclusion is accepted that no new safety signals could be identified based on the review of cases reporting lack of efficacy.

2.3.1.10.6. Unexpected therapeutic effect

Search Criteria: PTs Device effect increased; Drug effect faster than expected; Drug effective for unapproved indication; Therapeutic product effective for unapproved indication; Therapeutic response changed; Therapeutic response increased; Therapeutic response prolonged; Therapeutic response unexpected; Therapeutic product effect increased; Therapeutic product effect prolonged.

Clinical Trial Data

- There were no serious clinical trial cases with the above PTs reported during the reporting period.

Post-Authorization Data

- Number of cases: 472 (0.1% of 327,125 cases, the total PM dataset). MC cases (78).
- Country of incidence (≥2%): US (256), UK (78), Germany (42), Canada, Israel (16 each), France (10).
- Subjects' gender: female (253), male (152) and unknown (67).
- Subjects' age in years (n = 298), range: 16 - 101, mean 62.4, median 64.
- Medical history (n = 391): the most frequently (≥2%) reported medical conditions included Hypertension (27), Asthma (24), Pain (20), Arthritis (18), Arthralgia, Psoriasis (17 each), Rheumatoid arthritis (16), Chronic obstructive pulmonary disease, Diabetes mellitus (14 each), Dementia, Drug hypersensitivity (13 each), Dyspnoea, Hypersensitivity, Multiple sclerosis (12 each), Herpes Zoster (11), Anosmia, Anxiety, Fibromyalgia, Hypothyroidism, Parkinson's disease (10 each).
- COVID-19 Medical history (n = 35): COVID-19 (23), Suspected COVID-19 (11), COVID-19 pneumonia, SARS-CoV-2 test positive (1 each).
- Co suspects: antilymphocyte immunoglobulin, ginseng, hydrocortisone, metoprolol, ocrelizumab, tofacitinib, varicella zoster vaccine (1 each).
- Number of events: 1208 (of which 473 were events of interest).
- Relevant event seriousness: serious (16), non-serious (457).
- Most frequently reported relevant PTs (≥2%): Therapeutic response unexpected (456), Drug effective for unapproved indication (12).
- In the majority of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, breathing, dementia, skin conditions, inflammation, taste, smell, cognitive skills, blood sugar, asthma.
- Time to event onset (n = 129), range: 0 - 54 days.
    - <1 day: 33 events;
    - 1 day: 46 events;
    - 2-7 days: 31 events;
    - 8-14 days: 7 events;
    - 15-30 days: 9 events;
    - 31-181 days: 3 events.
- Relevant event outcome: resolved/resolving (50), resolved with sequelae (2), not resolved (35), unknown (386).
- Analysis by age group:
    - PM: Paediatric (1), Adults (151), Elderly (149) and Unknown (171). 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 the majority of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, breathing, dementia, skin conditions, inflammation, taste, smell, cognitive skills, blood sugar, asthma. In the majority of the cases, the subject's experienced the unexpected therapeutic effect following their 1st dose. No significant new information was identified with regards the use of BNT162b2 and unexpected therapeutic effect.

Rapporteur assessment comment: MAH's conclusion is accepted that no significant new information could be identified regarding unexpected therapeutic effect when using Comirnaty.

2.3.1.11. Update on special populations

2.3.1.11.1. Use in elderly patients

Clinical Trial Data

- Number of cases: 255 (36.0% of 704 cases, the total CT dataset; 121 were blinded therapy, 110 BNT162b2, 23 placebo and 1 BNT162b1).
- Country of incidence (≥2%): US (205), Argentina (31), Germany (10), Brazil (6)
- Subjects' gender: female (98), male (157).
- Subjects' age in years (n = 255), range: 65 – 87, mean 72.5, median 72.
- Number of events: 312
- Most frequently reported relevant PTs (≥2%): Atrial fibrillation (14), Condition aggravated (11), Osteoarthritis (8), Pneumonia (7).
- The 312 SAEs were assessed as not related to blinded therapy, BNT162b1, BNT162b2 or placebo.
- Relevant event outcome: fatal (27), resolved/resolving (240), resolved with sequelae (17), not resolved (25), unknown (3).

Post-Authorization Data

- Number of cases: 61,833 (18.9% of 327,125 cases, the total PM dataset). MC cases (30,242).
- Country of incidence (≥2%): US (15,652), UK (12,254), France (9163), Italy (4711), Germany (2412), Netherlands (2395), Spain (2114), Japan (1549), Sweden (1272).
- Subjects' gender: female (39,099), male (21,692) and unknown (1042).
- Subjects' age in years (n = 60,849), range: 65 – 95, mean 77.3, median 76.
- Medical history (n = 36,012): the most frequently (≥2000 occurrences) reported HLGT medical conditions included Vascular hypertensive disorders (11,153), Glucose metabolism disorders (incl diabetes mellitus) (5214), Allergic conditions (4461), Viral infectious disorders (3901), Cardiac arrhythmias (3754), Bronchial disorders (excl neoplasms (3384), Joint disorders (3291), Thyroid gland disorders (2640), Mental impairment disorders (2542), Central nervous

system vascular disorders (2422), Coronary artery disorders (2415), Lipid metabolism disorders (2210).

- COVID-19 Medical history (n = 36,012): the most frequently (≥25 occurrences) reported medical conditions included COVID-19 (2091), Suspected COVID-19 (912), SARS CoV-2 test positive (92), COVID-19 pneumonia (81), Exposure to SARS-CoV-2 (60), Asymptomatic COVID-19 (30), Coronavirus infection (29), COVID-19 immunisation (28).
- Co suspects (n = 1116) the most frequently (≥15 occurrences) reported co-suspect drugs included apixaban (99), acetylsalicylic acid (52), paracetamol (44), ibuprofen (30), tofacitinib (25), adalimumab (24), rivaroxaban (23), amoxicillin (20), methotrexate (19), warfarin (18), acenocoumarol (15).
- Number of events: 196,246 the most frequently (≥2%) reported PTs: Headache (7928), Fatigue (7620), Pyrexia (6967), Pain in extremity (4856), Nausea (4611), Chills (4353), Myalgia (4079), Malaise (4070), Arthralgia (3966), Asthenia (3700) Dizziness (3615), Vaccination site pain (3566), Pain (3360), Dyspnoea (2700), Diarrhoea (2699), Vomiting (2435), Pruritus (2283), COVID-19 (2151), Rash (2148), Hypertension (1619), Erythema (1570), Influenza like illness (1451), Herpes zoster (1408), Cough (1244).
- Relevant event seriousness: serious (82,506), non-serious (113,798).
- Relevant event outcome: fatal (9431), resolved/resolving (87,657), resolved with sequelae (2192), not resolved (36,929), unknown (60,878).
- Analysis by presence of comorbidities:
    - PM: Number of elderly subjects with comorbidities: 35,715 (11.0% of 327,827 cases, the total dataset).

      During the current reporting period, there were 2501 (48.9% of 5115 cases, total fatal dataset) fatal outcomes in the elderly populations with comorbidities compared to 263 (5.1%) in the non-elderly population with comorbidities.

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:
MAH's conclusion is accepted that no significant new information could be identified regarding the use of Comirnaty in the elderly.

2.3.1.11.2. Use in paediatric patients

Search Criteria: Paediatric cases are identified as cases where the Age Range derived field value for the patient is "Less than or equal to 17 years". Paediatric cases involving exposure to the vaccine through trans-mammary or transplacentally route are excluded.

Paediatric Subjects <12 Years of Age

Clinical Trial Data

- There were no serious clinical trial cases involving paediatric subjects aged less than 12 years during the reporting period.

Post-Authorization Data

- Number of cases: 132 (0.04% of 327,125 cases, the total PM dataset). MC cases (67).
- Country of incidence (≥2%): UK (60) and US (53).
- Subjects' gender: female (80), male (34) and unknown (18).
- Subjects' age in years (n = 119), range: 0.02-11, mean 4.7, median 4.0.
- Number of events: 343. The most frequently reported PTs (≥2%): Product administered to patient of inappropriate age (43), Off label use (37), Product use issue (26), Pyrexia (13), Fatigue, Headache (11 each), Pain in extremity (10), Nausea (8), Malaise and Myalgia (7 each).
- Event seriousness: serious (34), non-serious (309).
- Event outcome: fatal (2), resolved/resolving (110), not resolved (53), unknown (192).

Paediatric Subjects ≥12 Years and ≤ 15 Years of Age

Clinical Trial Data

- Number of cases: 14, all originated from Protocol C4591001 [2.0% of 702 cases, the total CT dataset; these cases involved blinded therapy (11), BNT162b2 (2) and placebo (1)].
- Country of incidence: US (all relevant 13 cases involving BNT162b2 and blinded therapy).
- Subjects' gender: female (7), male (6).
- Subjects' age in years (n = 13), range: 12 – 15, mean 13.7, median 14.
- Medical history (n = 13): the most frequently (≥2) reported medical conditions included Anxiety (9), Attention deficit hyperactivity disorder (8), Depression (7), Asthma, Migraine, Rhinitis allergic (3 each), Corrective lens user and Post-traumatic stress disorder (2 each).
- COVID-19 Medical history: no data in the relevant 13 cases.
- Co suspects: none.
- PTs reported in the relevant cases (16): Depression[1] (4), Suicidal ideation[1] (3), Appendicitis (2), Abdominal pain, Anal abscess, Anxiety[1], Constipation, Conversion disorder[1], Femur fracture and Focal peritonitis (1 each). All events were assessed as unrelated to BNT162b2 or blinded therapy.

  [1]: Out of the 9 cases reporting PTs included in the SOC Psychiatric disorders (Anxiety, Conversion disorder, Depression and Suicidal ideation), in 8 cases the subjects suffered from underlying psychiatric disorders (ie, anxiety, depression and attention deficit hyperactivity disorder).
- Time to event onset: n = 16, range: 1 - 77 days, median 38.5 days.
    - 1 day: 2 events;
    - 2-7 days: 2 events;
    - 15-30 days: 3 events;

- 31-181 days: 9 events.

- Duration of event: n = 2 : 4 days and 13 days.
- Event outcome: resolved/resolving (14), not resolved (2).

Post-Authorization Data

- Number of cases: 530 (0.2% of 327,125 cases, the total PM dataset). MC cases (191).
- Country of incidence (≥2%): US (482).
- Subjects' gender: female (243), male (258) and unknown (29).
- Subjects' age in years (n = 530), range: 12 – 15, mean 13.6, median 14.
- Medical history (n = 131): the most frequently (>2) reported medical conditions included Asthma (26), Food allergy (18), Attention deficit hyperactivity disorder (14), Autism spectrum disorder, Hypersensitivity (13 each), Epilepsy (9), Allergy to animal, COVID-19 (8 each) Seasonal allergy (7), Drug hypersensitivity (6), Anxiety, Depression (5 each), Migraine (4), Cystic fibrosis, Disability, Lactose intolerance, Immunodeficiency, Mycotic allergy, Seizure and Type 1 diabetes mellitus (3 each).
- COVID-19 Medical history (n = 8): the reported medical conditions included COVID-19 (8).
- Co suspects: COVID-19 Moderna (mRNA-1273) vaccine (2), COVID-19 vaccine NRVV AD26 JNJ 78436735, diphtheria vaccine toxoid, HPV vaccine, oxymetazoline, pertussis vaccine acellular and tetanus vaccine toxoid (1 each).
- Number of events: 1496.
- Event seriousness: serious (264), non-serious (1232).
- Most frequently reported PTs (≥2%): Pyrexia (87), Headache (70), Off label use (65), Fatigue (62), Pain in extremity (51), Product administered to patient of inappropriate age (47), Poor quality product administered (39), Product use issue125, Vomiting (35 each) and Nausea (34).
- Time to event onset (n = 892), range: <24 hours to 23 days, median 1 day:
    - <24 hours: 415 events;
    - 1 day: 281 events;
    - 2-7 days: 153 events;
    - 8-14 days: 24 events;
    - 15-23 days: 19 events.
- Duration of event (n = 41), range: <24 hours to 15 days, median 1 day:
    - <24 hours: 8 events:
    - 1 day: 18 events;
    - 2-7 days: 12 events;
    - 8-14 days: 1 event;
    - 15 days: 2 events.

- Relevant event outcome: resolved/resolving (368), resolved with sequelae (1), not resolved (176), unknown (956).

Paediatric Subjects ≥ 16 Years of Age

Clinical Trial Data

- Number of cases: 13, originated from Protocols C4591001 (7), C4591001-OPEN LABEL (5) and C4591017 (1) [1.9% of 702 cases, the total CT dataset; these cases involved blinded therapy (5) and BNT162b2 (8)].
- Country of incidence: US (13).
- Subjects' gender: female (7) and male (6).
- Subjects' age in years (n = 13), range: 16 – 17, mean 16.7, median 17.
- Medical history (n = 12): the most frequently (>2) reported medical conditions included Asthma (4), Attention deficit hyperactivity disorder, Anxiety, Depression, Major depression, Migraine, Seasonal allergy (3 each), Anxiety disorder and Insomnia (2 each).
- COVID-19 Medical history: no data in these 13 cases.
- Co suspects: escitalopram (1).
- PTs (13): Major depression (2), Abdominal pain, Anaphylactoid reaction, Appendicitis, Asthma, Bipolar I disorder, Chest pain, Deep vein thrombosis, Malnutrition, Overdose , Status migrainosus and Suicidal ideation (1 each, all assessed unrelated to BNT162b2 or blinded therapy, but the AE Anaphylactoid reaction that was assessed related to BNT162b2).
- Time to event onset (n = 12), range: from 1 day to 181 days, median 40.5 days:
    - 1 day: 1 event;
    - 2-7 days: 3 events;
    - 8-14 days: 1 event;
    - 15-30 days: 1 event;
    - 31-181 days: 6 events.
- Duration of event (n = 6) , range: from 5 hours to 10 days, median 4.5 days:
    - <1 day: 2 events (5 hours and 11 hours);
    - 3-7 days: 3 events;
    - 10 days: 1 event.
- Event outcome: resolved/resolving (11), not resolved (2).

Post-Authorization Data

- Number of cases: 914 (0.3% of 327,125 cases, the total PM dataset). MC cases (398).
- Country of incidence (≥2%): US (464), UK (201), Austria (96), Germany (37) and Israel (34).
- Subjects' gender: female (521), male (370) and unknown (23).
- Subjects' age in years (n = 806), range: 16 - 17, mean 16.5, median 16.

- Medical history (n = 337): the most frequently (≥2%) reported medical conditions included Suppressed lactation (52), Asthma (41), Food allergy (26), Drug hypersensitivity (19), Epilepsy (17), Immunodeficiency (16), Acne, Attention deficit hyperactivity disorder, Suspected COVID-19 (15 each), Anxiety (14), Hypersensitivity, Type 1 diabetes mellitus (13 each), Depression (12), Autism spectrum disorder, Pregnancy133 (11 each), COVID-19, Migraine (10 each), Seasonal allergy (9), Diabetes mellitus and Seizure, (8 each).
- COVID-19 Medical history (n = 30): the reported medical conditions included Suspected COVID-19 (15), COVID-19 (10), COVID-19 immunisation, Exposure to SARS-CoV-2 (2 each), Asymptomatic COVID-19 and SARS-CoV-2 test positive (1 each).
- Co suspects: COVID-19 Moderna (mRNA-1273) vaccine, ibuprofen (3 each), cannabidiol, infliximab, medroxyprogesterone, meningococcal group B RLP2086, meningococcal vaccine, mycophenolate mofetil, paracetamol, tacrolimus, tofacitinib and zonisamide (1 each).
- Number of events: 3035.
- Relevant event seriousness: serious (972), non-serious (2065).
- Most frequently reported PTs (≥2%): Headache (197), Fatigue (160), Pyrexia (155), Chills (93), Nausea (87), Dizziness (83), Pain in extremity (69) and Myalgia (64).
- Time to event onset: n = 2125 , range: from <24 hours to 51 days, median 0 day:
    - <24 hours: 1163 events;
    - 1 day: 537 events;
    - 2-7 days: 309 events;
    - 8-14 days: 68 events;
    - 15-30 days: 39 events;
    - 31-181 days: 9 events.
- Duration of event: n = 274 , range: from <24 hours to 29 days, median 1 day:
    - <24 hours: 33 events;
    - 1 day: 111 events;
    - 2-7 days: 112 events;
    - 8-14 days: 12 events;
    - 15-29 days: 6 events.
- Relevant event outcome: fatal (3), resolved/resolving (1413), not resolved (518), resolved with sequelae (10), unknown (1100).

Lot/Batch Number

- Lot/Batch Number (#) information by country was available in 789 cases of the total paediatric dataset with no related quality issues identified during investigations of the impacted lot/batch numbers.

Analysis by age group

- CT: Paediatric (27) and Non-Paediatric (675). A meaningful comparison between the different age groups is not possible due to the low number of paediatric cases.

- PM: Paediatric (1577) and Non-Paediatric (325,548). Upon review, case seriousness and case outcomes were generally similar between the overall paediatric dataset and the non-paediatric dataset.

  No significant differences in the reporting proportion of the most frequently reported AEs were noted between the paediatric dataset and the non-paediatric dataset, apart from the following PTs describing inappropriate administration of the vaccine, for which the reporting proportion is higher in the paediatric population: Off label use (7.8% vs 1.3%), Product administered to patient of inappropriate age (5.8% vs 0.0%) and Product use issue (4.4% vs 0.6%). This increase is explicable due to the fact that the vaccine was not authorized for subjects aged < 12 years by EMA until 31 May 2021 for subjects aged between 12 and 15 years.

  A slight increase in the reporting proportion for the paediatric subjects compared to the non-paediatric subjects was identified also for the following PTs: Poor quality product administered (6.0% vs 1.6%), Application site pain (3.5% vs 0.3%) and Myocarditis (3.1% vs 0.1%).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 181 (11.3% of 1604 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.

Analysis by dose

- Number of vaccine doses administered at the time of the event onset: 1 dose in 703 cases, 2 doses in 441 cases and number of doses was not specified in 460 cases.
- The comparison between the reporting proportion of the most commonly reported AEs in the overall paediatric population after administration of 1 dose or 2 doses of vaccine did not reveal significant differences, with the exception of the following PTs, for which increased reporting proportion was identified upon administration of the second dose of vaccine:
  - Pyrexia (10.1% after 1 dose vs. 26.7% after 2 doses);
  - Chills (4.7% after 1 dose vs. 10.7% after 2 doses);
  - Pain (4.7% after 1 dose vs. 9.1% after 2 doses);
  - Chest pain (3.4% after 1 dose vs. 10.2% after 2 doses);
  - Myalgia (1.8% after 1 dose vs. 5.2% after 2 doses);
  - Myocarditis (1.3% after 1 dose vs. 8.9% after 2 doses).
- Pyrexia, chills, pain and myalgia are events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS. Myocarditis was an ongoing signal during the reporting period and evaluation completed after the reporting period. Depending on the clinical picture, chest pain can be considered consistent with the events listed in Section 4.8 Undesirable effects of the CDS, as pain of musculoskeletal origin or be a symptom of myocarditis or pericarditis.

Literature - Review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric patients.

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 commonly reported AEs other than PTs involving inappropriate/unapproved administration of the vaccine or administration of product with quality issues (due to temperature excursions, storage and/or preparation errors) were events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS and a warning about very rare cases of myocarditis and pericarditis that have occurred more often in younger men and shortly after the second dose of vaccine was added to Section 4.4 Special warnings and precautions for use of the CDS and of the EU SmPC on 14 July 2021 and 12 July 2021, respectively, after DLP.

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:

The use of Comirnaty in children <12 years old is not within the current approved indication in the EU and therefore considered off-label use.

Please refer regarding the evaluation of the signal of myocarditis and pericarditis to the separate procedure EMEA/H/C/005735/SDA/032, EPITT ref. 19712.

Further characterization and evaluation of cases reporting myocarditis and pericarditis in the younger age population, will be addressed in the planned and ongoing PASS's, included in the updated EU RMP of Comirnaty (procedure EMEA/H/C/005735/II/0059).

The MAH should continue to closely monitor any new cases reporting myocarditis and/or reporting pericarditis in 12-15 years old and notify the Rapporteur in case of unexpected trends or findings.

No new safety information could be identified regarding the use of Comirnaty in 12-17 years old. The safety profile is overall comparable to that in adults.

2.3.1.11.3. Use in pregnant/lactating women

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

Clinical Trial Data

Cumulative of pregnancy cases

- Number of pregnancy cases: 152 (14.5% of the total 1048 cases from the CT dataset). These 152 cases represent 149 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 2 pregnancies). Cases originated from clinical studies C4591001 (141), C4591015 (9), BNT162-01 and C4591017 (1 each) and study treatment was reported as blinded therapy (79), BNT162b2 (43), and placebo (30).
- Country of incidence: US (101), Argentina (28), Brazil (15), South Africa (5), Germany (2) and Turkey (1).

- Of the 145 mother cases, 94 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure before pregnancy (65), Maternal exposure during pregnancy (25) and Exposure during pregnancy (4).
- Fifty-one (51) mother cases, 26 serious and 25 non-serious, reported additional clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases were coded to the PTs Abortion spontaneous (17), Maternal exposure before pregnancy (16), Maternal exposure during pregnancy (13), Abortion incomplete, Abortion spontaneous incomplete, Benign hydatidiform mole, Exposure during pregnancy, Hyperemesis gravidarum, Miscarriage of partner, Pre-eclampsia, Premature separation of placenta, Retained products of conception, Vaginal haemorrhage (1 each). Other reported clinical events coded to the PTs Dyspnoea and Pruritus (1 each). Of the 21 cases reporting spontaneous abortion or abortion related events in 10 cases, mother had a medical history of spontaneous abortion, alcohol/ tobacco use during pregnancy, obesity or gestational hypertension which might have contributed to the event and in 11 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
- Six (6) serious baby/foetal cases. Cases are classified according to pregnancy outcome:
    - Pregnancy outcome: Live birth with congenital anomaly: Four (4) of these cases reported 11 congenital anomalies that coded to the PTs Hypoxic-ischaemic encephalopathy, Neonatal respiratory failure, Shock, Intestinal perforation, Newborn persistent pulmonary hypertension, Non reassuring foetal heart rate pattern, Pneumoperitoneum, Renal tubular necrosis, Metabolic acidosis, Foetal heart rate abnormal, Neonatal pneumothorax (1 each). Of these 4 cases, in 3 cases foetus was exposed during 3rd trimester and in 1 case exposure occurred during 2nd trimester. Of these 4 cases, in 1 case reporting hypoxic-ischaemic encephalopathy, shock, newborn persistent pulmonary hypertension, metabolic acidosis, renal tubular necrosis, pneumoperitoneum, and intestinal perforation mother had a medical history of premature separation of placenta which might have contributed to the development of the events. In the remaining 3 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
    - Pregnancy outcome: Livebirth without congenital anomaly: Two (2) cases reported live birth babies without congenital anomaly but one case was reported with perinatal complication/post natal complications. Of these 2 cases, in 1 case, foetus was exposed during 1st trimester and in 1 case exposure occurred during 3rd trimester. The events reported in these 2 cases were coded to PTs Foetal hypokinesia, Hyperbilirubinaemia neonatal, Dehydration, and Hypernatraemia (1 each). Of these 2 cases, in 1 case mother was on multiple concomitant medications i.e., bupropion, escitalopram and paracetamol and in the remaining case there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
- Of the 152 cases, 149 cases provided pregnancy outcomes which are provided in Table 38 below. Pregnancy outcome was pending or not provided in the remaining 3 cases.

Table 38. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval

Pregnancy outcome	Prospective cases 144 (94.7% of pregnancy cases)					Retrospective cases 5 (3.3% of pregnancy cases)				
	Timing of exposure iu pregnancy					Timing of exposure in preguancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Uuknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	0
Spontaneous abortion	0	12	0	0	5	0	3	0	0	1
Elective termination (foetal defects)	0	0	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	9	0	0	3	0	0	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	0	0	0	0	0	0	0
Live birth with congenital anomaly	0	1	5	0	0	0	0	0	0	0
Live birth without congenital anomaly	0	51	4	0	54	0	1	0	0	0
Total	*0*	*73*	*9*	*0*	*62*	*0*	*4*	*0*	*0*	*1*

Post-Authorization Data

Pregnancy

- Number of pregnancy cases: 1661 (0.5% of the total 327,125 cases from the PM dataset). These 1661 cases represent 1607 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 53 pregnancies).
- Country of incidence (≥10 occurrences): US (472), UK (392), Germany (130), France (71), Canada (69), Mexico (61), Italy (60), Ireland (47), Portugal (42), Spain (37), Israel, Netherlands (30 each), Estonia (25), Brazil (20), Hungary (15), Japan (13), Romania (12), Poland (11), Australia, Austria (10 each).
- Of the 1604 mother cases, 659 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (383), Exposure during pregnancy (208), Maternal exposure timing unspecified (43), Maternal exposure before pregnancy (16), Pregnancy (9), Drug exposure before pregnancy (2), Foetal exposure during pregnancy (1).
- Nine hundred and forty-five (945) mother cases, 635 serious and 310 non-serious, reported additional clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases (≥5 occurrences) were coded to the PTs Abortion spontaneous (275), Vaginal haemorrhage (27), Abortion missed (21), Foetal death (16), Abortion (9), Gestational diabetes (7), Premature labour (6), Stillbirth, Uterine contractions during pregnancy (5 each). Other frequently reported (≥15 occurrences) clinical events coded to the PTs Headache (154), Fatigue (114), Pain in extremity (95), Pyrexia (83), Vaccination site pain (81), Myalgia (64), Chills (60), Pain (57), Nausea (55), Dizziness (42), Asthenia (34), Arthralgia (33), Vomiting (31), Lymphadenopathy (26), Oropharyngeal pain (25), COVID-19, Malaise (23 each),

Diarrhoea (19), Cough (17), Influenza like illness (15). The distribution of clinical events (≥15 occurrences) was similar in the pregnant mothers when compared with the general population.

- Fifty-seven (57) baby/foetal cases, 54 serious and 3 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: Nine (9) of these cases reported 9 congenital anomalies that coded to the PTs Anencephaly, Cerebrovascular accident, Congenital anomaly, Foetal cystic hygroma, Foetal malformation, Hydrops foetalis, Kidney duplex, Trisomy 21, Ventricular septal defect (1 each). Other clinical events reported in these cases coded to the PTs Premature baby, Tachycardia foetal, Ultrasound foetal abnormal (1 each). Of these 9 cases, information regarding trimester of exposure was provided in 2 cases. Of these 2 cases, in 1 case foetus was exposed during 1st trimester and in 1 case exposure occurred during 3rd trimester. In these 9 cases, there was limited information regarding obstetric history/ medical history of mother which precluded meaningful causality assessment.
    - Pregnancy outcome: Livebirth without congenital anomaly: Eighteen (18) cases reported live birth babies without congenital anomaly. Of these 18 cases, 2 cases reported normal newborn and 16 cases reported perinatal complication/post natal complications. Of these 18 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 1 case, foetus was exposed during 1st trimester and in 7 cases exposure occurred during 3rd trimester. The clinical events reported in these 18 cases were coded to PTs Premature baby (11), Foetal growth restriction (3), Foetal hypokinesia (2), Foetal heart rate increased, Foetal heart rate disorder, Ductus arteriosus premature closure, Umbilical cord thrombosis, Pulmonary arterial pressure abnormal, Respiratory disorder neonatal, Neutropenia neonatal, Ventricular hypertrophy, Bradycardia foetal and Neonatal respiratory acidosis (1 each). In these 18 cases, there was limited information regarding obstetric history and co suspect medications of mother which precluded meaningful causality assessment.
    - Pregnancy outcome: Stillbirth: Nine (9) cases reported foetal death/ neonatal death. Of these 9 cases, 5 cases reported stillbirth with foetal defects and remaining 4 cases reported stillbirth without foetal defect. Of these 9 cases, information regarding trimester of exposure was provided in 2 cases and the exposure happened during the 1st trimester of the pregnancy. The events reported in these 9 cases were coded to PTs Premature baby (3), Foetal heart rate abnormal, Foetal death, Stillbirth (2 each), Neonatal respiratory distress, Meconium aspiration syndrome, Foetal hypokinesia, PTEN gene mutation, Neonatal pneumothorax, Syndactyly, Foetal heart rate decreased, Macrocephaly, Death neonatal, Foetal movement disorder, Death and Hamartoma (1 each). In these 9 cases, there was limited information regarding obstetric history and co suspect medications of mother which precluded meaningful causality assessment.
    - Pregnancy outcome: Elective termination: Seven (7) cases reported elective termination of pregnancy. Of these 7 cases, 6 cases reported elective termination due to foetal defects and 1 case reported elective termination without foetal defects or unknown. Of these 7 cases, information regarding trimester of exposure was provided in 4 cases and the exposure happened during the 1st trimester of the pregnancy. The events reported in these 7 cases were coded to PTs Foetal growth restriction (3), Foetal heart rate abnormal (2), Anencephaly, Cleft palate, Congenital absence of cranial vault, Heart disease congenital, Hydrops foetalis, Foetal cystic hygroma,

Trisomy 21, (1 each).In these 9 cases, there was limited information regarding obstetric history and co suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: Fourteen (14) cases reported spontaneous abortion. Of these 14 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 7 cases, foetus was exposed during 1st trimester and in 1 case exposure occurred during 2nd trimester. The events reported in these 14 cases were coded to PTs Foetal growth restriction (5), Congenital anomaly, Anembryonic gestation (2 each), Foetal malformation, Foetal heart rate abnormal, Spine malformation, Small for dates baby, Foetal cystic hygroma, Abortion spontaneous and Foetal death (1 each). In these 14 cases, there was limited information regarding obstetric history and co suspect medications of mother which precluded meaningful causality assessment.

- Of the 1661 cases, 1089 cases provided pregnancy outcomes which are provided in Table 40. Pregnancy outcome was pending or not provided in the remaining 572 cases.

Table 40. Post-Authorization Data: Pregnancy Outcome during the Reporting Interval[a]

Pregnancy outcome	Prospective cases 841 (50.6% of pregnancy cases)					Retrospective cases 248 (14.9% of pregnancy cases)				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknowu	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unkuown
Ectopic pregnancy	0	0	0	0	1	0	1	0	0	0
Spontaneous abortion	0	26	0	0	26	0	60	5	0	106
Elective termination (foetal defects)	0	2	0	0	3	0	3	0	0	1
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	1	0	0	0
Stillbirth with foetal defects	0	2	0	0	0	0	2	0	0	6
Stillbirth without foetal defects	0	1	0	0	4	0	0	2	0	6
Live birth with congenital anomaly	0	2	0	0	1	0	0	1	0	2
Live birth without congenital anomaly	0	115	91	0	567	0	0	15	0	37
Total	***0***	***148***	***91***	***0***	***602***	***0***	***67***	***23***	***0***	***158***

a. 19 December 2020 through 18 June 2021.

Lactation

- Number of lactation cases: 966 (0.3% of the total 327,125 cases from the PM dataset).
- Breast feeding baby cases: 802, of which:
    - Six hundred and fifty-five (655) cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk and Maternal exposure during breast feeding) without the occurrence of any clinical events.

- One hundred and forty-seven (147) cases, 61 serious and 86 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk and Maternal exposure during breast feeding); the frequently reported clinical events (≥5 occurrences) were coded to the PTs Pyrexia (32), Rash (19), Diarrhoea, Infant irritability (11 each), Malaise (10), Crying, Infantile vomiting, Irritability (7 each), Poor feeding infant, Vomiting (6 each), Cough, Decreased appetite, Fatigue, Illness, Insomnia, Rhinorrhoea (5 each).

- Breast feeding mother cases: 164, of which:
  - Five (5) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
  - One hundred and fifty-nine (159) cases, 95 serious and 64 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>10 occurrences) were coded to the PTs Fatigue (36), Headache (29), Pain in extremity (22), Pyrexia (19), Nausea (17), Chills, Myalgia (15 each), Dizziness, Pain (14 each), Breast pain, Lymphadenopathy (11 each).

Literature

Literature article review supports the use of COVID-19 mRNA vaccine in pregnant and breast-feeding women; the vaccine was immunogenic in pregnant women and vaccine elicited antibodies were transported to infant cord blood and breast milk receipt. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern. Furthermore, antenatal COVID-19 mRNA vaccination induces a robust maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination.

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:

During the reporting period there are 1661 cases (0.5% of the total 327,125 cases from the PM dataset) reporting AEs in pregnant women and 966 cases (0.3% of the total 327,125 cases from the PM dataset) reporting AEs in breastfeeding women.

The exposure in pregnant and breastfeeding women is not known and therefore it is unclear if the frequency of AEs reported is consistent with the expectation.

The literature review reported four studies describing vaccination with BNT162b2 in pregnant and lactating women for which no specific safety issues were described (please refer to section Literature of 1.3.5 Findings from clinical trials and other sources).

Based on the limited data in the cumulative clinical trial data and the spontaneous cases, no new safety concern regarding exposure during pregnancy and breastfeeding could be identified.

2.3.1.11.4. Use in immunocompromised patients

Search criteria: Patients with Medical history of 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: 105 (15.0% of 702 cases, the total CT dataset; blinded therapy [51], BNT162b2 [43], BNT162b1 [1]; placebo [10]).
- Country of incidence: US (82), Argentina (15), Brazil, Germany, South Africa, and Turkey (2 each).
- Subjects' gender: female (61), and male (44).
- Subjects' age in years (n = 105), range: 17 – 85, mean 63.3, median 66.
- Medical history (n = 105): the most frequently (≥2%) reported relevant medical conditions included Hysterectomy (23), Breast cancer, Prostate cancer (13 each), Benign prostatic hyperplasia, Cholecystectomy (7 each), Basal cell carcinoma, Prostatectomy (6 each), Neoplasm malignant, Thyroidectomy (5 each), Appendicectomy, Breast conserving surgery, Cancer surgery, Colon cancer, Malignant melanoma, Tonsillectomy (4 each), Gastrectomy, Lung lobectomy, Lymphadenectomy, Mammoplasty, Sigmoidectomy, Spinal fusion surgery (3 each), Adenocarcinoma pancreas, Biopsy prostate, Colectomy, Leukaemia, Lung adenocarcinoma, Prostatomegaly, Radical prostatectomy, Skin cancer, Squamous cell carcinoma of skin, Testis cancer, Thyroid cancer, Thyroid mass (2 each). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history: None.
- Co suspects (n = 3): The reported co-suspect agents included alprazolam, azithromycin, calcium folinate, cyclobenzaprine, doxycycline, fluorouracil, irinotecan, oxaliplatin and sertraline (1 each).
- Number of events: 129.
- Most frequently reported clinical PTs (>2 occurrences): Breast cancer (6), Acute respiratory failure, Condition aggravated (4 each), Myocardial infarction (3).
- BNT162b2 related events coded to the PT: Acute myeloid leukaemia (1). Time to onset of event is 38 days and the event outcome is reported is not resolved. None of the events were related to blinded therapy.

Post-Authorization Data

- Number of cases: 11,995 (3.7% of 327,125 cases, the total PM dataset).
- MC cases (5651), NMC cases (6344).
- Country of incidence: UK (3585), US (2831), France (2008), Italy (673), Czech Republic (476), Spain (300), Germany (263); the remaining 1859 cases were distributed among 56 countries.

- Subjects' gender: female (8282), male (3541) and unknown (172).
- Subjects' age in years (n = 11,287), range: 12 – 105, mean 62.8, median 64.
- Medical history (n = 11,995). The most frequently (≥2%) reported relevant medical conditions included Immunodeficiency (1889), Breast cancer (1686), Neoplasm malignant (776), Prostate cancer (642), Thyroidectomy (568), Hysterectomy (567), Chemotherapy (451), Radiotherapy (443), Renal transplant (386), Neoplasm (343), Lung neoplasm malignant (270), Chronic lymphocytic leukaemia (267), Mastectomy (242), Thyroid cancer (237), Cholecystectomy (227), Splenectomy (218), Breast cancer female (205), Colon cancer (203), Malignant melanoma (190). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 936): COVID-19 (531), Suspected COVID-19 (367), COVID-19 pneumonia (28), Asymptomatic COVID-19 (9), Post-acute COVID-19 syndrome (1).
- Co suspects (n = 324): The most frequently (≥5 cases) reported co-suspect agents included lenvatinib (23), apixaban (17), palbociclib (10), pembrolizumab (9), COVID-19 Vaccine NRVV AD (8), trimethoprim/sulfamethoxazole (7), carboplatin, cisplatin, gemcitabine, ibuprofen (6 each), acetylsalicylate, levothyroxine, nivolumab, paclitaxel (5 each).
- Number of events: 46,821.
- Relevant event seriousness: serious (23,127), non-serious (23,718).
- Most frequently reported clinical PTs (≥3%): Headache (2207), Fatigue (2048), Pyrexia (1660), Pain in extremity (1250), Nausea (1223), Chills (1067), Myalgia (1009), Arthralgia (959), Vaccination site pain (910), Pain (896), Malaise (848), Dizziness (807), Asthenia (731), Dyspnoea (702), Lymphadenopathy (624), Diarrhoea (594), Vomiting (554), Pruritus (453), Influenza like illness (433), Rash (408), COVID-19 (369), and Paraesthesia (354).
- Time to event onset (n = 34,557 events), range: <24 hours to 121 days, median 1 day:
    - < 24 hours: 11,816 events;
    - 1 day: 9060 events;
    - 2-7 days: 8628 events;
    - 8-14 days: 2526 events;
    - 15-30 days: 1681 events;
    - 31-181 days: 846 events.
- Duration of event (n = 6424 of 14,222 events with outcome of resolved/resolved with sequelae):
    - < 24 hours: 661 events;
    - 1 day: 2040 events;
    - 2-7 days: 3012 events;
    - 8-14 days: 448 events;
    - 15-30 days: 173 events;
    - 31-181 days: 90 events.

- Relevant event outcome34: fatal (1498), resolved/resolving (21,566), resolved with sequelae (654), not resolved (10,164), unknown (13,232).
- The lot/batch number which reported ≥3% of cases reporting ADRs following use in immunocompromised patients is #EM0477 (325 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT Data: Paediatric (1), Adults (47) and Elderly (57). A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (34), Adults (5714), Elderly (5578) and Unknown (669).
    - 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 and Lymphadenopathy. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (1.5% [85 cases] in adults vs 4.5% [250 cases] in elderly). In majority of the elderly cases (172 of 250 cases) that reported the event coded to PT COVID-19, the co reported events was coded to the PTs Drug ineffective (74 cases) and Vaccination failure (98 cases). These cases are also summarized in Section 16.3.4.5 Lack of Therapeutic Efficacy).
    - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (8.2% [466 cases] in adults vs 2.0% [113 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:

MAH's conclusion is accepted that no new significant safety information could be identified in immunocompromised patients when exposed to Comirnaty.

After DLP of the PSUR 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. Please refer regarding the 3rd (booster) dose of Comirnaty to the separate procedure EMEA/H/C/005735/II/0067.

2.3.1.11.5. Use in patients with autoimmune or inflammatory disorders

Search Criteria: Patients with Medical history PTs included in HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction.

- Of the 26,352 cases, the most frequently reported PTs (≥3%) included: Headache (5847), Fatigue (4916), Pyrexia (3948), Nausea (3107), Pain in extremity (3017), Chills (2818), Arthralgia (2743), Myalgia (2657), Pain (2351), Vaccination site pain (2201), Dizziness (2166), Malaise (1874), Asthenia (1594), Dyspnoea (1415), Diarrhoea (1390), Lymphadenopathy

(1337), Pruritus (1185), Rash (1140), Vomiting (1095), Paraesthesia (990), Influenza like illness (833), Feeling abnormal (800).

- MC cases (11,811), NMC cases (14,664).
- Event seriousness: serious (45,555), non-serious (64,832).
- Event outcome: fatal (2248), resolved/resolving (52,605), resolved with sequelae (1594), not resolved (24,603), unknown (29,896).

The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

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 845 cases, 473 cases were determined to be non-contributory and are 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., atrial fibrillation, kidney disease, deep vein thrombosis, abdominal pain, throat swelling).

Therefore, 372 cases are included in the analysis below.

Clinical Trial Data

- Number of cases: 1 (0.1% of 702 cases, the total CT dataset; 1 blinded therapy). A [redacted] case, involving a 33-year-old male subject with a history of eosinophilic oesophagitis, experienced an eosinophilic oesophagitis flare (PT Condition aggravated) the same day he received his second dose of BNT162b2. The event resolved after 1 day and was considered unrelated to BNT162b2.

Post-Authorization Data

- Number of cases: 371 (0.1% of 327,125 cases, the total PM dataset).
- MC cases (156), NMC cases (215).
- Country of incidence (≥2%): UK (109), US (97), France (58), Germany, Italy (14 each), Spain (10), Canada, Netherlands (8 each).
- Subjects' gender: female (273), male (90) and unknown (8).
- Subjects' age years (n = 341), range: 17 - 95, mean 57.4, median 57.
- Relevant medical history: the most frequently (≥3%) reported medical conditions included: Rheumatoid arthritis (42), Hypothyroidism (31), Arthritis (26), Autoimmune disorder, Diabetes mellitus (25 each), Immunodeficiency (21), Colitis ulcerative (20), Sjogren's syndrome (18), Psoriasis (15), Ankylosing spondylitis, Immune thrombocytopenia (14 each), Autoimmune thyroiditis, Type 1 diabetes mellitus (12 each).
- COVID-19 Medical history (n = 21): COVID-19 (11), Suspected COVID-19 (9), SARS CoV-2 test positive (1).
- Co suspects: adalimumab, tofacitinib (2 each), acetylsalicylic acid, acitretin, amoxicillin, enalapril, estradiol, hydrochlorothiazide, latanoprost, methotrexate, patisiran, pregabalin, ramipril, rituximab (1 each).
- Number of events: 2128 (of which 376 were events of interest i.e., exacerbation/flare AEs).
- Relevant event seriousness: serious (264), non-serious (114).

- Most frequently reported relevant PTs (≥2%): Condition aggravated (247), Disease recurrence (118).
- Time to event onset (n = 224), range: 0 - 65 days, median 2 days.
    - <24 hours: 47 cases;
    - 1 day: 55 cases;
    - 2-7 days: 83 cases;
    - 8-14 days: 21 cases;
    - 15-30 days: 14 cases;
    - 31-181 days: 5 cases.
- Duration of event (n = 22), range: 0 - 21.5 days, median 5 days.
    - <24 hours: 2 cases;
    - 1 day: 2 cases;
    - 2-7 days: 11 cases;
    - 8-14 days: 5 cases;
    - 15-30 days: 2 cases.
- Relevant event outcome: fatal (2), resolved/resolving (140), resolved with sequelae (4), not resolved (116), unknown (115).
- Lot/Batch Number (n = 234): The most frequently reported lot number (≥10 cases): EM0477 (14), ER1741 (10).

Analysis by age group

- CT: Adult (1).
- PM: Paediatric (1), Adults (217), Elderly (124) and Unknown (29). 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 198 cases, 2 doses in 132 cases; in 76 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.

MAH's conclusion: Overall, there were 372 cases (1 CT case and 371 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:

During the reporting interval, the MAH narrowed the analysis and included exacerbation or flare of autoimmune or inflammatory disorders in the review, rather than all events, which is endorsed. Of a total of 26,352 cases, there were 372 cases (1 CT case and 371 PM cases [0.1% of the overall dataset]) that reported exacerbation/flares in subjects with autoimmune or inflammatory disorders. The median of the reported TTO was 2 days and 185 cases (83% of the 224 cases that provided a TTO) reported a TTO within 7 days.

After PSUR DLP - In the 9th MSSR (Aug 2021 data) assessment (EMEA/H/C/005735/MEA/002.8) the MAH was requested regarding (flare up) of autoimmune diseases: **1)** to discuss if there is an increased frequency of flare up of autoimmune disorders following Comirnaty vaccination, compared to background incidences of flare ups. For this, literature articles should be discussed and included, **2)** to present an updated review of myasthenia gravis (MG). The review should present new onset MG and MG flare/aggravation/exacerbation separately, and further details and a company causality assessment for each case, with specific focus on the MG flare should be presented, and **3)** to present new cases of capillary leak syndrome (CLS) and CLS flare, new follow-up information and any new information from published literature concerning cases of CLS and exacerbations in pre-existing CLS following COVID-19 vaccinations, including a company causality assessment for each case, with specific focus on the CLS flare. The requested additional data regarding flare up of autoimmune disorders following Comirnaty vaccination, was assessed in the 10th MSSR (Sept 2021 data; EMEA/H/C/005735/MEA/002.9) and no new safety concern was identified based on the current available data regarding flare-ups of autoimmune diseases (including a focus on rheumatoid arthritis relapse) and capillary leak syndrome. An updated review of myasthenia gravis will be provided by the MAH in the 11th MSSR.

The MAH should continue to closely monitor any new cases reporting flare up of autoimmune or inflammatory disorders following Comirnaty vaccination and notify the Rapporteur in case of unexpected trends or findings.

No new safety information could be identified regarding the use of Comirnaty in patients with autoimmune or inflammatory disorders.

2.3.1.11.6. Use in frail patients with co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis)

Search criteria for frail patients with co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis): Patients with Medical history of PTs included in HLGTs (Primary Path) Bronchial disorders (excl neoplasms), Heart failures, Mental impairment disorders, Movement disorders (incl parkinsonism), Nephropathies, Pulmonary vascular disorders, Renal disorders (excl nephropathies); HLTs (Primary Path) Autonomic nervous system disorders, Diabetes mellitus (incl subtypes), Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis, Motor neurone diseases, Muscle tone abnormal, Neuromuscular disorders NEC, Pulmonary hypertensions, Respiratory failures (excl. neonatal); patients with Medical history of ongoing Tuberculosis.

- Number of cases: 28,023 (8.6% of 327,125, the total PM dataset).
- MC cases (15,348), NMC cases (12,675).
- Case seriousness: serious (15,247), non-serious (12,776).

- Country of incidence: UK (6,889), US (6,708), France (3,694), Italy (1,503), Japan (1,415), Spain (986), Germany (874), Sweden (716), Czech Republic (691), Netherlands (485), Denmark (435), Austria (390), Norway (363), Finland (268), Ireland (254), Portugal (251), Belgium (249), Canada (221), Mexico (208), Switzerland (177), Hungary (166), Greece, Israel (145 each), Romania (69), Croatia (67), Panama (61), Poland (60), Estonia (51), Costa Rica (40), Brazil (36), Luxembourg, Malta (29 each), Slovenia (27), Singapore (26), Iceland, Slovakia (25 each), Australia (22), Bulgaria, Latvia (20 each), Puerto Rico (17), South Africa (16), Lithuania (15), Chile, Cyprus (14 each), Colombia, Serbia, Turkey (13 each), Saudi Arabia (8), Ecuador (6), Iraq, United Arab Emirates (5 each), Jordan, Peru, Philippines (4 each), Bermuda, Lebanon, New Zealand, Tunisia (3 each), Kuwait, Malaysia, Qatar (2 each), Albania, Argentina, Curacao, French Guiana, French Polynesia, Georgia, Guyana, Hong Kong, India, Korea, Republic of (South Korea), Oman, Ukraine, Uruguay, and Virgin Islands, U.S. (1 each).
- Subject's gender: female (19,139), male (8,506), and unknown (378).
- Subject's age in years (n = 26,891), range: 0.17-104, mean 61, median 61.
- Relevant subjects' medical histories most frequently reported (≥1,000 cases) coded to the PTs: Asthma (10,608), Hypertension (7,276), Diabetes mellitus (5,399), Type 2 diabetes mellitus (3,332), Chronic obstructive pulmonary disease (2,242), Drug hypersensitivity (1,783), Atrial fibrillation (1,489), COVID-19 (1,483), Chronic kidney disease, Hypersensitivity (1,335 each), Hypothyroidism (1,290), Cardiac failure (1,202), Depression (1,183), Food allergy (1,159), Seasonal allergy (1,151), Dementia (1,149), Obesity (1,119), and Suppressed lactation (1,064).
- Of the 114,369 events overall reported, the most frequent clinical events (≥1,000 occurrences) coded to the PTs: Headache (5,256), Fatigue (4,547), Pyrexia (4,323), Nausea (2,956), Chills (2,674), Pain in extremity (2,579), Myalgia (2,422), Dyspnoea (2,351), Dizziness (2,118), Vaccination site pain (2,087), Arthralgia (2,062), Pain (2,018), Malaise (1,995), Asthenia (1,779), Vomiting (1,338), Diarrhoea (1,333), Pruritus (1,264), Cough (1,168), Lymphadenopathy (1,035), and Rash (1,029); all these 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.
- Case outcome: fatal (2346), resolved/resolving (13,875), resolved with sequelae (482), not resolved (8,336) and unknown (2984).

Conclusion

The reporting proportion of not resolved cases (29.7%) and cases resolved with sequelae (1.7%) in frail subjects is similar to the reporting proportion observed in the overall population (23.5% for outcome of not resolved, 1.0% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (8.4%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (1.5%). This is expected, considering that most of the cases reporting a fatal outcome (80%) 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 (eg, 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:

During the reporting interval, a total of 28,023 cases were identified reporting use in frail patients with co-morbidities. As expected, the proportion of cases reporting fatal outcome was higher in frail subjects as compared to the overall population. Differences in the proportion of not resolved cases and cases resolved with sequelae were not apparent.

No significant new information could be identified regarding use in frail patients with co-morbidities.

2.3.1.12. Interactions with other Vaccines

Search criteria: HLT interactions

Of the 253 cases, 251 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- In 107 cases, the subject did not experience a drug interaction, but rather the reporters were inquiring about whether or not a drug interaction could potentially occur.
- In 144 cases (of which 65 were serious), the subjects experienced drug interactions with the following concomitant medications warfarin (7), alcohol, clozapine (5 each), apixaban, clopidogrel, methotrexate, steroids (unspecified) (4 each), adalimumab, lamotrigine, prednisone, sertraline, unspecified medications (3 each), acetaminophen, atorvastatin, blood thinners (unspecified), botulinum, diphenhydramine, glatiramer, guselkumab, hydroxyurea, ibuprofen, insulin, lithium, phenprocoumon, pregabalin, trazodone, rituximab (2 each), acenocoumarol, acetylsalicylic acid, acetylsalicylate lysine, amphetamine/dextroamphetamine, amitriptyline, amoxicillin/clavulanate, anaesthesia (unspecified), antibiotics (unspecified), allergy shot (unspecified), aripiprazole, atenolol, budesonide/formoterol/glycopyrronium, bupropion, cannabis, carbidopa/levodopa, cefuroxime, cephalexin, ciprofloxacin, clonazepam, contraceptive (unspecified), contrast medium, cortisone, denosumab, dexamethasone, diabetes medication (unspecified), diltiazem, dulaglutide, eletriptan, esomeprazole, fiorinal, fluindione, fluoxetine, food, gammaplex, gabapentin, ginseng, golimumab, heparin, hormone replacement therapy (unspecified), immunoglobin, immunosuppressant, immunotherapy, infliximab, interferon, ketoprofen, lanreotide, levodopa, levothyroxine, lisdexamfetamine, local anaesthetic, meclizine, mesalamine, methylprednisolone, metoprolol, metronidazole, mirtazapine, montelukast, movicol, mycophenolic acid, ocrelizumab, octocog alfa, olanzapine, omeprazole, osimertinib, oxycodone, oxycodone/paracetamol, palbociclib, pantoprazole, paroxetine, penicillin, psychiatric medication (unspecified), quetiapine, ropinirole, tadalafil, tafenoquine, tamsulosin, temazepam, tenofovir, tofacitinib, trimethoprim, ustekinumab, vitamin B12, zonisamide (1 each).

Two of the 253 cases reported an interaction with another vaccine and are discussed below.

Clinical trial data

There were no serious clinical trial cases reported during the reporting period.

Post-authorization data

- Number of cases: 2 (0.0% of 327,125 cases, the total PM dataset).
- MC case (1), NMC case (1).
- Country of incidence: Germany, US (1 each).
- Subjects' gender: female (1), male (1).
- Subjects' age (n = 1): 57 years.

- Medical history (n = 1): Pertussis.
- COVID-19 Medical history: None.
- Co-suspects (n = 1): Diphtheria vaccine toxoid, pertussis vaccine acellular 5- component, polio vaccine inact 3V (vero), tetanus vaccine toxoid.
- Number of events: 8 (of which 2 were events of interest).
- Relevant event seriousness: non-serious (2).
- Relevant PT: Drug interaction (2).
- Co-reported AEs: Circumstance or information capable of leading to medication error, Induration, Influenza like illness, Myalgia, Pain, Vaccination site swelling (1 each).
- Time to event onset: n = 1, <24 hours.
- Duration of event: Unknown (2).
- Relevant event outcome: Unknown (2).

Analysis by age group, comorbidities and dose

No comparison between the different age groups and presence of comorbidities can be done due to the limited number of cases.

Conclusion

Overall, of the 253 cases, 107 were no relevant as a drug interaction did not occur and in 144 cases, the drug interaction occurred with a concomitant medication rather than another vaccine. The were 2 cases in the overall post-marketing dataset that reported a vaccine interaction. In general, the most frequently co-reported events observed in subjects with vaccine interaction was consistent with those observed in the overall population. There is no indication of a safety signal of interference of immune response of vaccines noted based on a review of these cases. In one of the 2 cases, it was reported that BNT162b2 increased the vaccination reaction to diphtheria vaccine toxoid, pertussis vaccine acellular 5- component, polio vaccine inact 3V (vero), tetanus vaccine toxoid.

Rapporteur assessment comment: MAH's conclusion is accepted that no significant new information could be identified regarding interactions with other vaccines.

2.4. Characterisation of risks

After DLP, 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. The MAH proposes the following list of safety concerns for the next reporting period, subject to the PRAC approval of the EU-RMP version 2.3:

Table 41. Ongoing Safety Concerns

Important identified risks	Anaphylaxis Myocarditis and pericarditis[a]
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. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory Disorders
	Interaction with other vaccines
	Long-term safety data

a. Search criteria: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Rapporteur assessment comment:

Please refer regarding the inclusion of myocarditis and pericarditis as an important identified risk in the list of safety concerns (after DLP of current PSUR) to the separate procedure EMEA/H/C/005735/II/0059.

2.4.1. Characterisation of Important Identified and Potential Risks

- Important Identified Risk: Anaphylaxis
- Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Rapporteur assessment comment:

Please refer regarding the Important Identified Risk - Anaphylaxis - to section 2.3.1.1 Anaphylaxis of this AR.

Please refer regarding the Important Potential Risk - Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) – to section 2.3.2.1 VAED/VAERD 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 Use in pregnancy and while breast feeding to section 2.3.5.3 of this AR.

- Use in immunocompromised patients

Rapporteur assessment comment:

Please refer regarding Use in immunocompromised patients to section 2.3.5.5 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 section 2.3.5.7 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 section 2.3.5.6 of this AR.

- Interaction with other vaccines

Rapporteur assessment comment:

Please refer regarding Interaction with other vaccines to section 2.3.5.8 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:

This is noted.

3. Benefit evaluation

BNT162b2 is indicated in the EEA countries for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

Study C4591001 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with HIV, HCV, or HBV.

Efficacy analyses were performed with confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through 13 March 2021, representing up to 6 months of follow-up after Dose 2 for

participants in the efficacy population. Data of study C4591001 (see tables 44 – 48 of the PSUR, not shown here) demonstrates a high degree of efficacy against symptomatic and severe COVID-19 in non-immunocompromised people over 12 years of age, during the period at least 7 days following the second dose of vaccine. Efficacy is evident separately and at a similar level in people 12-15 years of age, 16-64 years of age, 65 to 74 years of age and 75 years of age. Efficacy also appears largely independent of risk factors (having at least 1 of the Charlson comorbidity index categories) and obesity. Efficacy is also high against severe disease after the first dose. This is anticipated to deliver effective prevention of COVID-19 in the community and reduced hospitalisation, severe morbidity and death from COVID-19.

Antibody waning, the need for a booster dose or revaccination

Neutralizing SARS-CoV-2 antibody titers and S1-binding IgG antibodies were evaluated at 6 months after Dose 2 for Study C4591001 Phase 1 participants who received BNT162b2 at 30 µg and the corresponding placebo recipients. Data were analysed for both younger (18 to 55 years of age) and older (65 to 85 years of age) Phase 1 age groups, which included N =15 each randomized in a 4:1 vaccine:placebo ratio.

Overall, SARS CoV-2 serum 50% neutralizing GMTs and S1-binding IgG GMCs at 6 months after Dose 2 showed a decline relative to the peak levels observed at 1 month after Dose 2, but still remained higher than both pre-vaccination and placebo control levels.

For both younger and older age groups, the observed neutralizing GMTs declined from 1 month after Dose 2 (Day 52) to 6 months after Dose 2 (Day 202) (see Figure 17 in PSUR, not shown here). In the younger age group, GMTs were 179.2 at 1 month after Dose 2 and 54.7 at 6 months after Dose 2; in the older age group, GMTs declined from 151.6 to 29.0 over this same interval.

Observed S1-binding GMCs at 6 months after Dose 2 also declined from peak values at 1 month after Dose 2, in both age groups (see Figure 18 in the PSUR, not shown here).

These Phase 1 data show persistence of a robust immune response elicited by BNT162b2 30 µg vaccination in adults for up to 6 months; and also suggest, based on the modest decline in GMTs and GMCs from 1 month to 6 months after receiving Dose 2, that vaccinees may benefit from a booster dose at 6 months or thereafter.

Booster groups are currently being evaluated in Study C4591001 for safety and immunogenicity of a third dose of BNT162b2 30 µg administered to adults 18 to 55 years of age, at approximately 6 months after completing the initial 2-dose series.

Rapporteur assessment comment:

Please refer regarding the 3rd (booster) dose of Comirnaty to the separate procedure EMEA/H/C/005735/II/0067.

4. Benefit-risk balance

Within the reporting interval, the existing indication was extended from "individuals 16 years of age and older" to "individuals 12 years of age and older". After the DLP, a booster dose (third dose) of Comirnaty for individuals 18 years of age and older was approved. Also, a third dose of Comirnaty for individuals 12 years of age and older who are severely immunocompromised was approved.

The following safety issues were identified and included as ADRs in the product information after initial MA: erythema multiforme, extensive swelling of the vaccinated limb, reaction associated with dermal fillers, hyperhidrosis, night sweats, asthenia, lethargy, decreased appetite, diarrhea, anaphylaxis, pain

in extremity, vomiting, paraesthesia and hypoesthesia. Also, the warning regarding anxiety and stress-related responses was updated.

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 reporting interval for Comirnaty, the benefit-risk balance of Comirnaty (single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2) 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 significant 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 immune thrombocytopenia the MAH is requested to provide:
    a. a case by case causality assessment of the immune thrombocytopenia cases considered BC level 1 cases;
    b. a case by case causality assessment of the immune thrombocytopenia cases considered BC level 2 cases;
    c. a thorough discussion and conclusion of the retrieved literature following the literature search;

    including a discussion on any consequences for the product information, if applicable.

6. MAH responses to Request for supplementary information

Request 1.

Regarding immune thrombocytopenia the MAH is requested to provide:

a. a case by case causality assessment of the immune thrombocytopenia cases considered BC level 1 cases;
b. a case by case causality assessment of the immune thrombocytopenia cases considered BC level 2 cases;
c. a thorough discussion and conclusion of the retrieved literature following the literature search;

including a discussion on any consequences for the product information, if applicable.

MAH's response

Data

The cases reviewed are those which were classified as Brighton Collaboration Level 1 or 2 and not presented as individual cases within the PSUR. They are from the dataset generated when the Pfizer

safety database was searched for BNT/Pfizer COVID-19 vaccine adverse event reports using MedDRA v 24.0 search strategy HLT Thrombocytopenias, received cumulatively to 18 Jun 2021.

Literature analysis

COVID-19 Infection and ITP

COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Lymphopenia may be considered as a cardinal laboratory finding, with prognostic potential. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio may also have prognostic value in determining severe cases. During the disease course, longitudinal evaluation of lymphocyte count dynamics and inflammatory indices, including LDH, CRP and IL-6 may help to identify cases with dismal prognosis and prompt intervention in order to improve outcomes. Biomarkers, such high serum procalcitonin and ferritin have also emerged as poor prognostic factors. Furthermore, blood hypercoagulability is common among hospitalized COVID-19 patients. Elevated D-Dimer levels are consistently reported, whereas their gradual increase during disease course is particularly associated with disease worsening. Other coagulation abnormalities such as PT and APTT prolongation, fibrin degradation products increase, with severe thrombocytopenia led to life- threatening disseminated intravascular coagulation (DIC), which necessitates continuous vigilance and prompt intervention.

Several cases of immune-mediated thrombocytopenia have been reported after COVID-19 infection. The ITP occurred not only during active COVID-19 infection, but also up to 10 days after the clinical COVID-19 symptoms subsided.

General information on ITP and vaccination (including COVID-19 vaccination)

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet counts due to increased destruction and impaired platelet production, partially related to the presence of autoantibodies directed toward platelet-membrane antigens. ITP manifestations include various degrees of cutaneous and/or mucosal purpura; life-threatening hemorrhages occur in less than 5% of adult patients. Onset is frequently insidious and low platelet counts often last beyond 6 months. In adults, the incidence of ITP is approximately 3.3 per 100 000 person-years. Studies have suggested that immunizations could be involved in the development of autoimmune disorders. This could be because of molecular mimicry, in which antigens of the host are recognized as being similar to antigens of the immunization, thus provoking the development of autoantibodies. Although several population-based studies have described an association between the measles-mumps-rubella vaccine and ITP in children, published evidence concerning the risk associated with other vaccines or with vaccination in adults is sparse and limited to a few case reports. The risk of ITP associated with adult vaccines therefore remains controversial.

Grimaldi-Bensouda *et al* performed a prospective case-control study to explore the incidence of ITP in relation to all vaccination in adults, with a special emphasis on vaccines against influenza and diphtheria-tetanus-pertussis-poliomyelitis (DTPP). The results of the study show that in an adult population, the exposure to common vaccines is on average not associated with an observable risk of developing ITP.

ITP is mainly a diagnosis of exclusion. There is no specific test that confirms the diagnosis, and clinicians therefore rely on the lack of distinguishing features of other diseases, which depends in part on the thoroughness of the evaluation. In some cases, alternative diagnoses may become apparent only during follow-up. For example, a Canadian ITP registry study that incorporated central expert adjudication of diagnosis with long-term follow-up reported that nearly one in seven patients initially diagnosed with ITP were ultimately given an alternative diagnosis.

Perhaps the most reliable inclusive 'diagnostic' test is a robust response to ITP-directed therapies.

Therefore, in previous database studies, investigators developed search strategies to enhance diagnostic accuracy. Distinguishing de novo ITP from exacerbation of undiagnosed, pre-existing ITP is another challenge and requires knowledge of pre-vaccination platelet counts, results that were not consistently available. As matter of fact, many patients may have platelet counts as low as 30,000 to 50,000 platelets per microliter while still remaining asymptomatic; transient reductions in platelet counts after infection and vaccination are common, in our experience; pre-vaccination platelet counts are infrequently available for patients who do not otherwise require regular medical attention. Overall, the concept that vaccination may induce ITP is not new or without precedent. Thrombocytopenia was frequently seen in children exposed to a live attenuated (weakened) vaccine against measles. In these cases, the average maximum fall in platelet counts approached 100,000 platelets per microliter; the maximum decrease was seen at 1 week after vaccination, and platelet counts generally returned to baseline levels within 3 weeks. Indirect evidence of viral infection of megakaryocytes was seen, suggestive of a component of impaired platelet production. The attributable risk of ITP, generally mild and resolving within weeks or months, is estimated to be about one case per 40,000 doses of the vaccine against measles–mumps–rubella, which is only slightly higher than that noted after natural infection with the viruses that cause these diseases. In the setting of vaccination against measles–mumps–rubella, a live, albeit weakened, virus is responsible for the 'development' of ITP. To attribute the observations in the current study to cases of de novo ITP, one would have to speculate that both mRNA-based vaccines against SARS-CoV-2 (such as BNT162b2) and adenovirus-based vaccines against SARS-CoV-2 (such as ChAdOx1), or their viral protein cargoes, elicited cross-reactive immunity (e.g., through molecular mimicry), altered a host protein or induced substantial immunological perturbation that led to the emergence of pre- existing autoreactive antibodies. On the one hand, this would seem to be somewhat novel, as ITP did not emerge as a complication of many other 'killed' vaccines given to adults, as assessed through the use of a national registry and case-controlled methodology. On the other hand, the unprecedented number of people vaccinated with these new viral or mRNA vectors in such a short period of time could render previous experience of limited relevance.

Attribution of a rare adverse event to vaccine exposure can exacerbate vaccine hesitancy, with important effects on public health. Seemingly, even exposure of 30,000–70,000 recipients to these two vaccines as part of the initial trials was insufficient to identify a risk of ITP, indicative of the need for continued surveillance, as exemplified by the current study, in which the authors estimate 1.13 (95% confidence interval, 0.62–1.63) additional cases of ITP occur per 100,000 first doses of ChAdOx1. Estimating the 'true effect' is hampered by the multiple challenges associated with the diagnosis of ITP and the low number of incident ITP events observed. Overall, the authors conclude there is no clear evidence of an association of ITP with the first dose of the BNT162b2 vaccine and there is a possible small increased risk of ITP with the ChAdOx1 vaccine. Nonetheless, the risk of vaccination-induced ITP at the rate proposed seems to be far lower than the many risks associated with COVID-19 itself.

Published studies

The study performed by Welsh KJ *et al* assessed cases of thrombocytopenia, including immune thrombocytopenia (ITP), reported to the Vaccine Adverse Event Reporting System (VAERS) following vaccination with mRNA COVID-19 vaccines. They analyzed VAERS reports of thrombocytopenia after vaccination with Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine. Overall, 15 cases of thrombocytopenia were identified among 18,841,309 doses of Pfizer-BioNTech COVID-19 Vaccine and 13 cases among 16,260,102 doses of Moderna COVID-19 Vaccine. The reporting rate of thrombocytopenia was 0.80 per million doses for both vaccines. Based on an annual incidence rate of 3.3 ITP cases per 100,000 adults, the observed number of all thrombocytopenia cases, which includes ITP, following administration of mRNA COVID-19 vaccines is not greater than the number of ITP cases expected. The authors concluded that number of thrombocytopenia cases reported to VAERS does not suggest a safety concern attributable to mRNA COVID-19 vaccines.

Rapporteur assessment comment:

The MAH describes the study of Welsh *et al* performed in VAERS that showed that the number of reported ITP cases for the mRNA COVID-19 vaccines is not greater that the number of expected ITP cases.

Grimaldi-Bensouda L *et al* performed a case-control study that explored potential associations between adult ITP and various routinely administered vaccines. A network of internal medicine and hematology centers across France recruited 198 incident (i.e., newly diagnosed) cases of ITP between April 2008 and June 2011. These cases were compared with 878 age- and sex-matched controls without ITP recruited in general practice. Sixty-six of 198 cases (33.3%) and 303 of 878 controls (34.5%) received at least 1 vaccine within the 12 months before the index date. They found no evidence of an increase in ITP after vaccination in the previous 6 or 12 months (adjusted odds ratio [OR] for the previous 12 months = 1.0; 95% confidence interval, 0.7-1.4). When the 2-month time window was used, higher ORs were observed for all vaccines (OR = 1.3). This increase was mainly attributable to the vaccination against diphtheria-tetanus-pertussis-poliomyelitis (OR = 1.5) and was not statistically significant. The results of the present study show that in an adult population, the exposure to common vaccines is on average not associated with an observable risk of developing ITP.

Rapporteur assessment comment:

The case-control study of Grimaldi-Bensouda *et al* described the assessment of the potential association between ITP and various routinely administered vaccines (in the period prior to the authorisation of the COVID-19 vaccines). No statistically significant increased risks were observed.

Li X *et al* characterize the incidence of different adverse event of special interest for COVID-19 vaccines across 8 countries. They studied 15 events: non-hemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, anaphylaxis, Bell's palsy, myocarditis/pericarditis, narcolepsy, appendicitis, immune thrombocytopenia, disseminated intravascular coagulation, encephalomyelitis (including acute disseminated encephalomyelitis), Guillain-Barre syndrome, and transverse myelitis. They extracted data from 13 databases, 126,661,070 people contributed 227,043,370 person-years of follow-up. Each database captured important different population demographics, and collectively represented all age and sex subgroups from eight countries**.** Regarding immune thrombocytopenia they found that it was reported largely rare in all age groups (rare (<1/1,000 to ≥1/10,000)).

Rapporteur assessment comment:

The MAH describes the study of Li *et al* performed on data from 13 databases that showed that ITP was reported rare in all age groups for the COVID-19 vaccines. No causality assessment was performed.

Case reports

Individual case reports have been published reporting ITP following COVID-19 vaccination (from Astra Zeneca, Moderna, Pfizer/Biontech, and Janssen vaccine). All cases related to vaccination with Pfizer/BioNTech vaccine have been included in the Argus safety database and have been discussed in the previous review. The cases that were better clinically described are included below. *Please note that the assessor only included the case reports related to Comirnaty below.*

- Shah SRA *et al* in their article report 3 cases of thrombocytopenia after vaccination. The cases are shortly summarized below.

Case #1: 53-year-old male with past medical history of Crohn's disease was admitted for myalgias and diffuse petechial rash 8 days after receiving second dose of Pfizer- BioNTech COVID-19 vaccine. A complete blood test showed a platelet count of 2 × 109/L. He received two doses of intravenous immunoglobulin and oral dexamethasone for 4 days resulting in normalization of platelet counts.

Case #2: 67-year male with past medical history of chronic ITP in remission was admitted for melena 2 days after receiving his first dose of Pfizer-BioNTech COVID- 19 vaccine. A complete blood test showed a platelet count of 2 × 109/L. Physical exam showed generalized petechiae. He received two doses of IVIG and oral dexamethasone for 4 days with gradual improvement in platelet counts.

Case #3: 59-year-old female with past medical history of chronic ITP secondary to SLE was admitted for bloody diarrhea 2 days after receiving her first dose of Johnson and Johnson COVID-19 vaccine. Physical exam was unremarkable. A complete blood test showed platelet count of 64 × 109/L which dropped to 27 × 109/L during hospital course. She received oral dexamethasone for 4 days with improvement in platelet counts.

- Akiyama *et al* discuss a case on a 20-year-old [redacted] woman 12 days after the 1st vaccination dose with BNT162b2 mRNA vaccine presented with subcutaneous hemorrhage in her extremities and trunk. Seventeen days after the vaccination, she developed oral bleeding and was admitted to the hospital. Her platelet count was low (16,000/μL). She had no alcohol drinking or smoking habits and had no medical or family history nor medications of note. The platelet count was within the reference level at the checkup performed 11 months prior. Bone marrow aspiration was normal. The patient was treated with a corticosteroid with resolution of the symptoms.

- Idogun PO et al report a 54-year-old female that presented with a three-week history of progressive and diffuse non-pruritic, painless, petechial rash on her lower extremities, chest, and abdomen. She reported increased mucosal bleeding and worsening ecchymosis. The patient had received the first dose of the Pfizer COVID-19 vaccine one week before the onset of the rash and had received the second dose five days prior to this presentation. Her past medical history was significant for congenital epidermal dysplasia, hypertension, overactive bladder, mild cognitive impairment, chronic kidney disease, as well as anxiety. Her family history was insignificant except for colon cancer in her mother. The patient's home medications included amlodipine, lisinopril, pravastatin, baclofen, tizanidine, and sucralfate. Initial laboratory findings showed a platelet count of 0/μL with an elevated D-dimer at 2.99 mg/L. Erythrocyte sedimentation rate (ESR) was elevated at 56 mm/hr, and the patient had mild transaminitis with alanine aminotransferase (ALT) of 56 U/L andaspartate aminotransferase (AST) of 45 U/L. Bone marrow biopsy revealed a hypercellular bone marrow with megakaryocytic hyperplasia. Given that the patient's workup had been negative for secondary causes of thrombocytopenia, she was then started on dexamethasone and IV immunoglobulin (IVIG), as a treatment for presumptive ITP.

Literature summary and discussion

Various studies have been conducted using different safety databases to examine the incidence of ITP associated with a number of vaccines. Specific to Covid-19 vaccines, the study by Welsh KJ *et al* concluded that number of thrombocytopenia cases reported to VAERS does not suggest a safety concern attributable to mRNA COVID-19 vaccines. Similarly, the study from Grimaldi-Bensouda L *et al* show that in an adult population, the exposure to common vaccines is not associated with an observable risk of developing ITP. In addition, Li X *et al* using data from 13 databases across 8 countries conclude that immune thrombocytopenia was reported rarely in all age groups (rare (<1/1,000 to ≥1/10,000)).

Several individual case reports have described ITP following COVID-19 vaccination. Even within these publications it is notable that some subjects had pre-existing autoimmune disease that confound the causality assessment. Other cases reported ITP in the context of an infection that may have been the trigger of ITP as well as cases that have underlying comorbidities and concomitant medications that may suggest an alternate aetiology.

Rapporteur assessment comment:

As requested, the MAH provided a literature review. Three studies were discussed of which two were specific for COVID-19 vaccines. One described a study in VAERS showing that the number of reported ITP cases was not higher than expected for the COVID-19 mRNA vaccines. The other study reported that ITP was reported largely rarely in all age groups. In the study assessing the association between ITP and non-COVID-19 vaccines it is described that no significant increased risk of ITP was found.

Furthermore, several case reports were described for which the assessor only included the summaries of those reported for Comirnaty. Four cases were described of which one reported a medical history of Crohn's disease (potential confounder) and one of chronic ITP in remission. In the remaining two cases no apparent confounding factors were reported. Also, in these cases several other viral causes (including COVID-19) were excluded.

BRIGHTON COLLABORATION LEVEL 1 AND LEVEL 2 CASE ASSESSMENT

The normal range for a platelet count is 150-450 $x10^9$/L, given the normal distribution of platelet counts a small percentage of the population will have a 'normal' platelet count <150 $x10^9$/L. Although there is a wide variation in platelet counts on a population level, it has been reported that platelet counts among healthy individuals remain stable over time. A platelet count which has significantly decreased within the normal range is still therefore significant – it may suggest a downward trajectory and a point of intervention. Knowledge of previous platelet counts is very useful in assessing the trend – whether stable, increasing or decreasing. Unfortunately, in spontaneous post-marketing data such information is usually lacking.

Of the 188 cases requested for individual causality assessment, 82 are classified as BC Level 1 and 106 as BC Level 2. The broad search strategy used to capture these cases has retrieved not only cases of ITP, but also those with alternative diagnoses, and many of thrombocytopenia for which an etiology is unclear. ITP is not a pharmacological or phenomenological event and as such no cases are classified as having a "certain" relationship to BNT162b2. Even in cases where there is a possible temporal relationship, given the nature of spontaneous reports and the lack of detail about prior platelet counts and therefore the trajectory of the platelet trend, certainty of causality cannot be applied.

ITP has an annual incidence rate of 3.3 cases per 100,000 adults. Coincidental onset with vaccination is therefore possible. Although hemorrhagic manifestations can occur, ITP is asymptomatic in many patients and found incidentally on complete blood count (CBC) assessment; asymptomatic cases identified incidentally with a temporal relationship to vaccination may have been pre-existing and co-incidentally become clinically apparent after vaccination.

BC level 1 cases

Among the cases requested to present, a total of 72 BC Level 1 cases did not report a previous platelet count for comparison. Two were described as being found incidentally.

BC Level 1 Cases Classified as WHO "Unassessable/unclassifiable"

Table 1 presents the numbers of cases with insufficient information provided to make a meaningful assessment of causality. In some cases, the time to onset may not be reported, the cases may lack important clinical detail and/or may not contain any medical history or concomitant medications. For

some cases the reported information is contradictory compromising a meaningful assessment of causality. For completeness and to comply with the request these are individually detailed in Appendix 2: Table 7 (not reproduced here).

Table 1. BC Level 1 Cases (n=35) considered Unassessable/unclassifiable (per WHO causality assessment criteria) *

Reason	Number of cases
Insufficient clinical details for meaningful causality assessment	28
Medical history not reported	28
Concomitant medications not reported	35

*Note each case may be represented in multiple categories

Rapporteur assessment comment:

As requested, the MAH provided more information on 82 BC level 1 cases. Of these, the MAH classified 35 BC level 1 cases as unassessable/unclassifiable since data on clinical details, medical history or concomitant medications was missing.

BC Level 1 Cases considered unlikely to be associated with BNT162b2

Table 2 presents the reasons for which cases were determined to be *unlikely* related to BNT162b2 per the WHO causality assessment criteria. Case [redacted] was found to be a duplicate of [redacted] and will be merged in MAH's safety database. For completeness and to comply with the request these are individually detailed in Appendix 2: Table 8. (not reproduced here)

Table 2. BC Level 1 cases (n=37) considered unlikely to be associated with BNT162b2 (per WHO causality assessment criteria) *

Reason	Number of cases
Onset the day of, or day after exposure to vaccine	5
Symptom onset prior to vaccination	1
Time-to-onset > 20 days	18
Confounding factor(s) in medical history	14
Confounding concomitant medication(s)	24
Concurrent infection/unknown temporal relationship of infection to event	7

*Note each case may be represented in multiple categories

Rapporteur assessment comment:

37 (one duplicate) BC level 1 cases were considered unlikely to be associated with Comirnaty.

BC level 1 cases of ITP with a possible causal association to BNT162b2

Seven cases with a possible causal association are presented in Table 3 (not reproduced here). The normalrange for platelets is 150-450 $x10^9$/L unless otherwise specified. Please note that only the MAH comments on the cases are reproduced here.

- [redacted] The reported time to onset is plausible with the clinical manifestation of the disease as depending on vaccination. The fast recovery without any specific treatment may suggest a pre-existing asymptomatic thrombocytopenia.
- [redacted]: The reported time to onset is plausible with the clinical manifestation of the disease as depending on vaccination even though the symptoms were mild and recovered without any treatment.
- [redacted] Symptomatic thrombocytopenia identified 10 days after Dose 1, temporal relationship plausible with the onset of disease related to vaccination.
- [redacted]: Incidental finding of asymptomatic thrombocytopenia with a plausible temporal association to Dose 1. A lack of clinical signs and symptoms means the onset could feasibly be prior to vaccination with becoming clinically apparent coincidental with vaccination. The clinical indication for a CBC work-up 4 days post vaccination is not provided.
- [redacted]: Plausible temporal association with BNT162b2 in a patient with no significant medical history or confounding medications.
- [redacted]: Plausible temporal association to vaccination without other obvious precipitating factor, although limited clinical investigation results are presented.
- [redacted] The reported time to onset of clinical symptoms is plausible for a temporal association. The reported medical history does not seem relevant to the presentation of the events associated with thrombocytopenia. Although the patient's age and bone marrow senescence may be factors, a contributory role of the vaccination to the onset of the event cannot be excluded.
- [redacted]: Presentation of TTP 4 days after Dose 2. Incomplete investigation results reported. Possibly related to vaccine.

Rapporteur assessment comment:

The MAH states that there were 7 BC level 1 cases with a possible causal association. However, in the table 8 cases were described. Except from one case, these were all reported in women. The median age was 49 years and ranged from 31 to 97 years. Of the 8 cases, 5 were reported after the first dose, 2 after dose 2 and for 1 case it was not reported. None of the cases was reported to be fatal. Of the cases, 2 recovered without treatment and 3 with treatment. For one case, it was known that treatment was provided although the outcome of the events was not reported. In the remaining case, no information was available on the treatment and outcome of the events.

BC level 2 cases

Of the cases requested for individual causality assessment by PRAC, 106 were classified as BC Level 2. Of note 95/106 cases did not have a previous platelet count available for comparison. Twelve cases were found incidentally after vaccination which limits the ability to pinpoint a time of onset (this reflects the criteria imposed; no symptoms are required for BC Level 2). Eight cases reported prior exposure to heparin.

BC level 2 cases classified as WHO "Unassessable/unclassifiable"

Table 4 presents the numbers of cases with insufficient information provided to make a meaningful assessment of causality. For completeness and to comply with the request these are individually detailed in Appendix 2: Table 9 (not reproduced here).

Table 4. BC Level 2 Cases (n=45) considered Unassessable/unclassifiable (per WHO causality assessment criteria) *

Reason	Number of cases
Insufficient clinical details for meaningful causality assessment	47
Medical history not reported	38
Concomitant medications not reported	59

*Note each case may be represented in multiple categories

BC level 2 cases classified as "unlikely"

Table 5 presents the reasons for which cases were determined to be *unlikely* related to BNT162b2 per the WHO causality assessment criteria. For completeness and to comply with the request these are individually detailed in Appendix 2: Table 10.

Table 5. BC Level 2 cases (n=59 considered unlikely to be associated with BNT162b2 (per WHO causality assessment criteria) *

Reason	Number of cases
Onset the day of, or day after exposure to vaccine	3
Symptom onset prior to vaccination	1
Time-to-onset > 20 days	9
Confounding factor(s) in medical history	22
Confounding concomitant medication(s)	18
Concurrent infection/unknown temporal relationship of infection to event	7

*Note each case may be represented in multiple categories

BC level 2 cases with a possible causal association to BNT162b2

Two cases with a possible causal association are presented below (Please note that only the MAH comments on the cases are reproduced here). The normal range for platelets is 150-450 $x10^9$/L unless otherwise specified.

- [redacted]: ITP with a plausible time to onset in a patient with no relevant medical history. Possibly related to BNT162b2.
- [redacted]: Although there is a temporal association with vaccination, clinical details of this case are lacking including an indication for long term use of omeprazole (reported since 2018).

Rapporteur assessment comment:

Of the 106 cases that were classified as BC level 2, 2 were considered possible related to Comirnaty. These were reported in females of 20 and 74 years old. Both occurred after the first dose. For one case it was reported that the events were resolving following treatment. No details on the treatment and outcome of the events were reported for the other case.

MAH's summary and conclusion

In most reports, important clinical information (such as medical history, validation of diagnosis, time from vaccination to onset of illness, and use of concomitant drugs) is missing or incomplete, and follow-up information is not available. In almost all cases a platelet count prior to vaccination was not available for comparison. Many cases reported underlying comorbidities and concomitant medications which confound causality assessment or pose alternate etiology.

The published literature studies also do not suggest a safety concern attributable to mRNA COVID-19 vaccines.

Pfizer/BioNTech mRNA Covid-19 vaccines is safe and efficacious against symptomatic COVID-19 in large randomized controlled trials, thus advantages associated with COVID-19 vaccination efficacious against symptomatic COVID-19 outbalance the risks involved.

Rapporteur assessment comment:

As requested, the MAH provided more information on the 82 BC level 1 and 106 BC level 2 cases. Of the BC level 1 cases, 35 were classified as unassessable/unclassifiable and 37 (including 1 duplicate) as unlikely to be related to Comirnaty. The MAH reports that 7 cases were possibly related to Comirnaty. To note, these numbers do not add up to a total of 82 cases (but add up to 80 cases). None of the possible related cases reported fatal outcome and two resolved without treatment. Of the 106 cases classified as BC level 2, 45 were considered to be unassessable/unclassifiable, 59 unlikely to be associated with Comirnaty, and 2 possible associated.

Although 8 BC level 1 cases (including literature reports) were considered possible related to Comirnaty, the number of cases is considered to be low, none of these cases reported fatal outcome and two cases recovered without treatment. Also, in the 11th MSSR (safety data up to October 2021) the O/E ratios for ITP were far below 1 (including those accounting for the backlog). It is therefore agreed with the MAH that based on the information provided, no new safety issue is identified. Routine monitoring will continue.

Issue solved.

7. Comments from Member States

MS1, MS2 and MS3

Endorsed the Rapporteur's assessment report with no further comment.

Rapporteur assessment comment:

The endorsements are appreciated.

MS4

The PRAC Rapps AR is in general endorsed.

Hypoesthesia and paraesthesia

We endorse the Rapporteur's comment that hypoesthesia and paraesthesia shall be included in the SmPC section 4.8 and PIL section 4.

Rapporteur assessment comment:

The endorsement is appreciated.

Heterologous vaccination:

In the next PSUR we propose that MAH assess if the safety profile of Comirnaty is consistent with different time intervals between dose 1 and 2. The MAH should also assess the safety profile when used in heterologous vaccination schedules with other vaccines. This should be discussed in the PSUR under off-label use and in other relevant sections. We understand that this issue is challenging,

however as there is a need for some countries to use heterologous vaccination schedules, we consider the question important.

Rapporteur assessment comment:

The importance of the safety profile in heterologous vaccination schedules is acknowledged. The GVP Module VII-PSUR states: "Because clinical development of a medicinal product frequently continues following marketing authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate." Therefore, the PRAC Rapporteur assumes that the MAH will address the safety issues with different time intervals between dose 1, 2 and 3, and usage of Comirnaty in heterologous vaccination schedules with other vaccines in the next PSUR, if applicable. An additional question for the next PSUR is added.

Serious hypertension:

The MAH has identified 546 cases of serious hypertension that is medically confirmed. However, none of these cases, including fatal cases, have been presented by the MAH. In our opinion, the review did not allow for a conclusion to be drawn based on the very limited data presented. We propose to ask the MAH to conduct a cumulative review of serious hypertension (of any duration) in the next MSSR with data from all sources, including a discussion on any plausible mechanisms. Striking cases/index cases should be presented in detail.

Rapporteur assessment comment:

As stated in current AR (section 2.2.1.5 Serious hypertension), a cumulative review of cases reporting serious hypertension is provided by the MAH. The RCT data did not report an imbalance, 5 cases in treatment group and 5 cases in placebo group. Post-marketing 634 cases were retrieved of which 546 medical confirmed. There were no safety signals emerged based on the presented cumulative review. Therefore, there is no reason to request for a subsequent cumulative review of cases reporting serious hypertension at the moment. The MAH should continue to monitor serious hypertension and notify the Rapporteur in case of unexpected trends or findings.

Menstrual disorders:

Due to the continuously (November - December) very high numbers of ICSRs reporting of menstrual disturbances (e.g. long-lasting meno-/metrorrhagias and amenorrheas) and post menopausal bleedings, we would like to flag that we are considering submitting signals in EPITT for amenorrheas, severe menstrual bleedings and post-menopausal bleedings.

Rapporteur assessment comment:

The DLP of current PSUR is 18-06-2021. Therefore, cases from November and December 2021 are not included in the current PSUR. However, menstrual disorders have been evaluated in previous Comirnaty MSSRs in which it was concluded that the data did not support a causal association with Comirnaty. Therefore, when considering a signaling in EPITT regarding menstrual disorders it is expected that more convincing additional evidence besides a high number (of an already high incidence disorder like menstrual disorders) of cases is needed to confirm the start of a signal procedure.

MS5

Overall, MS5 agrees with the PRAC Rapp assessment report. However, MS5 has a comment regarding the potential risk of exacerbation (flare-up) of a pre-existing auto-immune (AI) or inflammatory disorder.

MS5 considers that the potential risk of exacerbation (flare-up) of a pre-existing auto-immune (AI) or inflammatory disorder would need to be closely monitored not only in the post vaccination period with Comirnaty but also with the other COVID-19 vaccines.

Therefore, as previously requested for other COVID-19 vaccine, MS5 suggests to closely monitor this topic and to request from the MAH the following:

- A cumulative review of exacerbation (flare-up) of pre-existing AI/Inflammatory disorders to be presented 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.

In addition, the MAH should present full case narratives of exacerbation (flare-up) of pre-existing AI/Inflammatory disorder in patient with known pre-existing AI/Inflammatory disorder at steady stage and without other reported alternate aetiology or contributing factor.

The full case narratives should at least contain : time from First Dose to Onset (days) of the exacerbation (flare-up), time from last dose to onset, Medical History (including date first symptoms and diagnostic of AI/Inflammatory disorders) and current medications.

If the MAH considers that an update to the product information is needed, suggestion for SmPC text and corresponding frequency calculations should be presented, as appropriate. The MAH should also consider based on the updated information in the next PSUR whether the current risk characterization of the missing information category "Use in Subjects with Autoimmune or Inflammatory Disorders" should be updated.

As mention above, the plausible mechanism of action for exacerbation of autoimmune and inflammatory disorders post vaccination is unknown. Thus the rationale could also be applied to all marketed COVID-19 vaccines and therefore, MS5 also proposes to harmonize the safety monitoring for this potential risk across others COVID-19 vaccines.

Rapporteur assessment comment:
We agree with the CMS and an additional request for the next PSUR is included.

MS6

In general the PRAC Rapporteur assessment is endorsed, but we have the following comment:

<u>Backlog of processed cases</u>

In the Table 11, the MAH presents the characteristics of the backlog cases still not processed at the end of the reporting interval. It could be agreed that they does not represent a profile different to the already processed cases. However, this huge number (44.5% of the total PSUR dataset) could have a great impact in the OE analyses performed, in particular, for safety topics already evaluated and for which a conclusion has been reached as part of the MSSRs. Therefore, the MAH should be urgently prompted for the proper management and reporting of backlog cases according to legal requirements.

Rapporteur assessment comment:

We agree with the MS and two requests for the next PSUR regarding the backlog cases were already included: 1) 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, and 2) to perform overall O/E analyses using at least no risk window, 14-day risk window and 21-day risk window and additionally perform sensitivity O/E analyses which include the processed cases plus the backlog cases.

Clinical Studies information

The MAH has not provided any detailed data on the ongoing clinical trials: number of subjects already included, analysis of interim results in terms of safety. Only the statement "no clinically important safety information has emerged" is included, and the cumulative summary tabulation is of little value. Of special relevance will be to have insights on the ongoing study in pregnant women.

The same applies to the 2 US ongoing observational studies: details on progress and an analysis of interim results should be provided.

Furthermore, the status of the studies included in the RMP should be provided.

Rapporteur assessment comment:

During the reporting the period, the MAH states that no clinically important safety information has emerged from the ongoing clinical trials and no new safety information arising from non-interventional studies was reported. This is in line with the GVP Module VII-PSUR: "If the marketing authorisation holder is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this sub-section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals."

The MAH states in the PSUR that the studies included in the RMP are all ongoing. These PASS's have their own defined milestones for reporting updates, interim results etc, which will be assessed in separate procedures. Besides the final study reports, the MAH should summarise in the PSUR relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-sponsored (non)interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes), if applicable.

Fatal cases

Distribution of events with fatal outcome should be compared with the available statistics of distribution of the most frequently expected fatalities in the age specific general population.

It is not clear how morbidities have been analysed. The MAH states that there were no differences observed in the pattern of fatal events reported between the group with comorbidities and the one without comorbidities, whereas one would expect a different pattern, should comorbidities play a role in the fatal outcome.

O/E analysis of sudden death has not been provided.

Time to onset is provided as time to fatal events onset, being therefore time to onset described for 8127 events corresponding to 5042 fatal cases. In order to have a clearer picture, time to onset should be provided by case (either to the occurrence of the first event or to the fatality itself).

Rapporteur assessment comment:

The overall and age-stratified O/E analyses of Death are presented in Appendix 6c of the PSUR with O/E ratios below 1. The PT used is Fatal clinical outcome which includes Sudden Death. Age-stratified background rates for death were calculated from Centers for Disease Control and Prevention, National Center for Health Statistics data.

We do not consider that an additional O/E analyses for cases reporting sudden death (n=332) and a time to onset to fatal outcome provided by case will alter the conclusion that no new safety risk could be identified based on assessment of the cases with fatal outcome during the reporting period.

Haemorrhages

Although the search of haemorrhage has been performed using the SMQ haemorrhage, for the O/E analysis, only the subset of cases reported with the term "haemorrhage" have taken into account, considering a background incidence from Pfizer Internal Data Healthcare specific. The MAH should clarify which terms have been considered for the background incidence estimate.

Rapporteur assessment comment:

We assume that the PTs presented in table 1 (Preferred Terms Used to Identify Clinical Trial and Spontaneously Reported Adverse Events of Special Interest) of Appendix 6c (O/E analyses for AESIs) are used to estimate the background incidence from Pfizer Internal Data Healthcare for the multiple concerned AESIs including haemorrhage. However, this is not stated/confirmed by the MAH in the PSUR. Therefore, an additional request for next PSUR is included: The MAH is requested to clarify which terms have been considered for the background incidence estimate for the multiple concerned AESIs including haemorrhage when using the Pfizer Internal Data Healthcare.

Pregnancy and lactation

The cases concerning pregnancy and lactation constitute 0.5% and 0.3% of the total of cases from the PM dataset. However, 107,027 out the 145,825 unlocked cases (73%) were female patient and 68,837 cases (47%) were of childbearing age (age between 18 and 50 years). The MAH should defined the strategies put in place to identify, manage and prioritize the pregnancy cases among these unlocked cases.

The literature review about pregnancy only includes four articles related to immunogenicity. The MAH is reminded to include all publications about the safety of vaccine in pregnant women. Some articles about pregnancy has been published during the PSUR interval (Shimabukuro et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons, NEJM Jun 2021) or near DLP (Goldstein et al, Association between BNT162b2 vaccination and incidence of SARs-Cov-2 infection in pregnant women, JAMA July 2021) and so they should have been considered for the PSUR.

A 34.43% of the post-marketing cases 572 out 1661 post-marketing cases did not have information about the outcome of the pregnancy. In addition, 602 out the 841 prospective cases (72%) did not have information about the time of vaccination during the pregnancy and that precluded the causality assessment of the cases. The MAH should make all efforts to complete the follow-up of the pregnant woman cases.

Regarding information on pregnancy, it has been observed that the MAH has not performed O/E analysis for spontaneous abortion neither in the MSSR nor in the PSUR. This analysis of an important pregnancy outcome should be requested to the MAH. If disproportionality is observed, a qualitative analysis of the causality of the cases (regarding TTO, maternal age, other risk factors as previous medical history, concomitant treatments…) should be performed.

Regarding the data in lactation, the MAH only provided information about the most frequently reported clinical events (≥ 5 occurrences). However, some relevant cases in lactating infants were described across other sections of the PSUR. For instance, three relevant cases were identified in the section thromboembolic events reported in very young paediatric patients. In two of them the breastfeeding boys (5-month and 15-month-old) developed thromboembolic events (TTP and TIA) closely to the mother vaccination (2 days and 5 days after respectively). Therefore, the relevant cases evaluated under signals or health authorities requests that concern to lactating children should be described with detail also in this section.

Rapporteur assessment comment:

We agree with the comments of the MS regarding pregnancy and lactation that the MAH should define the strategies put in place to identify, manage and prioritize the pregnancy cases among these unlocked cases, should include all publications during the reporting interval and make all efforts to complete the follow-up of the pregnant woman cases, and should describe with detail the relevant cases evaluated under signals or health authorities requests that concern to breastfed children in section 'Use in pregnant/lactating women' of the PSUR. For these comments additional requests for next PSUR are included.

The Comirnaty exposure in pregnant women is not known and therefore O/E analyses cannot be performed. Besides, a request to perform an additional O/E analysis for spontaneous abortion without relevant information/signal for a possible safety concern is not considered needed. However, we agree that it is unclear if the frequency of AEs reported including spontaneous abortion is consistent with the expectation. Future results from studies evaluating the safety in pregnancy should give more clarity regarding pregnancy outcomes in relation to Comirnaty exposure.

MS7

Overall, we endorse the PRAC Rapp report, and have the following comments:

1. We propose removal of "anaphylaxis" from the risk management plan. During the period of one year of intense monitoring of the safety concern and assessed within the MSSRs and PSUR, this important identified risk has been thoroughly characterized with no effect the benefit-risk ratio. Therefore, we propose that this safety issue is monitored through regular pharmacovigilance activities or if deemed really necessary it can be included as a safety issue for which regular updates through PSUR can be provided.
2. Similarly, as for anaphylaxis, we propose removal of "Vaccine-associated enhanced disease (VAED), including Vaccine associated respiratory enhanced disease (VAERD)" from the risk management plan. This important potential risk has been monitored closely during the period of one year and assessed through the MSSRs and PSUR and no new safety concern is identified regarding VAED/VAERD. Therefore, we propose that this safety issue is monitored through regular pharmacovigilance activities.
3. In line with previous comments, we propose discontinuation of the Data Capture Aids/Follow-up questionnaires regarding "anaphylaxis" and "VAED/VAERD" as these issues are now considered sufficiently characterized and the FU questionnaires present a significant

administrative burden for the member states.

Rapporteur assessment comment:

Although there is nearly an 1-year period of intense monitoring of the safety concerns related to Comirnaty exposure which include Anaphylaxis and VAED/VAERD, these safety concerns are under evaluation in several PASS's which are included in the pharmacovigilance plan of the Comirnaty RMP. Also, recently the indication was extended to children aged 5-11 years and a third/booster dose was approved of which the post-marketing safety information collection and reporting has just started. Therefore, the safety concerns Anaphylaxis and VAED/VAERD should not be removed from the Comirnaty RMP.

PERIODIC SAFETY UPDATE REPORT #1
for
ACTIVE SUBSTANCE: COVID-19 mRNA vaccine (nucleoside modified) (BNT162b2)

ATC CODE: J07BX03[1]

AUTHORISATION PROCEDURE in the EU: Centralised

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DATE OF THIS REPORT: 19 AUGUST 2021

SIGNATURE: [redacted] **Date**: 19 August 2021

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Please note that this report may contain unblinded clinical trial information.

[1] Implementation as new ATC code starting from 01 January 2022.

[2] Earliest conditional approval date.

EXECUTIVE SUMMARY

This is the 1st Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (nucleoside modified) (Coronavirus disease 2019 [COVID-19] mRNA Vaccine, COMIRNATY®, hereafter referred to as BNT162b2)[3], covering the reporting interval 19 December 2020 through 18 June 2021.

BNT162b2 is a white to off-white frozen dispersion (pH: 6.9 – 7.9), provided as concentrate for dispersion for injection (sterile concentrate) as multidose vial to be diluted before use. The multidose vial contains 6 doses of 0.3 mL after dilution; low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 µl. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Each dose contains 30 micrograms of BNT162b2 embedded in lipid nanoparticles (LNPs).

The vaccine also contains ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water for injections as excipients.

The active substance of the COVID-19 mRNA vaccine is a highly purified single-stranded, 5'-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

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 (S) antigen, which may contribute to protection against COVID-19.

It is administered intramuscularly in the deltoid muscle after dilution as a series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.

BNT162b2 is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.[4]

Cumulatively, it is estimated that 53,499 subjects have participated in BNT162b2 sponsor-initiated clinical trials worldwide, with 46,577 subjects exposed to BNT162b2, 30 subjects exposed to BNT162a1, 411 exposed to BNT162b1, 96 subjects each exposed to BNT162b3

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

[4] On 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 years and the European Commission adopted a decision accordingly on 31 May 2021.

and BNT162c2. There were 330 subjects exposed to BNT162b2s01, 4757 exposed to blinded therapy and 1202 to placebo.

There were 1711 out of the 53,499 subjects participating in BioNTech and Fosun CTs, of which 1103 participated in the Chinese studies conducted by Fosun.

There were 557 subjects who received BNT162b2 as a study drug or as a comparator in another Pfizer clinical development program (B747).

From the receipt of the first temporary authorization for emergency supply on 01 December 2020 through 18 June 2021, approximately 774,478,440 doses of BNT162b2 were shipped worldwide, corresponding to 642,817,105 estimated administered doses.

During the current reporting interval (19 December 2020 through 18 June 2021), approximately 765,980,340 doses of BNT162b2 were shipped worldwide, corresponding to 635,763,682 estimated administered doses.

BNT162b2 has received conditional marketing authorisation approval in 45 countries and has received temporary authorisation for emergency supply in 38 countries. In addition, WHO had approved the emergency use listing of BNT162b2.

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

The actions summarized below have been taken for safety reasons during the reporting interval.

- On 15 January 2021, following fatal events involving elderly patients vaccinated with BNT162b2 in Norway, the Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.

- On 05 February 2021, Health Canada requested to issue a joint Pfizer-Health Canada Health Product Risk Communication (HPRC) to communicate revisions to Product Monograph (addition of 6-dose vial information and text on anaphylaxis). Final HPRC was approved on 08 February 2021.

- In March 2021, complaints for leakages were reported to the MAH in Hong Kong, with 19 vials with leakages reported from 3 different vaccination sites in the country; overall 26 vials with leakages and/or loose caps were reported. All vials were from 1 batch, the only batch in use for vaccination in Hong Kong and Macau. During the investigation, it became apparent that the root cause of the reported product quality complaints is a combination of the container closure process (crimping) at 1 single CMO and of the specific transport conditions on dry ice that are required for BNT162b2. Vaccination in Hong Kong and Macau was stopped as soon as the issue became apparent (24 March 2021). A total of 2 batches (210102 and 210104) have been affected (including the one being used and another one already shipped to Hong Kong, but still in storage) and were quarantined. The root cause of the reported product quality complaints was clearly identified through analysis of the data generated and collected as of 31 March

2021. Due to the identified root cause the MAH could exclude any influence on batches that were on the market anywhere outside of Hong Kong and Macau. The CMO in question has not manufactured any batch that was released for any market other than Hong Kong and Macau.

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 4.0 dated 19 May 2021, in effect at the end of the reporting period. The previous CDS versions (1.0 dated 12 February 2021, 2.0, dated 02 March 2021 and 3.0, dated 20 April 2021) were also in effect during the reporting period. Safety-related changes included updates of the following sections: 4.4 Special warnings and precautions for use (version 4.0), 4.8 Undesirable effects (versions 4.0, 3.0 and 2.0), 5.1 Pharmacodynamic properties (version 4.0), Appendix A, Appendix B and Appendix C (version 4.0).

The first CDS was issued on 12 February 2021; prior to that date, the combined EUA Fact Sheet for the HCP and Full EUA Prescribing Information (PI) and the EU-SmPC were the RSIs.

The first EU-SmPC was issued on 21 December 2020. The EU-SmPC was updated without safety-related changes, on 08 January 2021 (number of doses from the same vial) and on 28 January 2021.

The first BNT162b2 combined EUA Fact Sheet for the HCP and EUA PI, dated 11 December 2020, was in effect during the reporting period. Safety-related updates of the BNT162b2 combined EUA Fact Sheet for the HCP and EUA PI occurred on 23 December 2020 (monitoring of vaccinee for the occurrence of immediate adverse reactions in the Warnings Section of the Fact Sheet and in the Warning and Precautions Section of the PI) and on 25 January 2021, to add anaphylaxis to the Adverse Reactions and Overall Safety Summary section.

During the reporting period, the following signals were addressed:

- Signals determined not to be risks:

  Seizure, Thromboembolic events, Delayed skin reaction, Delayed syncope, Eye pain and eye swelling, Herpes zoster including ophthalmic herpes zoster, Appendicitis, Hearing loss and tinnitus, Extensive swelling of the limbs, Reaction associated with dermal fillers, Injection site pruritis, Insomnia, Overdose, Deaths (including elderly or frail individuals), Facial nerve palsy.

- Signals determined to be risks:

  Dizziness for the process of vaccination rather than the vaccine substrate[5], Hyperhidrosis, Night sweats, Asthenia, Lethargy, Decreased appetite, Vaccine stress-related responses,

[5] In Table 15 Dizziness, Tachycardia and Paraesthesia are subsumed as "Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia)".

Tachycardia[5], Diarrhea, Pain in extremity (Arm), Anaphylaxis, Vomiting, Hypersensitivity, other than anaphylaxis, Paraesthesia[5].

- Ongoing signals:

  Immune thrombocytopenia, Trigeminal neuralgia, Myocarditis and pericarditis, Hypertensive crisis with intracranial haemorrhage.

During the reporting period, monitoring was requested or was proposed by the MAH in previous Summary Monthly Safety Reports (SMSRs) for

- Lymphopenia, Immune thrombocytopenia,[6] Hearing loss and tinnitus,[6] Hypoglycemia, Serious hypertension, Hemophagocytic syndrome, Serious arrhythmias, Acute pancreatitis, Acquired haemophilia, and Menstrual disorders.

In alignment with the European Union Risk Management Plan (EU-RMP) in effect at the beginning of the reporting period version 1.0 (EMEA/H/C/005735/0000) dated 21 December 2020 and with subsequent EU-RMP versions 1.1 (EMEA/H/C/005735/II/0019[7]), 2.0 (EMEA/H/C/005735/II/0030 currently approved by the EMA[8]) and 2.1 (EMEA/H/C/005735/II/0036, under evaluation[9]) 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 (eg, 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.

After the data lock point (DLP) of this PSUR, based on the Signal of Myocarditis and pericarditis for COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY (EPITT No. 19712) - EMA/PRAC/325882/2021 recommendation dated 08 July 2021, the MAH updated the RSI (CDS version 5.0 dated 14 July) and EU-SmPC to include information about myocarditis and pericarditis following vaccine administration and has distributed a Direct

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[6] Referred as signal in Table 15.

[7] The EU-RMP v 1.1 was submitted (Type II variation [EMEA/H/C/005735/II/0019]) revising the post-authorization vaccine effectiveness study C4591014 currently included in the RMP (Category 3) as a commitment and adding 2 not sponsored vaccine effectiveness epidemiology studies (WI235284 and WI255886). The CHMP opinion was dated 16 April 2021.

[8] The EU-RMP v 2.0 was submitted to include data on paediatric individuals 12 and 15 years of age. On 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 year and the European Commission adopted a decision accordingly on 31 May 2021.

[9] The EU-RMP v 2.1 was submitted to include new data from the clinical database (6-month post Dose-2) and from the safety database to the data on individuals 16 years of age and older initially submitted on December 2020.

Healthcare Professional Communication (DHPC) to address these findings. The DHPC was distributed starting from 19 July 2021 to all EU member states where the respective vaccines are authorised. The EU-RMP version 2.3[10] was submitted to EMA on 06 August 2021. With respect to approved version 2.0, the list of safety concerns in the version 2.3 was updated with the inclusion of myocarditis and pericarditis as important identified risk and the Pharmacovigilance plan was consequently updated.

After DLP, Immune thrombocytopenia was closed and categorized as no risk, Trigeminal neuralgia and Hypertensive crisis with intracranial haemorrhage were closed as non-validated signals.

Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2, the benefit-risk profile of BNT162b2 remains favorable. No additional changes to the BNT162b2 RSI or additional risk minimisation activities are warranted in addition to those above mentioned.

[10] The consolidated version 2.2 (merging versions 2.0 and 2.1) with no new safety information has been submitted on 29 July 2021. This version is still under review and not effective yet.

TABLE OF CONTENTS

EXECUTIVE SUMMARY 2
LIST OF TABLES 11
LIST OF FIGURES 14
APPENDICES 15
LIST OF ABBREVIATIONS 17
1. INTRODUCTION 22
2. WORLDWIDE MARKETING APPROVAL STATUS 22
3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS 23
4. CHANGES TO REFERENCE SAFETY INFORMATION 24
5. ESTIMATED EXPOSURE AND USE PATTERNS 25
5.1. Cumulative Subject Exposure in Clinical Trials 25
5.2. Cumulative and Interval Patient Exposure from Marketing Experience 26
6. DATA IN SUMMARY TABULATIONS 30
6.1. Reference Information 30
6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials 30
6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources 30
6.3.1. General Overview – All Cases 31
6.3.1.1. Clinical Trials Data 33
6.3.1.2. Post-Authorization Data 44
6.3.1.3. Conclusion 57
6.3.2. General Overview - Unlocked Cases 58
6.3.2.1. Clinical Trials Data 59
6.3.2.2. Post-Authorization Data 59
6.3.2.3. Conclusion 61
7. SUMMARIES OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL 61
7.1. Completed Clinical Trials 61
7.2. Ongoing Clinical Trials 61
7.3. Long-term Follow-up 63
7.4. Other Therapeutic Use of Medicinal Product 63

7.5. New Safety Data Related to Fixed Combination Therapies....63
8. FINDINGS FROM NON-INTERVENTIONAL STUDIES....63
9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES....64
9.1. Other Clinical Trials....64
9.2. Medication Errors....66
10. NON-CLINICAL DATA....76
11. LITERATURE....76
12. OTHER PERIODIC REPORTS....83
13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS....84
14. LATE-BREAKING INFORMATION....84
15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED....84
15.1. Lymphopenia....88
15.2. Immune thrombocytopenia....89
15.3. Hearing Loss and Tinnitus....90
15.4. Hypoglycaemia....90
15.5. Serious Hypertension....91
15.6. Haemophagocytic Syndrome....91
15.7. Serious Arrhythmias....92
15.8. Acute Pancreatitis....92
15.9. Acquired Haemophilia....93
15.10. Menstrual Disorders....94
16. SIGNAL AND RISK EVALUATION....95
16.1. Summary of Safety Concerns....95
16.2. Signal Evaluation....96
16.2.1. Evaluation of Closed Signals....96
16.2.1.1. Evaluation of Closed Signals During the Reporting Interval Assessed under any Regulatory Procedure....96
16.2.1.2. Evaluation of Closed Signals During the Reporting Interval not Assessed as part of any Regulatory Procedure....97
16.2.2. Signal Evaluation Plan for Ongoing Signals....108
16.3. Evaluation of Risks and New Information....109
16.3.1. Evaluation of Important Identified Risks....113
16.3.2. Evaluation of Important Potential Risks....118

16.3.3. Evaluation of Other Risks (not categorised as important).....125
16.3.3.1. Adverse Events of Special Interest (AESIs).....125
16.3.3.2. Clinical Reactogenicity Data on Individuals Previously exposed or not to SARS-COV-2.....174
16.3.3.3. Local Adverse Reactions.....175
16.3.3.4. Systemic Adverse Reactions.....179
16.3.3.5. Severe Reactogenicity.....187
16.3.3.6. Age-Related Adverse Reactions.....189
16.3.3.7. Vaccination Stress/Anxiety related ADRs.....194
16.3.4. Evaluation of Special Situations.....197
16.3.4.1. Death.....198
16.3.4.2. Overdose.....207
16.3.4.3. Abuse, Misuse, and Drug Dependency.....210
16.3.4.4. Occupational Exposure.....212
16.3.4.5. Lack of Therapeutic Efficacy.....214
16.3.4.6. Off-Label Use.....219
16.3.4.7. Unexpected Therapeutic Effect.....221
16.3.5. Update on Special Patient Populations.....223
16.3.5.1. Use in Elderly Patients.....223
16.3.5.2. Use in Paediatric Patients.....226
16.3.5.3. Use in Pregnant/Lactating Women.....234
16.3.5.4. Use in Patients with Co-Morbidities.....246
16.3.5.5. Use in Immunocompromised Patients.....250
16.3.5.6. Use in Patients with Autoimmune or Inflammatory Disorders.....253
16.3.5.7. Use in Frail Patients with Co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis).....256
16.3.5.8. Interactions with other Vaccines.....258
16.4. Characterisation of Risks.....260
16.4.1. Characterisation of Important Identified and Potential Risks.....260
16.4.2. Description of Missing Information.....264
16.5. Effectiveness of Risk Minimisation (if applicable).....265
17. BENEFIT EVALUATION.....266

17.1. Important Baseline Efficacy and Effectiveness Information 266
17.2. Newly Identified Information on Efficacy and Effectiveness.....275
17.3. Characterisation of Benefits.....277
18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS.....277
18.1. Benefit-Risk Context – Medical Need and Important Alternatives 277
18.2. Benefit-Risk Analysis Evaluation 282
18.2.1. Benefits.....283
18.2.2. Risks 283
18.2.3. Overall Benefit-Risk.....286
19. CONCLUSION AND ACTIONS.....286

LIST OF TABLES

Table 1. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide 27
Table 2. Interval Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide 28
Table 3. EEA - Cumulative and Interval Number of Administered Doses by Age Group and Dose 1 and Dose 2 29
Table 4. Japan - Cumulative and Interval Number of Administered Doses by Health Workers and Elderly and Dose (1st and 2nd) 30
Table 5. Selected Case Characteristics - All Cases Received during the Reporting Interval 31
Table 6. Case Summary: All Cases Received during the Reporting Interval 32
Table 7. Clinical Trial Data: Events Reported in ⩾2%* Cases 38
Table 8. Post-Authorization Data: Events Reported in ⩾2%* Cases 49
Table 9. Most Frequently Reported Lot Numbers 56
Table 10. Post-Authorization Cases – Analysis by Dose 57
Table 11. Selected Case Characteristics - Unlocked Cases at the End of the Reporting Interval 58
Table 12. Post-Authorization Data: Events Reported in ⩾2%* of Unlocked Cases 59
Table 13. Most reported Countries for Medication Error Cases 67
Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval 77
Table 15. Overview of Signals 85
Table 16. Ongoing Safety Concerns 95
Table 17. Signal Evaluation Plan for Ongoing Signals 109
Table 18. Follow-up for COVID-19 Vaccine Cases Received through Eudravigilance 110
Table 19. Follow-up for COVID-19 Vaccine Cases Received Outside of the Eudravigilance Process 111
Table 20. Evaluation of Important Identified Risks 113
Table 21. All Report Types - Number of Anaphylaxis Cases 115
Table 22. Regulatory Authority Reports – Number of Anaphylaxis Cases 117
Table 23. Evaluation of Important Potential Risks 118
Table 24. All Report Types - Number of VAED/VAERD Cases 123
Table 25. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome 182

Table 26. Analysis of Systemic Adverse Reactions by Presence of Selected Comorbidities, Event Seriousness and Event Outcome 184
Table 27. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome 185
Table 28. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups....191
Table 29. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups....191
Table 30. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups....191
Table 31. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups....193
Table 32. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups....193
Table 33. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups....193
Table 34. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval....203
Table 35. Post-Authorization Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval....204
Table 36. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval 206
Table 37. Post-Authorization Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval....206
Table 38. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval 237
Table 39. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval....240
Table 40. Post-Authorization Data: Pregnancy Outcome during the Reporting Interval...244
Table 41. Ongoing Safety Concerns 260
Table 42. Characterisation of Important Risks 261
Table 43. Description of Missing Information 264

Table 44. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period 267

Table 45. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period 268

Table 46. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period 270

Table 47. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up 272

Table 48. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 to 15 Years of Age Evaluable Efficacy (7 Days) Population 274

Table 49. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021 278

Table 50. Summary of Important Risks 285

Table 51. Overall Benefit-Risk for BNT162b2 286

LIST OF FIGURES

Figure 1. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities 34

Figure 2. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities, Gender and Age Group 35

Figure 3. Clinical Trial Data: Fatal Case Outcome by Presence/Absence of Comorbidities and Age Group 37

Figure 4. Clinical Trial Data: Total Number of SAEs by MedDRA SOC 38

Figure 5. Clinical Trial Data: SAEs Reported in ⩾2% of Cases by Gender 39

Figure 6. Clinical Trial Data: SAEs Reported in ⩾2% of Cases by SOC and Age Group 40

Figure 7. Clinical Trial Data: Events Reported in ⩾2% of Cases by Age Group within Gender 43

Figure 8. Post-Authorization Data: Case Outcome by Presence/Absence of Comorbidities 45

Figure 9. Post-Authorization Data: Case Outcome by Presence/Absence of Comorbidities, Gender and Age Group 46

Figure 10. Post-Authorization Data: Fatal Case Outcome by Presence/Absence of Comorbidities and Age Group 48

Figure 11. Post-Authorization Data: Total Number of Events by MedDRA SOC and Event Seriousness 49

Figure 12. Post-Authorization Data: Events Reported in ⩾2% of Cases by Gender 51

Figure 13. Post-Authorization Data: Events Reported in ⩾2% of Cases by SOC and Age Group 51

Figure 14. Post-Authorization Data: Events Reported in ⩾2% of Cases by Age Group within Gender 55

Figure 15. Events Reported in ⩾2% of All Clinical Trial Cases by Age Group 192

Figure 16. Events Reported in ⩾2% of All Post-Authorization Cases by Age Group 194

Figure 17. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Phase 1, 2 Doses, 21 Days Apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population 276

Figure 18. Geometric Mean Concentrations and 95% CIs: S1-Binding IgG Level Assay – Phase 1, 2 Doses, 21 Days Apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population 277

APPENDICES

APPENDIX 1 REFERENCE INFORMATION (19 MAY 2021) 287
APPENDIX 1.1 SAFETY RELATED CHANGES TO RSI 328
APPENDIX 1.2 CORE DATA SHEET (12 FEBRUARY 2021) 343
APPENDIX 1.3 CORE DATA SHEET (02 MARCH 2021) 363
APPENDIX 1.4 CORE DATA SHEET (20 APRIL 2021) 384
APPENDIX 1.5 COMBINED EUA FACT SHEET FOR HEALTHCARE PROVIDERS AND FULL EUA PRESCRIBING INFORMATION (11 DECEMBER 2020) 407
APPENDIX 1.6 COMBINED EUA FACT SHEET FOR HEALTHCARE PROVIDERS AND FULL EUA PRESCRIBING INFORMATION (23 DECEMBER 2020) 436
APPENDIX 1.7 COMBINED EUA FACT SHEET FOR HEALTHCARE PROVIDERS AND FULL EUA PRESCRIBING INFORMATION (05 JANUARY 2021) 466
APPENDIX 1.8 COMBINED EUA FACT SHEET FOR HEALTHCARE PROVIDERS AND FULL EUA PRESCRIBING INFORMATION (25 JANUARY 2021) 496
APPENDIX 1.9 EU-SmPC (21 DECEMBER 2020) 526
APPENDIX 1.10 EU-SmPC (08 JANUARY 2021) 558
APPENDIX 1.11 EU-SmPC (28 JANUARY 2021) 593
APPENDIX 2.1 CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS 626
APPENDIX 2.1.1 CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS FROM NON-PFIZER (LICENSING PARTNER) CLINICAL TRIALS 653
APPENDIX 2.2 CUMULATIVE AND INTERVAL SUMMARY TABULATION OF SERIOUS AND NON-SERIOUS ADVERSE REACTIONS FROM POST-MARKETING DATA SOURCES 655
APPENDIX 2.3 CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA 884
APPENDIX 2.3B CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM BIONTECH DEVELOPMENT PROGRAMS 886
APPENDIX 2.3C CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM FOSUN DEVELOPMENT PROGRAMS 887
APPENDIX 2.3.1 CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM OTHER PFIZER DEVELOPMENT PROGRAMS 888
APPENDIX 3 TABULAR SUMMARY OF SAFETY SIGNALS 889
APPENDIX 3.1 SIGNAL EVALUATION ..... NO DATA
APPENDIX 4.1 LISTING OF COMPLETED (CONCLUDED WITH FINAL CLINICAL STUDY REPORT) INTERVENTIONAL SAFETY STUDIES ..... NO DATA
APPENDIX 4.2 LISTING OF ONGOING (STARTED OR CONCLUDED WITH NO FINAL CLINICAL STUDY REPORTS) INTERVENTIONAL SAFETY STUDIES 903

APPENDIX 4.3 LISTING OF COMPLETED (CONCLUDED WITH FINAL CLINICAL STUDY REPORT) NON-INTERVENTIONAL SAFETY STUDIES .....NO DATA
APPENDIX 4.4 LISTING OF ONGOING (STARTED OR CONCLUDED WITH NO FINAL CLINICAL STUDY REPORTS) NON-INTERVENTIONAL SAFETY STUDIES 904
APPENDIX 5 LIST OF SOURCES OF INFORMATION USED TO PREPARE THE PSUR .....NO DATA
APPENDIX 6A REGULATORY AUTHORITIES REQUEST(S) FOLLOWING REVIEW OF SMSR (NOT CONSIDERED AS A SIGNAL).....906
APPENDIX 6A.1 LYMPHOPENIA CUMULATIVE REVIEW 908
APPENDIX 6A.2 HYPOGLYCAEMIA CUMULATIVE REVIEW 914
APPENDIX 6A.3 SERIOUS HYPERTENSION CUMULATIVE REVIEW 920
APPENDIX 6A.4 HAEMOPHAGOCYTIC SYNDROME CUMULATIVE REVIEW 926
APPENDIX 6B REGULATORY AUTHORITIES REQUEST(S) FOLLOWING REVIEW OF SMSR.....933
APPENDIX 6B.1 IMMUNE THROMBOCYTOPENIA.....935
APPENDIX 6B.2-1 HEARING LOSS (SERIOUS CASES) 955
APPENDIX 6B.2-2 TINNUTUS.....966
APPENDIX 6B.3 SERIOUS ARRHYTHMIAS 984
APPENDIX 6B.4 PANCREATITIS.....990
APPENDIX 6B.5 ACQUIRED HAEMOPHILIA.....1000
APPENDIX 6B.6 MENSTRUAL DISORDERS 1011
APPENDIX 6C OBSERVED VERSUS EXPECTED ANALYSES FOR ADVERSE EVENTS OF SPECIAL INTEREST 1029
APPENDIX 6D.1 INTERVAL SUMMARY TABULATION OF FATAL REPORTS.....1058
APPENDIX 6D.2 CUMULATIVE SUMMARY TABULATION OF FATAL REPORTS 1088
APPENDIX 6E SAFETY EFFECTS OF MIXED SCHEDULE .....NO DATA
APPENDIX 6.1 PROPOSED PRODUCT INFORMATION (REGIONAL APPENDIX) .....NO DATA
APPENDIX 6.2 PROPOSED ADDITIONAL PHARMACOVIGILANCE AND RISK MINIMISATION ACTIVITIES (REGIONAL APPENDIX).....NO DATA
APPENDIX 6.3 SUMMARY OF ONGOING SAFETY CONCERNS (REGIONAL APPENDIX) .....NO DATA
APPENDIX 6.4 REPORTING OF RESULTS FROM POST-AUTHORISATION SAFETY STUDIES (REGIONAL APPENDIX).....NO DATA
APPENDIX 6.5 EFFECTIVENESS OF RISK MINIMISATION (REGIONAL APPENDIX) .....NO DATA
APPENDIX 7 CUMULATIVE MARKETING AUTHORISATION STATUS.....NO DATA
APPENDIX 8 CHARACTERISATION OF IMPORTANT RISKS.....NO DATA

LIST OF ABBREVIATIONS

ABG	arterial blood gas
ACE2	angiotensin-converting enzyme 2
ADAMTS-13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADEM	acute disseminated encephalomyelitis
ADR	adverse drug reaction
AE	adverse event
AERP	adverse event reporting proportion
AESI	adverse event of special interest
AHA	acquired hemophilia A
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de santé
anti-SSA	anti-Sjogren's-syndrome-related antigen A
anti-SSB	anti-Sjogren's-syndrome-related antigen B
aPTT	activated plasma thromboplastin time
AR	assessment report
ARDS	acute respiratory distress syndrome
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
aTTP	acquired thrombotic thrombocytopenic purpura
BC	Brighton Collaboration
BISAP	bedside index of severity in acute pancreatitis
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
C3, C4	complements level
CAP	community acquired pneumonia
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMI	Charlson comorbidity index
CMO	contract manufacturing organizations
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 vaccine global access

COVID-19	coronavirus disease 2019
COVID-19 vaccine mRNA (mRNA 1273)	Spikevax COVID-19 Moderna
Cr	blood creatinine
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial, computed tomography
CVST	cerebral venous sinus thrombosis
DCA	data capture aid
DHPC	direct healthcare professional communication
DIC	disseminated intravascular coagulation
DLP	data lock point
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
DSU	drug safety unit
DVT	deep vein thrombosis
EBV	Epstein-Barr Virus
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEA	European economic area
EEG	electroencephalogram
EF	ejection fraction
EMA	European Medicines Agency
ENT	ear nose throat
ER	emergency room
EU	European Union
EUA	emergency use authorization
FDA	(US) Food and Drug Administration
FEIBA	factor eight inhibitor bypassing activity
FU	follow-up
FVIII	clotting factor VIII
GI	gastrointestinal
GMC	geometric mean concentration
GMR	geometric mean ratio
GMT	geometric mean titer
GVHD	graft versus host disease
GVP	Good Pharmacovigilance Practice
HA	Health Authority
HBV	hepatitis B virus
HCP	healthcare professional
HCT, Hct	hematopoietic stem cell transplant, haematocrit

HCV	hepatitis C virus
Hgb	haemoglobin
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HLGT	(MedDRA) high level group term
HLT	(MedDRA) high level term
HPRC	Health Product Risk Communication
HPV	human papillomavirus vaccine
HR	heart rate
HRT	hormone replacement therapy
HSV-1	herpes simplex virus type-1
HTN	hypertension
HZ	herpes zoster
IBD	International Birth Date
ICH	International Conference on Harmonisation, intracranial haemorrhage
ICSR	individual case safety report
ICU	intensive care unit
IgA, IgG, IgM	immunoglobulin A, immunoglobulin G, immunoglobulin M
INR	international normalized ratio
IR	incidence rate
ITP	immunothromobocytopenia
IU	international units
IVIG	intravenous immune globulin
K	blood potassium
LDH	lactate dehydrogenase
LMICs	low- and middle-income countries
LNP	lipid nanoparticles
LOC	loss of consciousness
LOE	lack of efficacy
LoQ	list of questions
LP	lumbar puncture
MAH	marketing authorisation holder
MC	medically confirmed
MCA	middle cerebral artery
ME	myalgic encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	middle East respiratory syndrome coronavirus
MHRA	(UK) Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
NA, Na	not applicable, blood sodium
NAAT	nucleic acid amplification test

NCA	national competent authority
NEC	not elsewhere classified
NIS	non-interventional study
NMC	non-medically confirmed
NMDA	N-methyl-d-aspartate
NSAID	nonsteroidal anti-inflammatory drug
O/E	observed versus expected
OWD	our world in data
PASS	post-authorisation safety study
PBRER	periodic benefit risk evaluation report
PC	product complaint
pCO_2	partial pressure of carbon dioxide
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PE	pulmonary embolism
PEG	polyethyleneglycol
PI	prescribing information
PM	post-authorization
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	(MedDRA) Preferred Term
PTEN	phosphatase and tensin homolog
PVFS	postviral fatigue syndrome
PVP	pharmacovigilance plan
PY	person-years
RA	regulatory authority
RBD	receptor binding domain
RMP	Risk Management Plan
RNA	ribonucleic acid
ROAPS	RSV in older adults and pregnant women study
RSI	reference safety information
RSV	respiratory syncytial virus
RT-PCR	reverse transcription-polymerase chain reaction
S	spike
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SMSR	summary monthly safety report
SOC	(MedDRA) system organ class
SPEAC	Safety Platform for Emergency vACcines
SR	sinus rhythm

SRD	safety receipt date
SSRM	safety surveillance risk management
Th1	T helper cell type 1
Th2	T helper cell type 2
TIA	transient ischaemic attack
TND	test-negative design
TTP	thrombotic thrombocytopenic purpura
TTS	thrombocytopenia thrombosis syndrome
UK	United Kingdom
UMC	Uppsala Monitoring Center
US	United States
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine effectiveness
WBC	white blood cell
WHO	world health organisation

1. INTRODUCTION

This is the 1st Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (nucleoside modified) (Coronavirus disease 2019 [COVID-19] mRNA Vaccine, COMIRNATY®, hereafter referred to as BNT162b2), covering the reporting interval 19 December 2020 through 18 June 2021.

The format and content of this PSUR is in accordance with the Guideline on GVP Module VII—Periodic safety update report (EMA/816292/2011 [December 2013]), with ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, January 2013]) and corePSUR19 guidance (EMA/362988/2021 [08 July 2021]).

BNT162b2 is a white to off-white frozen dispersion (pH: 6.9 – 7.9), provided as concentrate for dispersion for injection (sterile concentrate) as multidose vial to be diluted before use. The multidose vial contains 6 doses of 0.3 mL after dilution; low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Each dose contains 30 micrograms of BNT162b2 embedded in lipid nanoparticles (LNPs).

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

The vaccine also contains ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water for injections as excipients.

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. No dosage adjustment is required in elderly individuals ≥65 years of age. It is administered intramuscularly in the deltoid muscle after dilution as a series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.

Pfizer is responsible for the preparation of the PSUR on behalf of license partners according to the Pharmacovigilance Agreement(s) in place. Data from respective license partner(s) are included in the report when applicable.

2. WORLDWIDE MARKETING APPROVAL STATUS

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020. At the DLP, BNT162b2

is approved for use in individuals 16 years and older in 45 countries and it is also approved for use in individuals 12 - 15 years of age in 38 countries. BioNTech is the MAH in 34 countries, Pfizer in 10 countries and in 1 country the local Ministry of Health acted as MAH.

BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK[11] on 01 December 2020. At the DLP, BNT162b2 has received temporary authorisation for emergency supply[12] for use in individuals 16 years and older in 38 countries and it is also approved for use in individuals 12 - 15 years of age in 23 countries. BioNTech is the MAH in 10 countries, Pfizer in 26 countries and Hemas in 1 country. Both BioNTech and Pfizer are MAHs in UK for the initial temporary authorization under regulation 174. In addition, WHO had approved the emergency use listing of BNT162b2 for which BioNTech is the MAH.

Overall BNT162b2 received an approval in 82 countries[13]; BioNTech is the MAH in 44 countries, Pfizer in 36 countries, Hemas and the local Ministry of Health in 1 country each.

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

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

The actions summarized below have been taken for safety reasons during the reporting interval.

- On 15 January 2021, following fatal events involving elderly patients vaccinated with BNT162b2 in Norway, the Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.

- On 05 February 2021, Health Canada requested to issue a joint Pfizer-Health Canada Health Product Risk Communication to communicate revisions to Product Monograph (addition of 6-dose vial information and text on anaphylaxis). Final HPRC was approved on 08 February 2021.

- In March 2021, complaints for leakages were reported to the MAH in Hong Kong, with 19 vials with leakages reported from 3 different vaccination sites in the country; overall 26 vials with leakages and/or loose caps were reported. All vials were from 1 batch, the only batch in use for vaccination in Hong Kong and Macau. During the investigation, it became apparent that the root cause of the reported product quality complaints is a combination of the container closure process (crimping) at 1 single CMO and of the

[11] Upon that on 22 April 2021 conditional marketing authorisation approval was also granted in the UK, both the authorisation for emergency supply under regulation 174 and the conditional marketing authorization approval are currently active.

[12] It includes Emergency Use Authorization, Emergency Use Listing, Import License, Importation authorization, Interim Order, Pandemic Special Access Route, Special Import Permit, and Temporary authorization.

[13] Excluding WHO as non-country specific approval and counting once UK with 2 authorizations.

specific transport conditions on dry ice that are required for BNT162b2. Vaccination in Hong Kong and Macau was stopped as soon as the issue became apparent (24 March 2021). A total of 2 batches (210102 and 210104) have been affected (including the one being used and another one already shipped to Hong Kong, but still in storage) and were quarantined. The root cause of the reported product quality complaints was clearly identified through analysis of the data generated and collected as of 31 March 2021. Due to the identified root cause the MAH could exclude any influence on batches that were on the market anywhere outside of Hong Kong and Macau. The CMO in question has not manufactured any batch that was released for any market other than Hong Kong and Macau.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The reference safety information (RSI) for this PSUR is the COVID-19 mRNA vaccine Core Data Sheet (CDS) version 4.0 dated 19 May 2021, in effect at the end of the reporting period and included in Appendix 1. The previous CDS versions (1.0 dated 12 February 2021, 2.0, dated 02 March 2021 and 3.0, dated 20 April 2021) were also in effect during the reporting interval. Safety-related changes included updates of the following sections: 4.4 Special warnings and precautions for use (version 4.0), 4.8 Undesirable effects (versions 4.0, 3.0 and 2.0), 5.1 Pharmacodynamic properties (version 4.0), Appendix A, Appendix B and Appendix C (version 4.0).

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

The first CDS was issued on 12 February 2021; prior to that date, the EU-SmPC and the combined EUA Fact Sheet for the HCP and Full EUA Prescribing Information (PI) were the RSIs.

The first EU-SmPC was issued on 21 December 2020. The EU-SmPC was updated without safety-related changes on 08 January 2021, to indicate that the use of 6 doses/vial in place of 5 doses/vial was approved. It was specified that low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 µliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. The EU-SmPC dated 08 January 2021 was updated without safety-related changes on 28 January 2021.

The first BNT162b2 combined EUA Fact Sheet for the HCP and EUA PI, dated 11 December 2020, was in effect during the reporting period. Safety-related updates of the BNT162b2 combined EUA Fact Sheet for the HCP and EUA PI occurred on:

- 23 December 2020, to include a statement in the Warnings Section of the Fact Sheet and in the Warning and Precautions Section of the PI to monitor vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines.

- 25 January 2021, to add anaphylaxis to the Adverse Reactions and Overall Safety Summary section.

The BNT162b2 combined EUA Fact Sheet for the HCP and EUA PI was updated without safety-related changes, on 05 January 2021, to indicate that the use of 6 doses/vial in place of 5 doses/vial was approved (with the same wording of the EU-SmPC).

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 53,499 subjects have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

- BNT162a1: 30 subjects;
- BNT162b1: 411 subjects;
- BNT162b3: 96 subjects;
- BNT162c2: 96 subjects;
- BNT162b2: 46,577 subjects (of which, 23,514 subjects received BNT162b2, 21,235 subjects received BNT162b2 post-unblinding and had received placebo before, 959 had received BNT162b2/placebo and 869 subjects received a blinded boost with either BNT162b2 or BNT162b2s01 and had received BNT162b2 before);
- BNT162b2s01[14]: 330 subjects;
- Blinded therapy: 4757 subjects, and
- Placebo: 1202 subjects.

There were 1711 out of the 53,499 subjects participating in BioNTech and Fosun CTs, of which 1103 participated in the Chinese studies conducted by Fosun.

Subject demographics data (eg, age, gender, race) for 'C459' CTs is presented by treatment group in Appendix 2.3. Cumulative CT exposures with demographic data from BioNTech and Fosun CTs is presented in Appendix 2.3B and Appendix 2.3C.

Of note, BNT162b2 is also being utilized in another Pfizer clinical development program (B747): 557 subjects received BNT162b2 as a study drug or as a comparator in the clinical study B7471026[15]. Subject demographics data (eg, age, gender, race) by treatment groups are presented in Appendix 2.3.1.

[14] BNT162b2s01 is also referred to as BNT162b2SA.

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

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

It is not possible to determine with certainty the number of individuals who received BNT162b2 during the period of this review.

The worldwide number of shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 83% of the shipped doses were administered. This ratio represents the proportion of doses cumulatively administered (as per public available data for the EEA[16] countries and the US[17]) out of those cumulatively shipped (based on MAH data according to the shipment tracker [Order Book][18]).

With these caveats in mind, it is estimated that:

- approximately 774,478,440 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorization for emergency supply on 01 December 2020 through 18 June 2021, corresponding to 642,817,105 estimated administered doses;

- approximately 765,980,340 doses of BNT162b2 were shipped worldwide during the current reporting interval from 19 December 2020 through 18 June 2021, corresponding to 635,763,682 estimated administered doses.

Data about the number of COMIRNATY® doses administered are published for EEA, Japan and US in the respective Health Authorities' websites. COMIRNATY® exposure data by age group are available for some EEA countries and for Japan (elderly and health workers, Table 4). Currently there are no available public data that allow to estimate the COMIRNATY® exposure by gender.

Cumulative and interval worldwide estimated exposure[19] by dose, and region based on or extrapolated from internal data (number of shipped doses) and published data (number of doses administered) is displayed in Table 1 and Table 2.

[16] Approximately 83% of the doses shipped in the EU-EEA countries were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the EU-EEA countries, the total number of vaccine doses administered as per report on https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab, as of 18 June 2021.

[17] Approximately 83.9% of the doses shipped in the US were administered; this proportion has been calculated considering, out of total number of vaccine doses distributed in the US, the total number of vaccine doses administered as per report on https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 18 June 2021.

[18] The Order Book is the most accurate tracker of shipment used as data source for all the Regions and Countries; US shipment data not available in the Order Book were taken from the Order Management Dashboard and data for Hong Kong, Macau and Germany were provided by BioNTech.

[19] Including data from license partners.

Table 1. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	41.8	**323502270**	**268506884**
European Union[a] (27)	33.3	257628345	213831526
Additional EEA Countries[a] (3)	0.5	3559335	2954248
Other Countries[b]	8.0	62314590	51721110
North America[c]	29.8	**230593605**	**191392692**
US	26.6	205645305	170685603
Canada	3.2	24948300	20707089
Central and South America[d]	7.4	**57644730**	**47845126**
Asia	19.5	**150739485**	**125113773**
Japan[a]	12.2	94169790	78160926
Other Countries[e]	7.3	56569695	46952847
Oceania	0.7	**5681520**	**4715662**
Australia/New Zealand[a]	0.7	5681520	4715662
Other Countries	0.0	0	0
Africa[f]	0.8	**6316830**	**5242969**
Total	**100.0**	**774478440**	**642817105**

a. Conditional approval.
b. Includes:
- UK, with both authorisation for emergency supply under regulation 174 and the conditional marketing authorisation approval,
- Albania, Kosovo, North Macedonia and Switzerland with conditional approval,
- Georgia, Serbia and Ukraine with authorization for emergency supply,
- Azerbaijan, Bosnia and Moldova where BNT162b2 was shipped for COVAX,
- Turkey where it was shipped according to a pharmacovigilance agreement in place by the MAH and the Turkish government.

c. Authorization for emergency supply.
d. Includes:
- Brazil and Peru with conditional approval,
- Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Panama and Uruguay with authorisation for emergency supply,
- Bolivia where BNT162b2 was shipped for COVAX;

e. Includes:
- Hong Kong, Malaysia and South Korea with conditional approval,
- Bahrain, Iraq, Israel, Jordan, Kuwait, Lebanon, Macau, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Singapore, Sri Lanka and United Arab Emirates with authorization for emergency supply,
- Bangladesh, Bhutan, Laos, Maldives, Mongolia, Philippines and West Bank & Gaza where BNT162b2 was shipped for COVAX;

f. Includes:
- Rwanda, Tunisia and South Africa where BNT162b2 received authorisation for emergency supply,
- Angola, Botswana, Cape Verde, Chad, Ivory Coast, Libya and Togo where BNT162b2 was shipped for COVAX.

Out of the cumulative estimated shipped and administered doses, 213,475,665 and 177,184,802 respectively, were shipped to Rest Of World (Non-EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa).

Table 2. Interval Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	41.6	**318930495**	**264712311**
European Union[a] (27)	33.6	257628345	213831526
Additional EEA Countries[a] (3)	0.5	3559335	2954248
Other Countries[b]	7.5	57742815	47926536
North America[c]	29.7	**227476530**	**188805520**
US	26.5	202771005	168299934
Canada	3.2	24705525	20505586
Central and South America[d]	7.5	**57644730**	**47845126**
Asia	19.6	**149930235**	**124442095**
Japan[a]	12.3	94169790	78160926
Other Countries[e]	7.3	55760445	46281169
Oceania	0.7	**5681520**	**4715662**
Australia/New Zealand[a]	0.7	5681520	4715662
Other Countries	0.0	0	0
Africa[f]	0.8	**6316830**	**5242969**
Total	**100.0**	**765980340**	**635763682**

a. Conditional approval.
b. Includes:
- UK, with both authorisation for emergency supply under regulation 174 and the conditional marketing authorisation approval,
- Albania, Kosovo, North Macedonia and Switzerland with conditional approval,
- Georgia, Serbia and Ukraine with authorization for emergency supply,
- Azerbaijan, Bosnia and Moldova where BNT162b2 was shipped for COVAX,
- Turkey where it was shipped according to a pharmacovigilance agreement in place by the MAH and the Turkish government.

c. Authorization for emergency supply.
d. Includes:
- Brazil and Peru with conditional approval,
- Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Panama and Uruguay with authorisation for emergency supply,
- Bolivia where BNT162b2 was shipped for COVAX.

e. Includes:
- Hong Kong, Malaysia and South Korea with conditional approval,
- Bahrain, Iraq, Israel, Jordan, Kuwait, Lebanon, Macau, Oman, Palestine, Pakistan, Qatar, Saudi Arabia, Singapore, Sri Lanka and United Arab Emirates with authorization for emergency supply,
- Bangladesh, Bhutan, Laos, Maldives, Mongolia, Philippines and West Bank & Gaza where BNT162b2 was shipped for COVAX;

f. Includes:
- Rwanda, Tunisia and South Africa where BNT162b2 received authorisation for emergency supply,
- Angola, Botswana, Cape Verde, Chad, Ivory Coast, Libya and Togo where BNT162b2 was shipped for COVAX.

During the reporting interval, out of the estimated shipped and administered doses, 207,851,865 and 172,517,048 respectively, were shipped to Rest Of World.

With regard to the EEA published data (number of administered doses, number of doses administered as 1st dose and 2nd dose by country)[16], the cumulative and interval pictures are overlapping considering the first available data are starting from the 53rd week of the year. Table 3 displays the available data with regard to number of doses administered as first or second dose.

Table 3. EEA - Cumulative and Interval Number of Administered Doses by Age Group and Dose 1 and Dose 2

	<18 years		18-24 years		25-49 years		50-59 years		60-69 years		70-79 years		≥80 years		All[b]	
Countries	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
Austria			167555	47702	971199	342616	641838	314720	546224	395763	393795	343964	355207	333226	3135921	1785206
Belgium			166728	64131	1408198	429906	849729	432004	840119	736020	536927	523117	379786	368636	4193346	2557731
Bulgaria	266	189	15278	11513	159468	133713	99168	85240	121185	102251	92622	76077	28906	23204	517254	432452
Croatia	2280	255	42259	8569	317338	102782	198754	84438	222771	128620	135422	96913	60943	47868	977487	469190
Cyprus			17984	10944	116794	78519	47914	42806	38710	34614	23140	18821	25185	23655	269737	209366
Czechia	16771	521	124179	27930	1465870	351932	727173	335423	730020	551387	545166	488903	247876	233858	3843810	1990215
Denmark			160444	22357	447539	156710	629283	113376	555667	406034	518812	509466	238233	235276	2550785	1443219
Estonia	2738	217	19446	4813	121570	46108	56404	41242	51754	43140	56113	51820	41253	38412	346867	225631
Finland			61362	8770	831073	85286	481133	71374	348956	69582	449416	240046	256030	236973	2427970	712031
France															24326612	12868715
Germany															28250232	20472529
Greece			26492	14949	771439	360626	699135	528149	476183	383765	599397	555891	501387	479715	3090855	2331578
Hungary	140853	80059	163126	76516	867158	595910	310562	251589	370538	333408	307408	291502	203466	195665	2360581	1828050
Iceland			12113	3307	50143	27544	16532	14965	14290	13542	9173	8743	12410	12334	114697	80434
Ireland			41574	22891	529757	182446	341416	243352	78469	60161	306069	278298	169889	158073	1472938	948542
Italy	236199	4016	911472	228860	5613161	1811641	4626670	1727223	3069219	2100315	2426244	2010958	3490947	3320810	20902474	11212843
Latvia			22531	15621	114418	96539	40493	33501	31994	25690	14130	11102	6068	4803	263132	204368
Liechtenstein															5483	3831
Lithuania	13981	707	56909	26792	255693	171088	141155	120218	152207	139020	99695	94176	57027	48916	764295	600966
Luxembourg			1520	1239	73003	18864	50700	48169	31139	30120	13128	12717	18550	18135	194297	134808
Malta			18843	12790	89993	78043	21670	21705	18653	19610	36278	37112	21583	19858	207544	193777
Netherlands															6213306	3484049
Norway															1306486	937807
Poland			608505	197615	3690822	1951594	1702115	1220780	1931938	1542381	1966597	1836281	961394	915070	11251269	7683325
Portugal	2201	765	33504	25324	693279	315197	749493	298839	598816	511126	477845	445734	575661	552248	3128600	2148468
Romania	26558	23235	266386	219774	1309771	1219816	644430	609328	750019	718764	444435	426774	146176	138833	3589468	3355093
Slovakia			75234	28771	457959	250535	169916	127800	249662	220386	231902	219288	82806	77104	1267479	923884
Slovenia	5059	726	17768	5571	114339	59404	94655	72449	106076	92438	99017	91676	67672	61190	499527	382728
Spain	4641	2745	105814	84748	3436349	868561	4278583	2549569	1051898	969309	3513927	3448266	2680133	2635045	15071210	10558191
Sweden			59666	35857	703182	238904	814215	267874	695462	577755	557804	527731	424263	403758	3254592	2051890
Grand Total	**451547**	**113435**	**3196692**	**1207354**	**24609515**	**9974284**	**18433136**	**9656133**	**13081969**	**10205201**	**13854462**	**12645376**	**11052851**	**10582665**	**145798254**	**92230917**

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6, cumulative period as of week 24, 2021).
b. Population may include also subjects of unknown age.

Table 4. Japan - Cumulative and Interval Number of Administered Doses by Health Workers and Elderly and Dose (1st and 2nd)

	Dose Number		
	1st Dose	**2nd Dose**	**Total**
Elderly	16308903	4834436	21143339
Medical workers	5463305	4320082	9783387
Total	**21772208**	**9154518**	**30926726**

Source: PMDA website https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html
(English site: https://japan.kantei.go.jp/ongoingtopics/vaccine.html)
Data split by Tradename and dose (1st and 2nd) is only available on the Japanese website, and not on the English website.
Data downloaded on 21 June 2021. Cumulative and interval period data are overlapping.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 24.0 has been used to code adverse events/reactions in summary tabulations.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in clinical trial cases received by the MAH. This appendix is organized according to MedDRA SOC.

6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 provides a cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. This tabulation includes serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources. The cumulative data include all data up to 18 June 2021 and the interval data are from 19 December 2020 to 18 June 2021. This appendix is organized according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non-interventional sources.

Please note that adverse event totals presented for safety topic evaluations in Section 16 *Signal and Risk Evaluation* may differ from Appendix 2.2 totals, due to the fact that Appendix 2.2 only displays the number of serious reactions from non-interventional studies and solicited sources as described above, whereas the safety topic evaluation includes all reported events. Cases from non-interventional studies and other non-interventional solicited sources must contain at least 1 serious related event to meet PSUR inclusion criteria and may also contain additional events that are considered unrelated, all of which would be evaluated.

6.3.1. General Overview – All Cases

A total of 327,827 case reports (702 from CT[20] and 327,125 from PM[21]) containing 1,172,887 events fulfilled criteria for inclusion in this PSUR. Refer to Appendix 2.1 and Appendix 2.2 for the summary tabulations of all cases received during the current reporting period. Selected characteristics of all cases received during the reporting interval are shown in Table 5 and Table 6.

Table 5. Selected Case Characteristics - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases	CT [a,b] No. of Cases	PM No. of Cases
No. of Cases		327,827	702	327,125
Gender	Female	233,948	329	233,619
	Male	75,340	371	74,969
	Unknown/No Data	18539	2	18,537
Age (years)	N	280,285	695	279,590
	Min-Max[c]	6 days – 121 years	12 – 87 years	6 days – 121 years
	Mean	50.3	55.4	50.3
	Median	49	58	49
Age group	≤ 17	2076	33[d]	2043[e]
	18-30	41,247	39	41,208
	31-50	107,416	182	107,234
	51-64	68,685	191	68,494
	65-74	26,991	175	26,816
	≥ 75	35,097	80	35,017
	Unknown	46,315	2[f]	46,313[g]
Country of occurrence (≥2% of all cases)	United States (US)	68,331	494	67,837
	United Kingdom (UK)	67,305	0	67,305
	Italy	45,791	0	45,791
	France	21,858	0	21,858
	Mexico	15,712	0	15,712
	Netherlands	14,840	0	14,840
	Spain	13,076	0	13,076
	Germany	11,796	20	11,776
	Japan	9766	2	9764
Case Seriousness	Serious	100,808	702	100,106
	Non-serious	227,019	0	227,019

[20] Clinical Trials cases include cases originated from 6 interventional trials (C4591001, C4591001-OPENLABEL, C4591005, C4591015, C4591017, C4591020) for which Pfizer acts as lead development party, from 3 BioNTech interventional trials (BNT162-01-OPENLABEL, BNT162-01 – RN9391R00 and BNT162-04) and from 2 Fosun (BioNTech License Partner) interventional trials (BNT162-03, BNT162-06) with BioNTech third party acting as lead development party.

[21] Post-Authorisation.

Table 5. Selected Case Characteristics - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases	CT [a,b] No. of Cases	PM No. of Cases
Case Outcome	Resolved/Resolving	172,162	540	171,622
	Resolved with sequelae	3319	41	3278
	Not resolved	76,960	72	76,888
	Fatal	5115	46	5069
	Unknown	70,271	3	70,268
Presence of comorbidities [h]	Yes	51,390	314	51,076
	No	276,437	388	276,049

a. BioNTech is the Sponsor of all Clinical Trials; for the following Clinical Trials (C4591001, C4591005, C4591015, C4591017, C4591020), Pfizer acts as lead development party and for the Clinical Trials (BNT162-03, BNT162-06), BioNTech Third Party act as lead development party.
b. Includes 12 cases from BioNTech and Fosun sponsored Interventional Studies.
c. Includes only patients to whom BNT162b2 or study therapy was administered directly; does not include exposure during pregnancy or via breastfeeding.
d. Includes 6 cases involving exposure during pregnancy.
e. Includes 30 cases with contradictory demographic information (physical characteristics not consistent with paediatric age), 9 cases which upon review were determined not to involve paediatric patients, 79 cases involving exposure during pregnancy, and 347 cases involving exposure via breastfeeding.
f. Includes 1 case involving exposure during pregnancy.
g. Includes 549 cases involving exposure during pregnancy and 324 cases involving exposure via breastfeeding.
h. Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, Frail patients with co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis) described as special populations in Section 16.3.5.5, Section 16.3.5.6 and Section 16.3.5.7, respectively.

Table 6. Case Summary: All Cases Received during the Reporting Interval

Clinical Trial Data	**Total number of cases:** 702 **Total number of SAEs:** 883 **Number of SAEs assessed as related to BNT162:** BNT162b2 (7), BNT162b1 (2) **SAEs assessed as related to BNT162:** Acute myeloid leukaemia[a], Anaphylactoid reaction[c], Cystitis[d], Hyperthyroidism[a], Myalgia[a], Myocardial infarction[a], Polymyalgia rheumatica[a], Portal vein thrombosis[a], Thyroid mass[a] (1 each). **Most frequently reported (≥2%) medical history (HLGT):** Vascular hypertensive disorders (254), Lipid metabolism disorders (184), Glucose metabolism disorders (incl diabetes mellitus) (122), Gastrointestinal motility and defaecation conditions (117), Depressed mood disorders and disturbances (103), Joint disorders (100), Appetite and general nutritional disorders (94), Anxiety disorders and symptoms (81), Allergic conditions (78), Bronchial disorders (excl neoplasms) (69), Coronary artery disorders, Thyroid gland disorders (66 each), Lifestyle issues (63), Sleep disorders and disturbances (54), Cardiac arrhythmias (52), Gastrointestinal therapeutic procedures (50), Respiratory disorders NEC (47), Bone and joint therapeutic procedures, Musculoskeletal and connective tissue disorders NEC (46 each), Prostatic disorders (excl infections and inflammations) (45), Headaches (44), Age related factors (42), Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders), Peripheral neuropathies, Infections – pathogen unspecified (39 each), Obstetric and gynaecological therapeutic procedures (37), Therapeutic procedures and supportive care NEC, Vascular therapeutic

Table 6. Case Summary: All Cases Received during the Reporting Interval

	procedures (36 each), General system disorders NEC (29), Purine and pyrimidine metabolism disorders (28), Viral infectious disorders (27), Bone disorders (excl congenital and fractures), Central nervous system vascular disorders (26 each), Bone and joint injuries, Gallbladder disorders (24 each), Cognitive and attention disorders and disturbances, Hepatobiliary therapeutic procedures, Injuries NEC, Renal disorders (excl nephropathies) (22 each), Upper respiratory tract disorders (excl infections) (21), Nervous system, skull and spine therapeutic procedures, Neurological disorders NEC, Psychiatric disorders NEC (20 each), Abdominal hernias and other abdominal wall conditions, Cardiac therapeutic procedures, Vitamin related disorders (19 each), Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Gastrointestinal signs and symptoms, Head and neck therapeutic procedures, Vision disorders (17 each), Male genital tract therapeutic procedures (16), Anaemias nonhaemolytic and marrow depression, Hepatic and hepatobiliary disorders, Reproductive neoplasms male malignant and unspecified, Sexual function and fertility disorders, Skin appendage conditions (15 each). **Most frequently reported (≥2) co-suspect medications:** Insulin detemir (2).
Post-marketing Sources	**Total number of cases:** 327,125 **Medically confirmed:** MC (182,620), NMC (144,505) **Total number of events:** 1,172,004 **Event seriousness[b]:** serious (321,919), non-serious (850,284) **Most frequently reported (≥2%) medical history (HLGT):** Allergic conditions (24,580), Viral infectious disorders (22,192), Vascular hypertensive disorders (19,822), Lifestyle issues (15,668), Bronchial disorders (excl neoplasms) (13,177), Breast disorders (11,473), Glucose metabolism disorders (incl diabetes mellitus) (10,270), Thyroid gland disorders (8485), Joint disorders (7663). **Most frequently reported (≥20) co-suspect medications:** COVID-19 Moderna (mRNA 1273) vaccine (209), COVID-19 AstraZeneca vaccine (151), paracetamol (124), apixaban (120), ibuprofen (103), tofacitinib (97), adalimumab (78), acetylsalicylic acid (44), lenvatinib (35), etanercept, prednisone (34 each), palbociclib (33), treprostinil (32), diphenhydramine, methylprednisolone (31 each), acetylsalicylate lysine, clopidogrel, levothyroxine, rivaroxaban (29 each), methotrexate, sodium chloride (28 each), warfarin (26), amoxicillin (21), pregabalin, atorvastatin, macrogol (20 each).

a. Assessed as related by the Investigator and unrelated by the Sponsor.
b. In some cases, events could be reported as serious and non-serious occurrences.
c. Assessed as related by both the Investigator and the Sponsor.
d. Assessed as unrelated by the Investigator and related by the Sponsor.

6.3.1.1. Clinical Trials Data

Case outcomes by age group, gender and presence of comorbidities in clinical trial cases are presented in Figure 1, Figure 2 and Figure 3. Across all age groups, there were slightly more male than female patients reporting adverse events. Overall, the proportion of cases with a fatal outcome is higher when comorbidities[22] are reported (Figure 1). Equal numbers of male

[22] Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, Frail patients with co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis) described as special populations in Section 16.3.5.5, Section 16.3.5.6 and Section 16.3.5.7, respectively.

and female patients experienced a fatal outcome in the presence of comorbidities (Figure 2-A), while more male than female patients experienced a fatal outcome in the absence of comorbidities (Figure 2-B). In the presence of comorbidities, the highest number of fatal outcomes occurred in the 51-64 year age group (Figure 2 C); in the absence of comorbidities, the highest number of fatal outcomes occurred in the 31-50 year age group (Figure 2-D and Figure 3). Please also see Section 16.3.4.1 *Death* and Section 16.3.5.5, Section 16.3.5.6 and Section 16.3.5.7.

Figure 1. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities

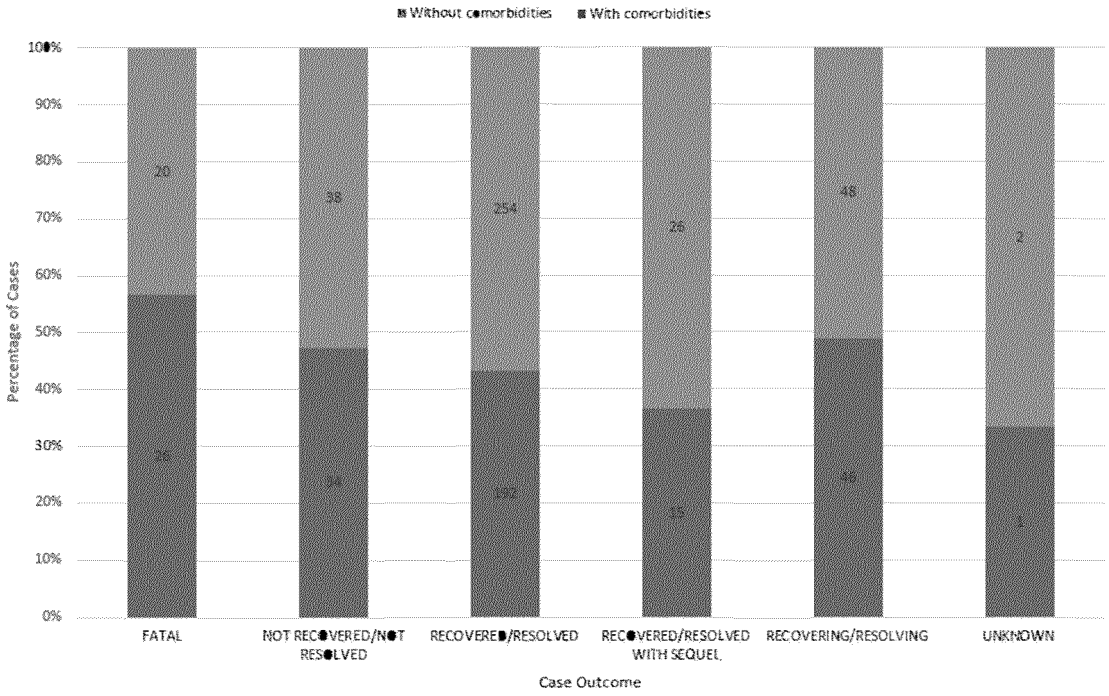
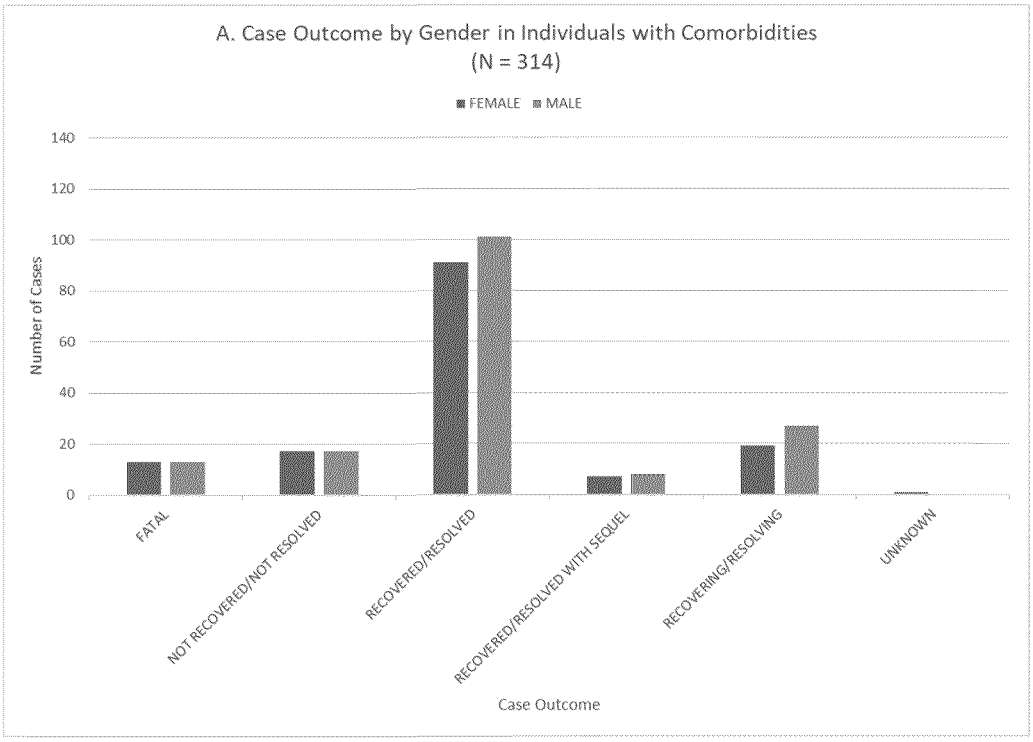
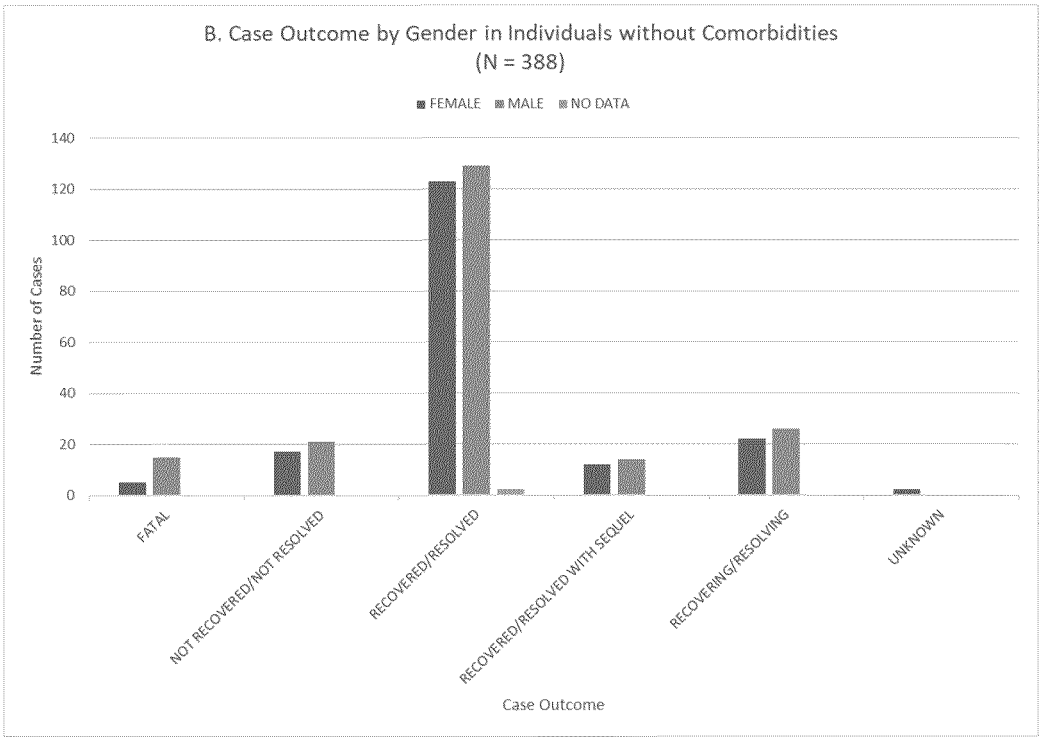
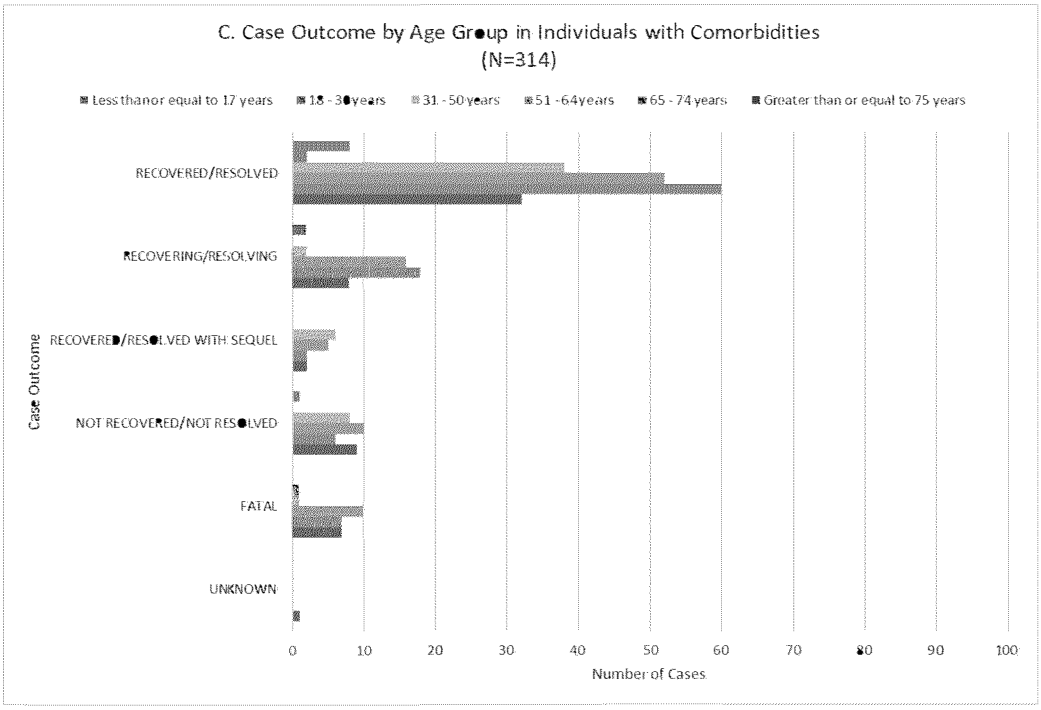


Figure 2. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities, Gender and Age Group







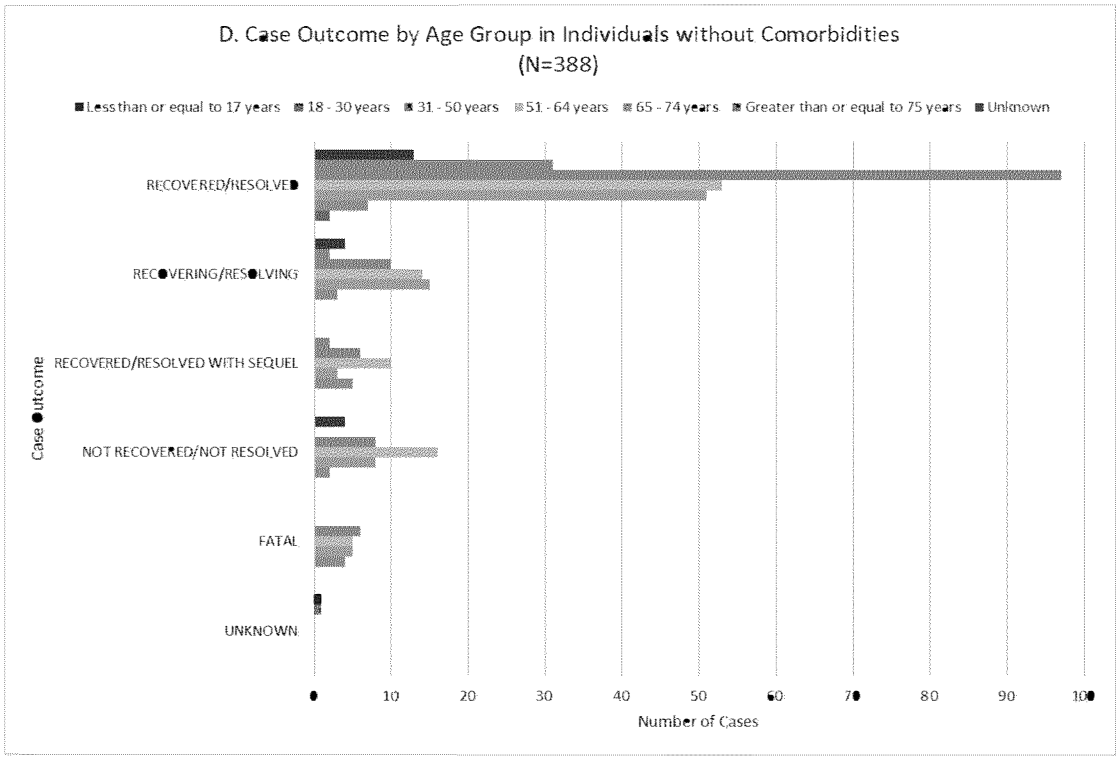
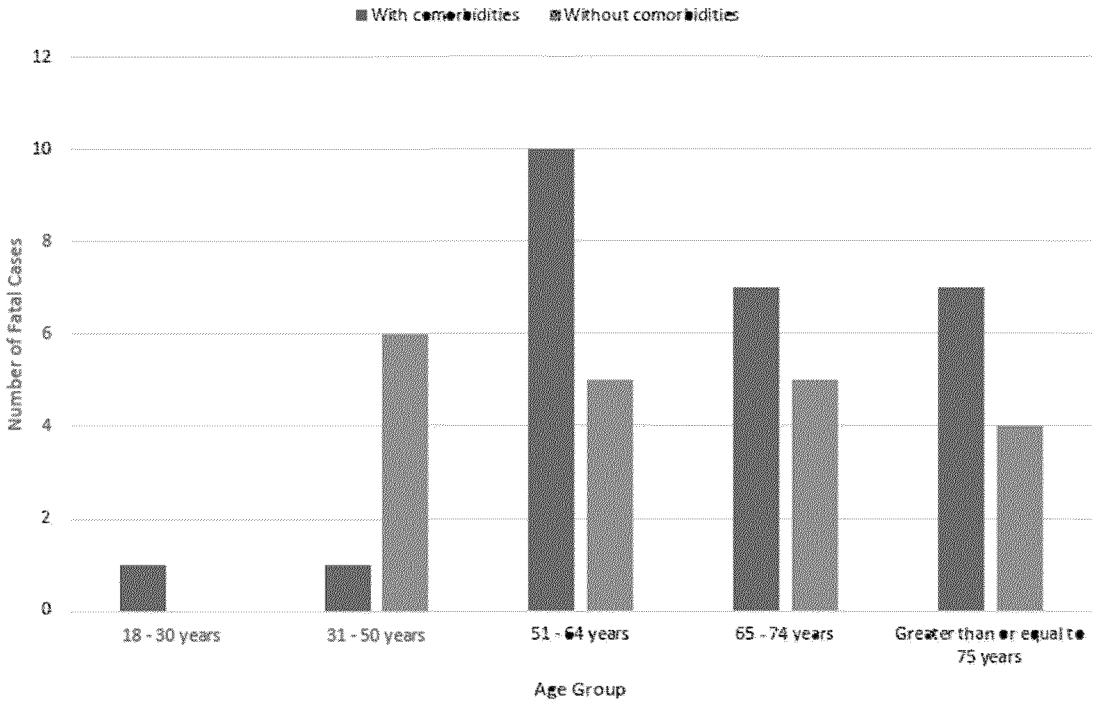
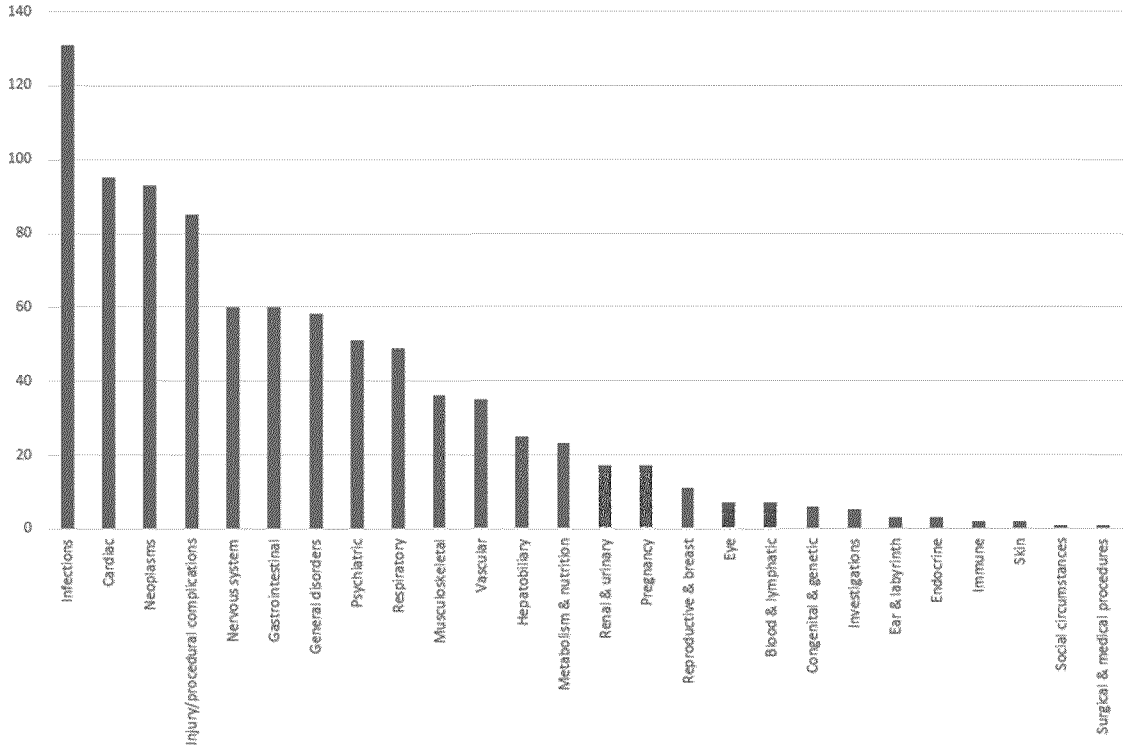


Figure 3. Clinical Trial Data: Fatal Case Outcome by Presence/Absence of Comorbidities and Age Group



As shown in Figure 4, the MedDRA SOCs containing the greatest number of reported events (≥2%) from clinical trial data were Infections and infestations (131); Cardiac disorders (95); Neoplasms benign, malignant and unspecified (incl cysts and polyps) (93); Injury, poisoning and procedural complications (85); Gastrointestinal disorders; Nervous system disorders (60 each); General disorders and administration site conditions (58); Psychiatric disorders (51); Respiratory, thoracic and mediastinal disorders (49); Musculoskeletal and connective tissue disorders (36); Vascular disorders (35); Hepatobiliary disorders (25); Metabolism and nutrition disorders (23); Pregnancy, puerperium and perinatal conditions; and Renal and urinary disorders (17 each). Of note, multiple adverse events may be reported in a single case.

Figure 4. Clinical Trial Data: Total Number of SAEs by MedDRA SOC



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 June 2021.

Table 7. Clinical Trial Data: Events Reported in ≥2%* Cases

	Reporting Period 19 Dec 2020 - 18 Jun 2021	**Cumulatively through 18 Jun 2021**
MedDRA SOC MedDRA PT	**AEs (AERP%)** **N = 702**	**AEs (AERP%)** **N = 1048**
Cardiac disorders		
Acute myocardial infarction	15 (2.14%)	20 (1.91%)
Atrial fibrillation	15 (2.14%)	25 (2.39%)
General disorders and administration site conditions		
Condition aggravated	29 (4.13 %)	36 (3.44%)
Infections and infestations		
Appendicitis	19 (2.71%)	32 (3.05%)
Pneumonia	15 (2.14%)	24 (2.29%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	13 (1.85%)	21 (2.00%)
Total number of events	**883**	**1306**

***** Reporting proportion (% of total CT cases) in the current reporting period or cumulatively.

The frequently reported events are not listed or consistent with listed events as per the current Investigator's Brochure. However, it should be noted that none of these events were considered to be related to BNT162 by either the Investigator or Sponsor (see Table 6).

During the reporting interval, the distribution of the events reported in ≥2% of cases by gender is presented in Figure 5. More of these events were reported in male than in female subjects. The distribution of the AEs reported in more than 2% of the cases by age group and SOC is shown in Figure 6, and the distribution by age group within gender is shown in Figure 7. Although there is no clear association between the numbers of events and age groups, overall the highest numbers of events were reported in older patients (51 years and older), with the exception of appendicitis and "condition aggravated," which were reported more frequently in younger patients (50 years and younger).

Figure 5. Clinical Trial Data: SAEs Reported in ≥2% of Cases by Gender

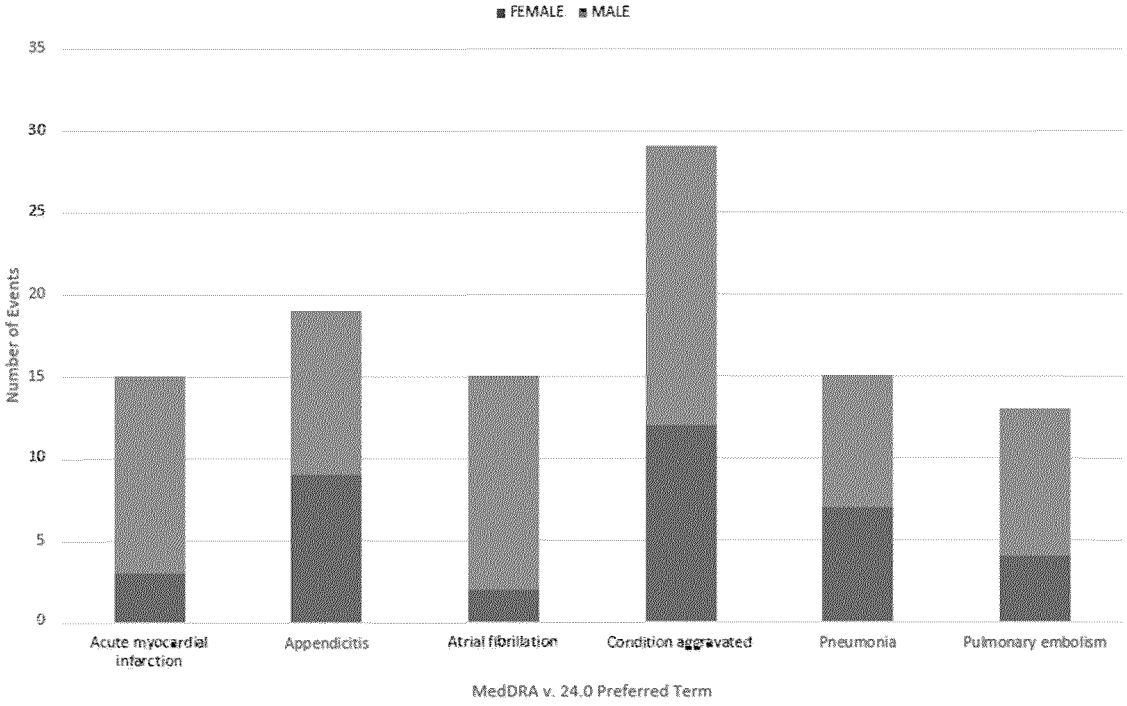
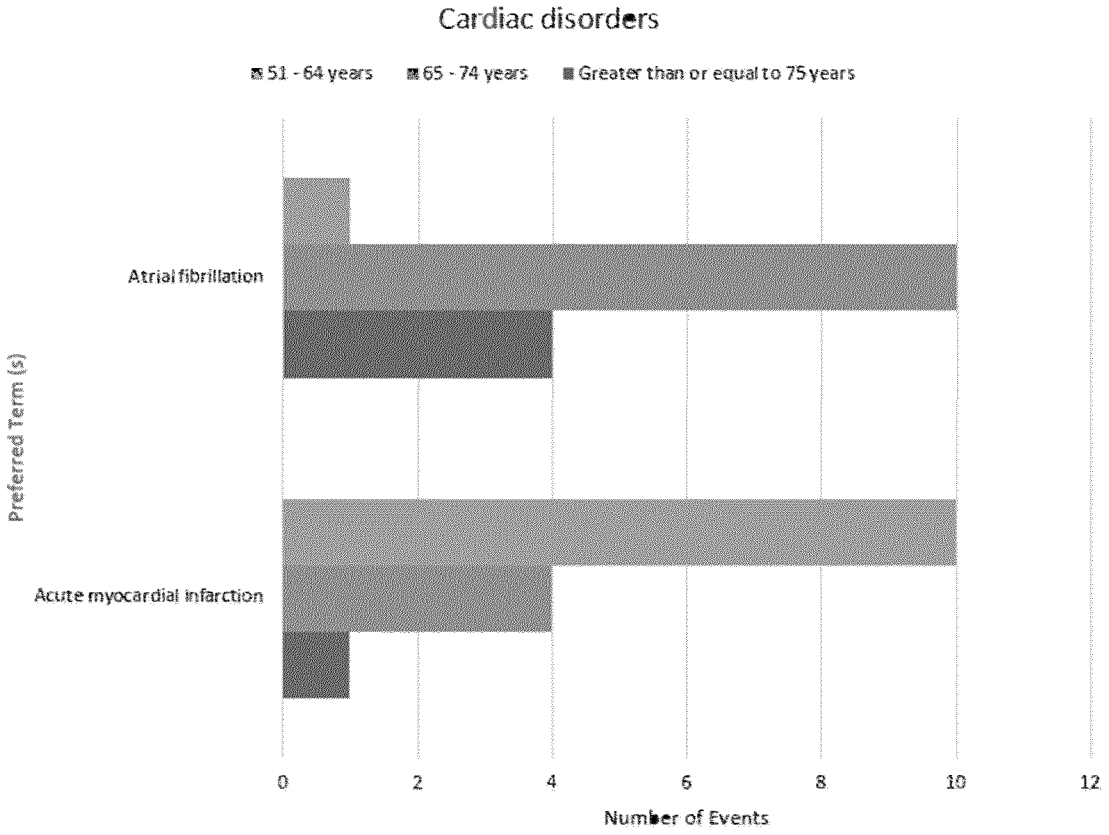
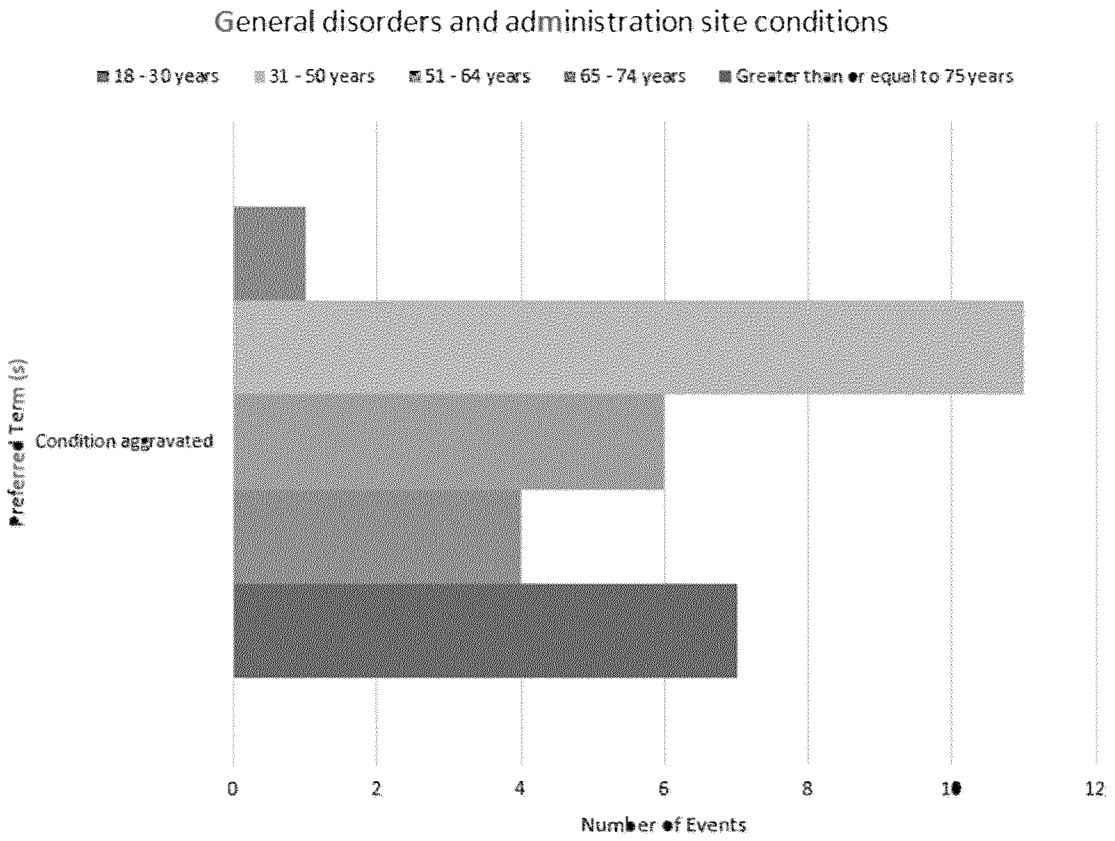
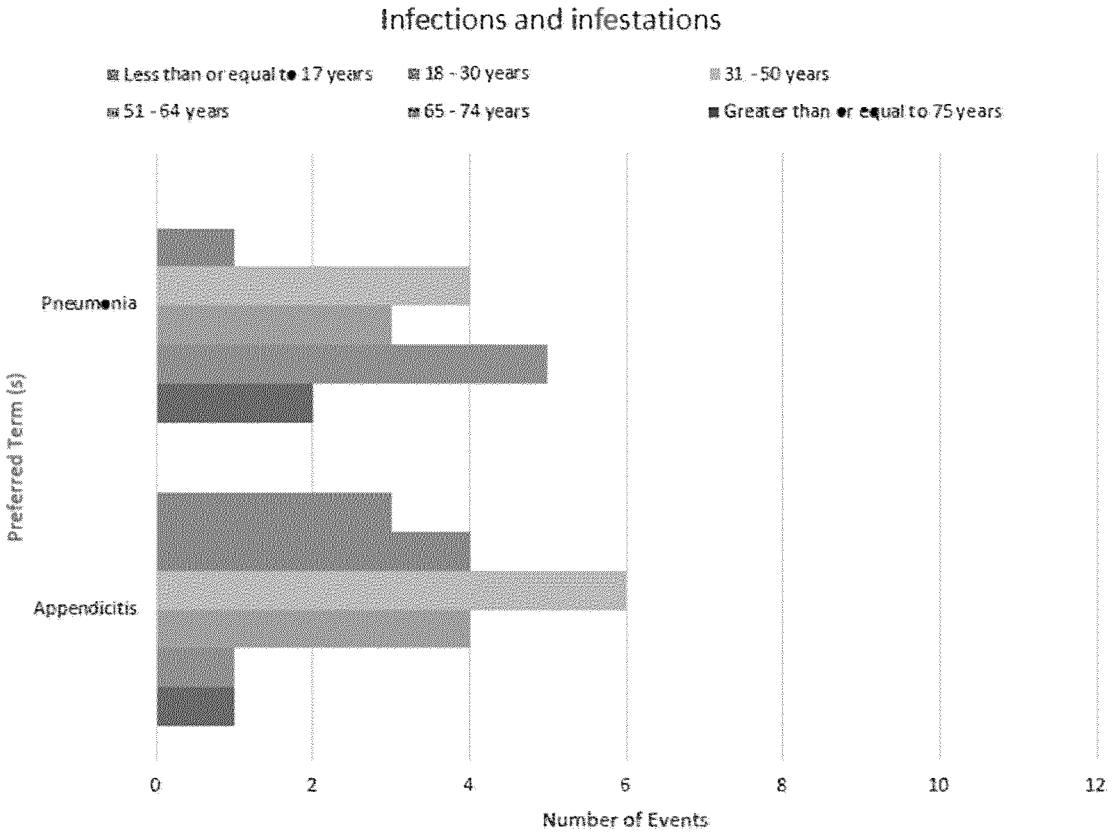


Figure 6. Clinical Trial Data: SAEs Reported in ≥2% of Cases by SOC and Age Group







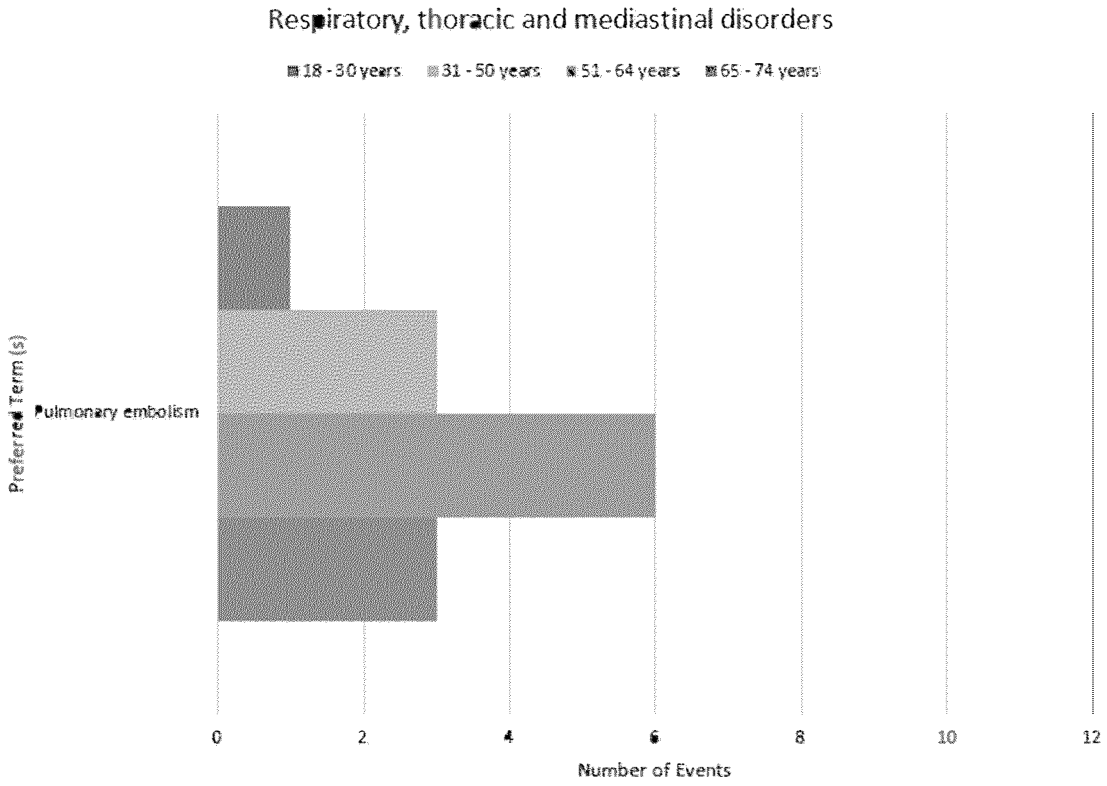
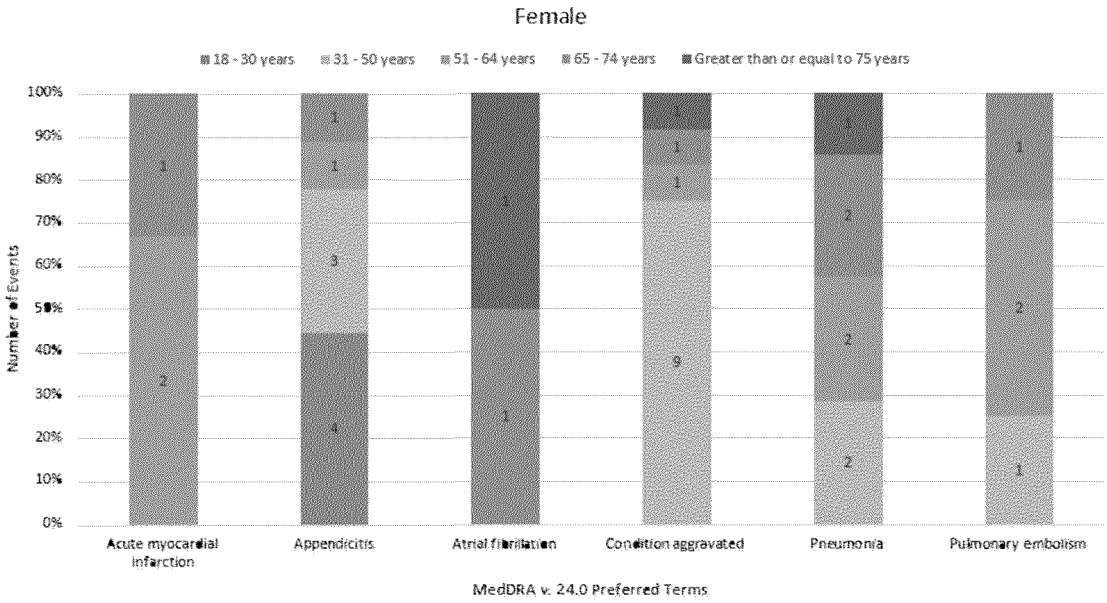
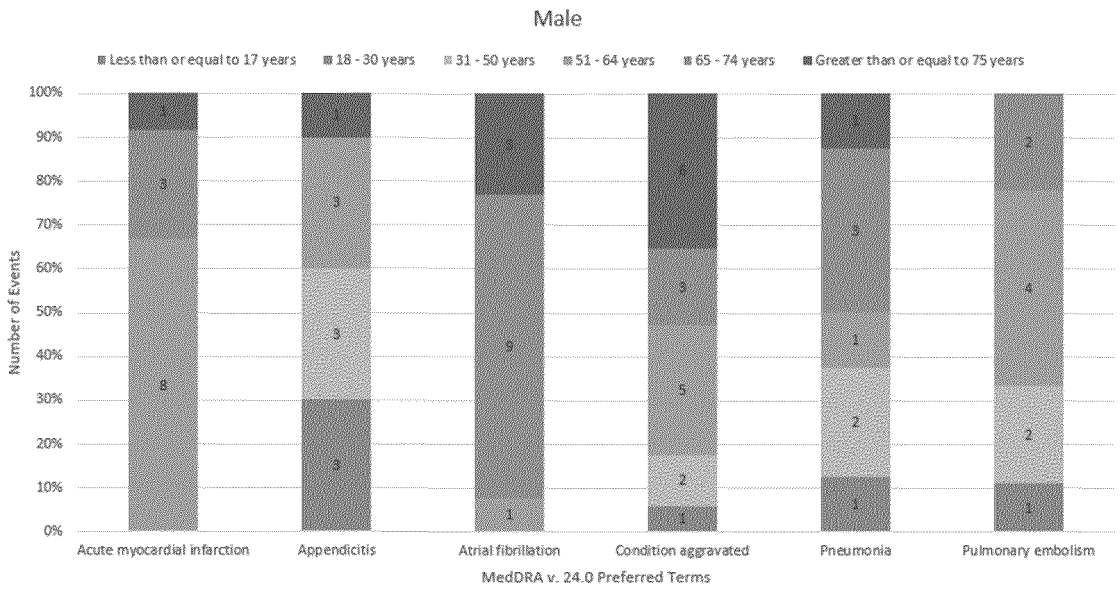


Figure 7. Clinical Trial Data: Events Reported in ≥2% of Cases by Age Group within Gender





6.3.1.2. Post-Authorization Data

Case outcomes by age group, gender and presence of comorbidities in post-marketing cases are presented in Figure 8, Figure 9 and Figure 10. Across all age groups, there were many more female than male patients reporting adverse events. Overall, the proportion of cases with a fatal outcome is slightly higher when comorbidities[22] are reported (Figure 8). Among the cases with a fatal outcome, there is a similar pattern for gender both in the presence and in the absence of comorbidities (Figure 9-A and Figure 9-B). The age group with the highest number of cases with fatal outcomes are individuals aged 75 years and older, either in the presence or absence of comorbidities (Figure 9-C, Figure 9-D and Figure 10). Please also see Section 16.3.4.1 *Death* and Section 16.3.5.7 *Use in Frail Patients with Co-Morbidities e.g., COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, Active Tuberculosis*).

Figure 8. Post-Authorization Data: Case Outcome by Presence/Absence of Comorbidities

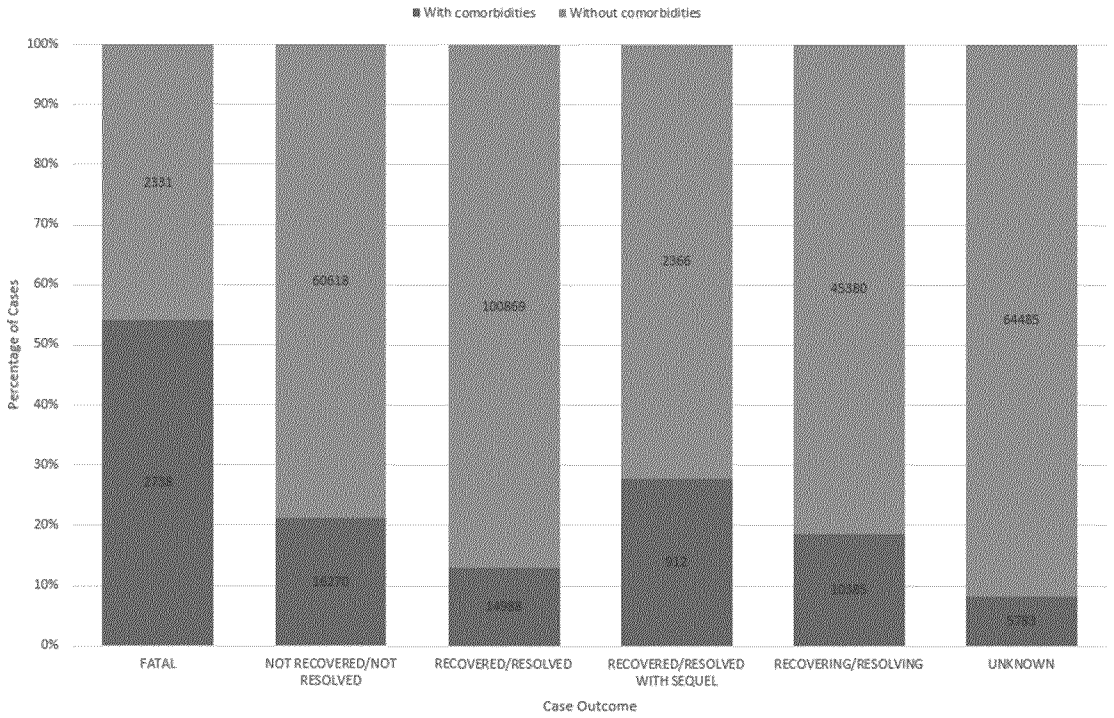
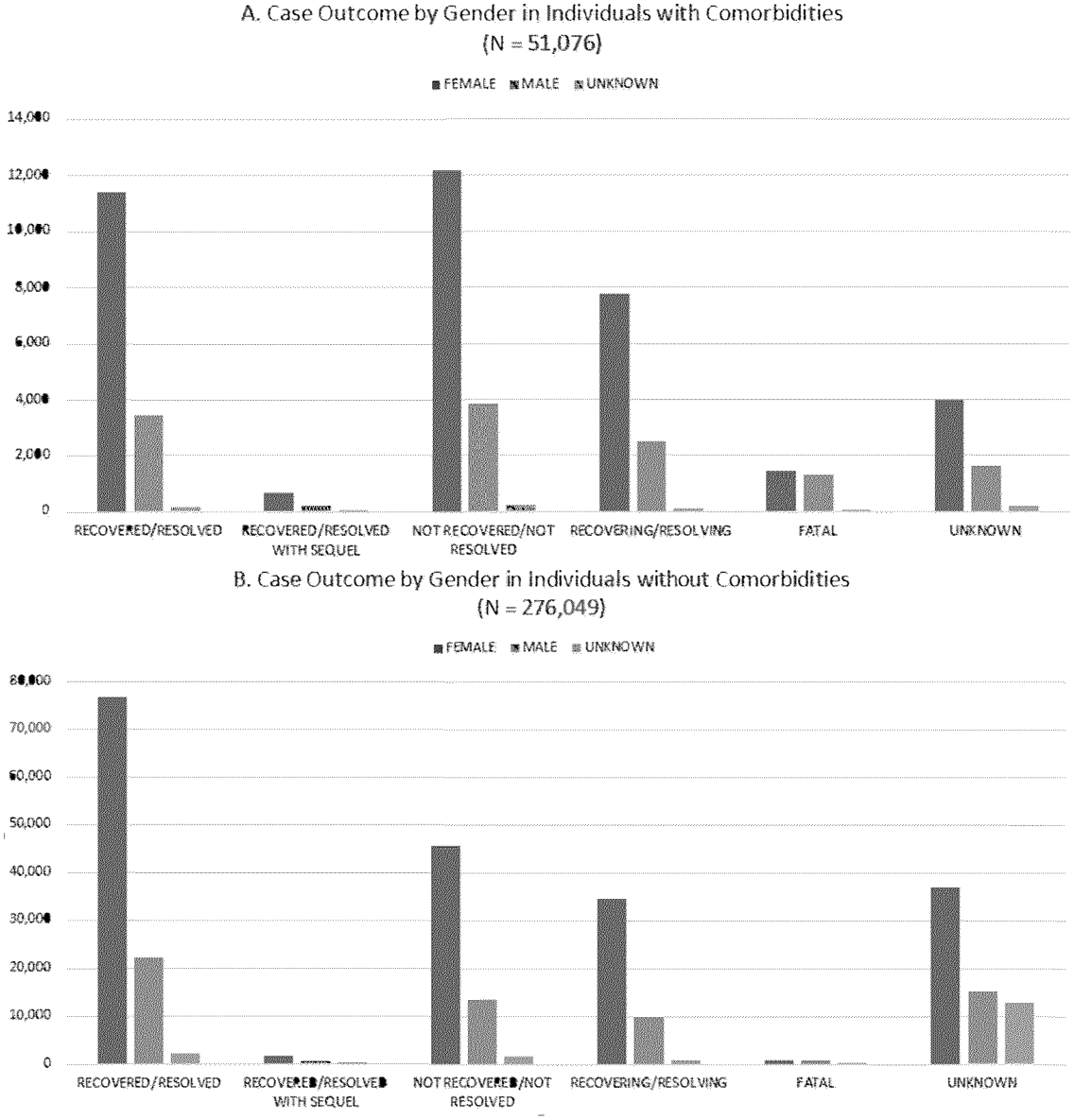
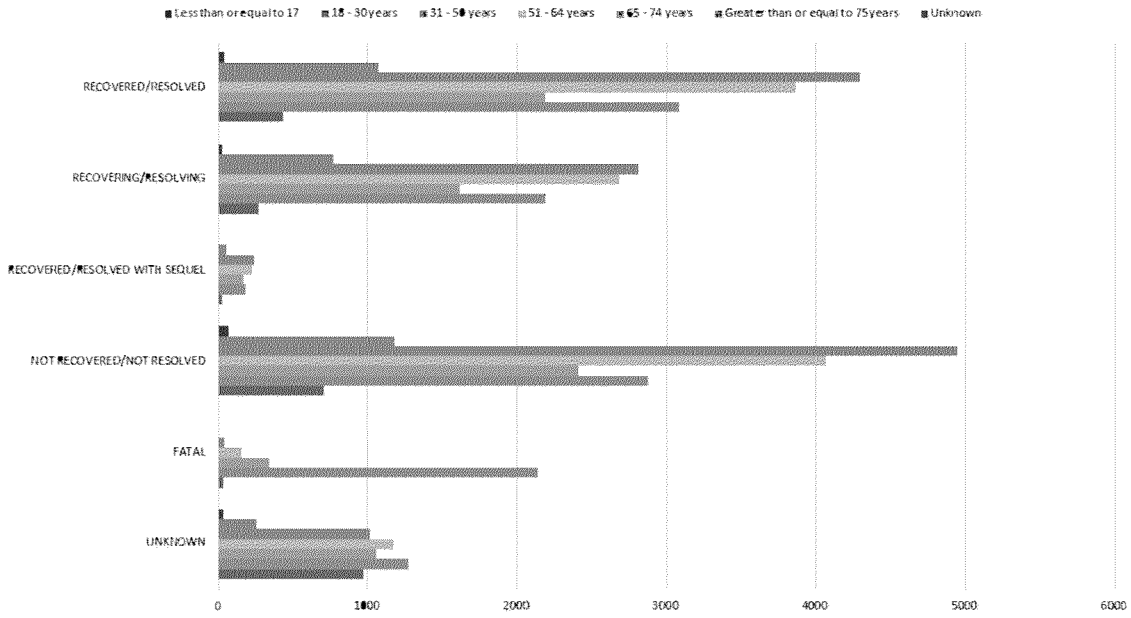


Figure 9. Post-Authorization Data: Case Outcome by Presence/Absence of Comorbidities, Gender and Age Group



C. Case Outcome by Age Group in Individuals with Comorbidities
(N = 51,076)



D. Case Outcomes in Individuals without Comorbidities
(N = 276,049)

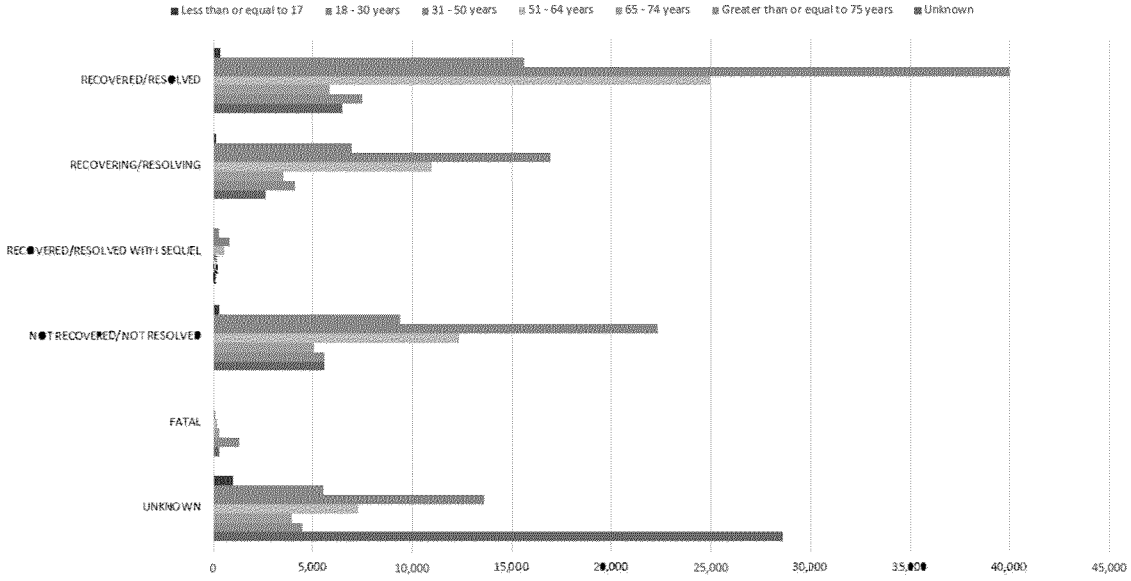
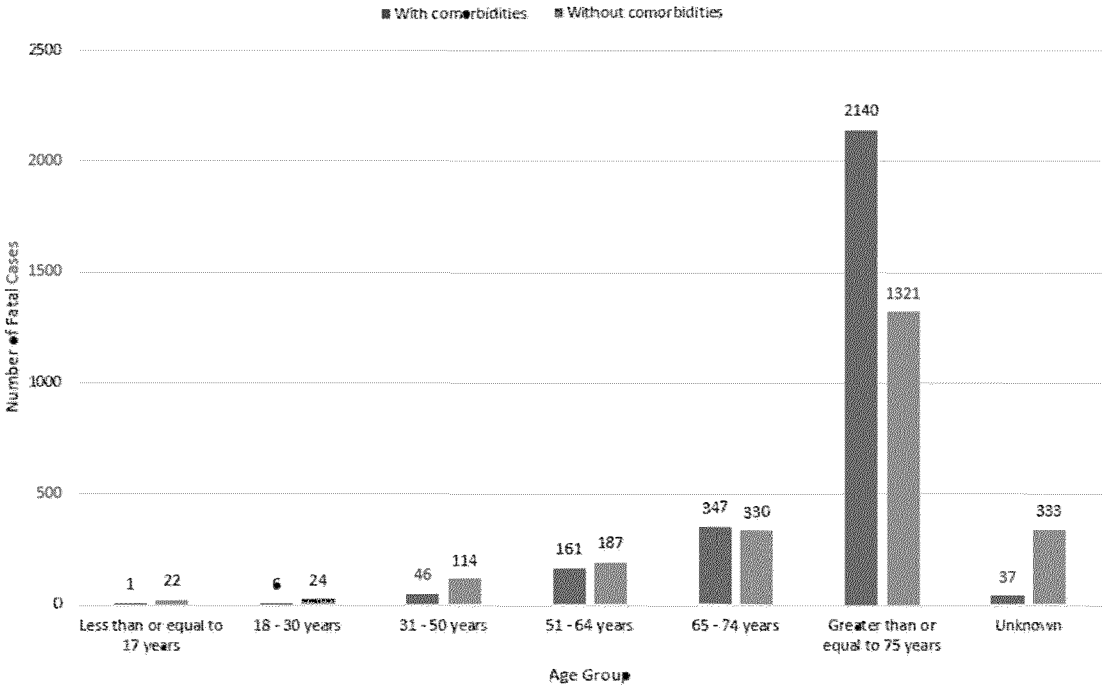
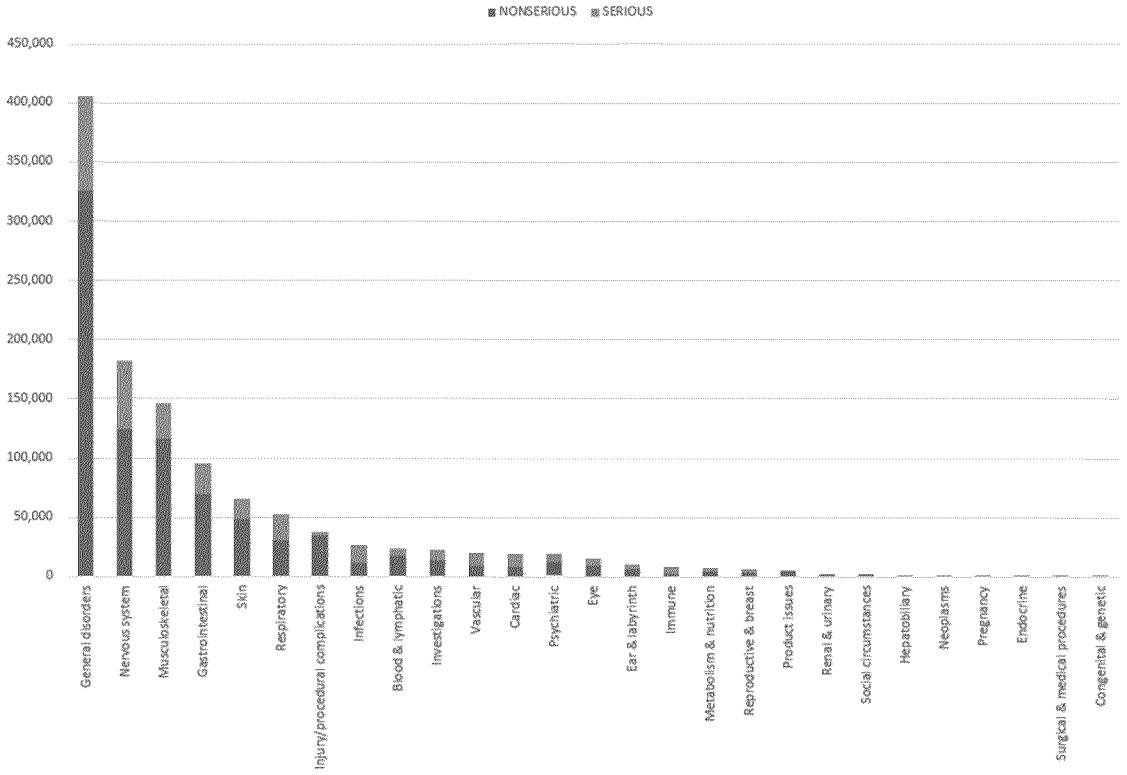


Figure 10. Post-Authorization Data: Fatal Case Outcome by Presence/Absence of Comorbidities and Age Group



As shown in Figure 11, the MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (405,301); Nervous system disorders (181,899); Musculoskeletal and connective tissue disorders (146,042); Gastrointestinal disorders (94,762; Skin and subcutaneous tissue disorders (65,167); Respiratory, thoracic and mediastinal disorders (52,493); Injury, poisoning and procedural complications (37,587); Infections and infestations (26,765); Blood and lymphatic system disorders (23,448); Investigations (22,448); Vascular disorders (19,979); Cardiac disorders (19,219); Psychiatric disorders (18,193); Eye disorders (14,890); Ear and labyrinth disorders (10,753); Immune system disorders (8531); and Metabolism and nutrition disorders (6884). Of note, multiple adverse events may be reported in a single case.

Figure 11. Post-Authorization Data: Total Number of Events by MedDRA SOC and Event Seriousness



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 reporting interval as compared to the cumulative period through 18 June 2021.

Table 8. Post-Authorization Data: Events Reported in ≥2%* Cases

	Reporting Period 19 Dec 2020 - 18 Jun 2021	Cumulatively through 18 Jun 2021
MedDRA SOC **MedDRA PT**	**AEs (AERP%)** **N = 327,125**	**AEs (AERP%)** **N = 327,603**
Blood and lymphatic system disorders		
Lymphadenopathy[a]	18,545 (5.67%)	18,553 (5.66%)
Gastrointestinal disorders		
Nausea[a]	37,730 (11.53%)	37,768 (11.53%)
Diarrhoea[a]	13,182 (4.03%)	13,194 (4.03%)
Vomiting[a]	11,416 (3.49 %)	11,423 (3.49%)
General disorders and administration site conditions		
Pyrexia[a]	64,242 (19.64%)	64,284 (19.62%)
Fatigue[a]	54,683 (16.72%)	54,724 (16.70%)
Chills[a]	41,227 (12.60%)	41,256 (12.59%)
Vaccination site pain[a]	36,986 (11.31%)	37,046 (11.31%)
Paina	25,715 (7.86%)	25,748 (7.86%)
Malaise[a]	27,788 (8.49%)	27,805 (8.49%)

Table 8. Post-Authorization Data: Events Reported in ≥2%* Cases

	Reporting Period 19 Dec 2020 - 18 Jun 2021	Cumulatively through 18 Jun 2021
MedDRA SOC **MedDRA PT**	**AEs (AERP%)** **N = 327,125**	**AEs (AERP%)** **N = 327,603**
Asthenia[a]	24,391 (7.46%)	24,404 (7.45%)
Injection site pain[a]	10,105 (3.09%)	10,105 (3.08%)
Influenza like illness	8603 (2.63%)	8608 (2.63%)
Infections and infestations		
COVID-19[b]	8154 (2.49%)	8157 (2.49%)
Musculoskeletal and connective tissue disorders		
Myalgia[a]	49,382 (15.10%)	49,402 (15.08%)
Arthralgia[a]	35,410 (10.82%)	35,426 (10.81%)
Pain in extremity[a]	28,312 (8.65%)	28,346 (8.65%)
Nervous system disorders		
Headache[a]	83,686 (25.58%)	83,758 (25.57%)
Dizziness[a]	23,935 (7.32%)	23,978 (7.32%)
Paraesthesia[a]	9532 (2.91%)	9543 (2.91%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea[c]	11,042 (3.38%)	11,058 (3.38%)
Cough[c]	7701 (2.35%)	7707 (2.35%)
Skin and subcutaneous tissue disorders		
Pruritus[a]	11,302 (3.45%)	11,318 (3.45%)
Rash[a]	10,665 (3.26%)	10,686 (3.26%)
Erythema[a]	7888 (2.41%)	7900 (2.41%)
Sensitive skin	7434 (2.27%)	7434 (2.27%)
Total number of events	**1,172,004**	**1,173,395**

a. Listed or consistent with listed AEs in current RSI.
b. Listed per case processing conventions, except for fatal cases; for summary of relevant cases of COVID-19 see Section 16.3.3.1.3 *COVID-19 AESIs*.
c. Consistent with anaphylactic reactions listed in the current RSI.
* Reporting proportion (% of all post-authorization cases) in the current reporting period.

Most of the frequently reported events are listed or consistent with listed events as per the current RSI.

During the reporting interval, the distribution of the events reported in more than 2% of the cases by gender is presented in Figure 12. The observed imbalance in the female gender distribution reflects the imbalance in the gender distribution of the cases received in the reporting period.

The distribution of the AEs reported in more than 2% of the cases by age group and by SOC is shown in Figure 13, and the distribution by age group within gender is shown in Figure 14. Across the SOCs, the largest number of events is reported overall in the 31-50 years age group, except for the PT COVID-19 in the SOC Infection and infestations, for which the number of occurrences in the 75 years and older age group was slightly higher (when the age was known).

Figure 12. Post-Authorization Data: Events Reported in ≥2% of Cases by Gender

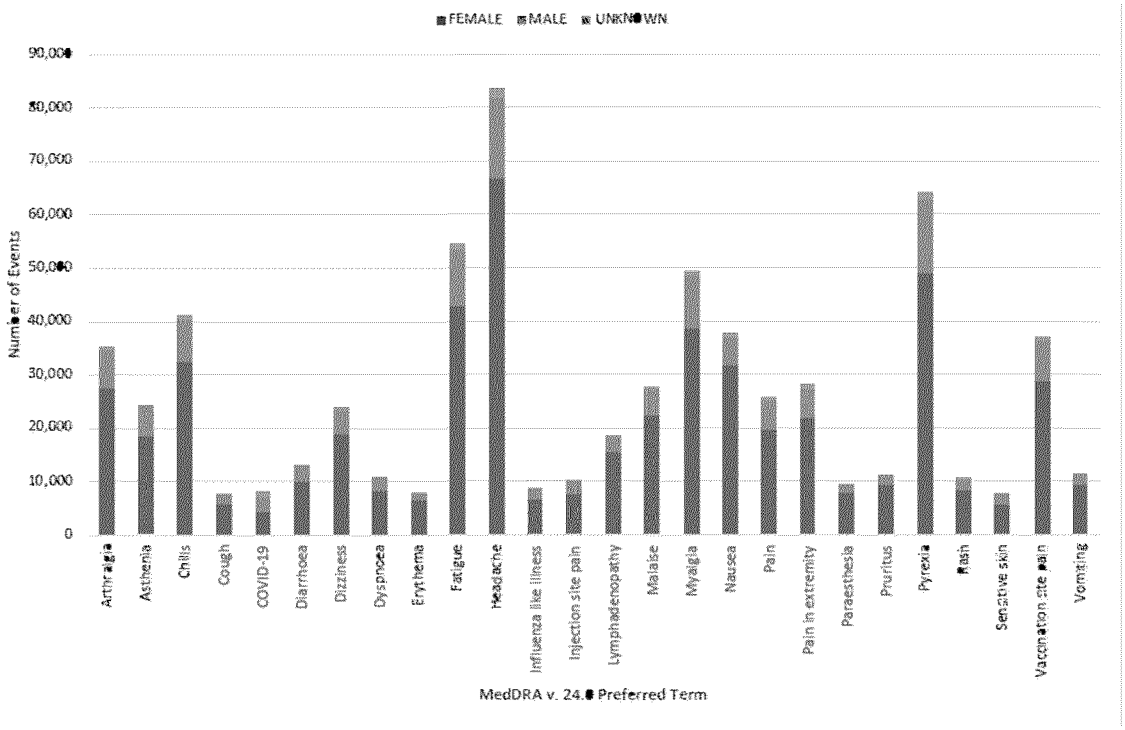
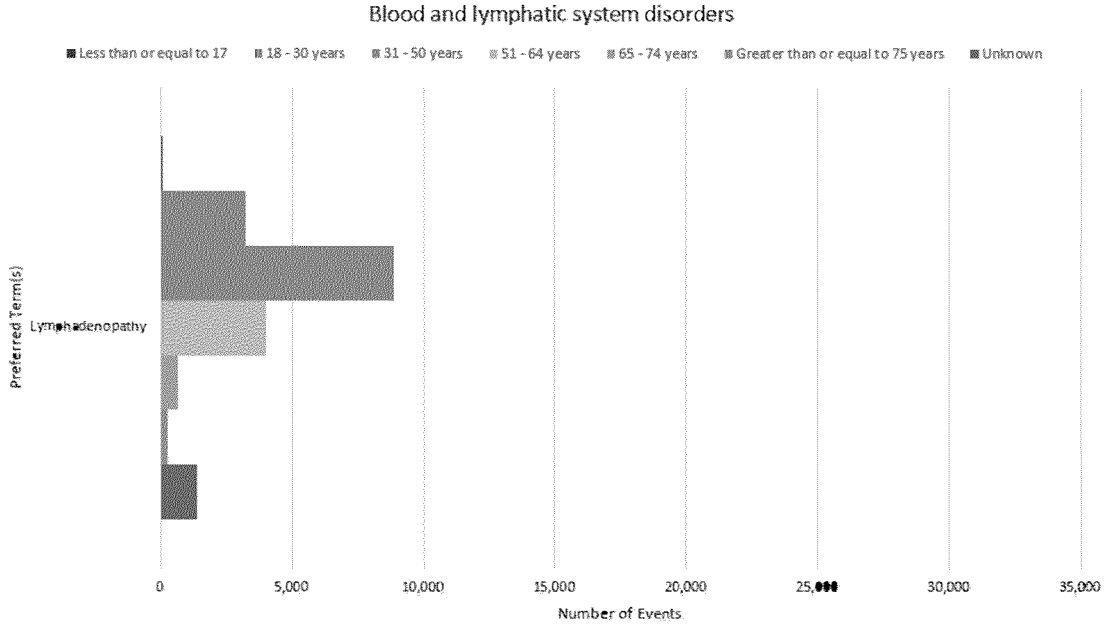
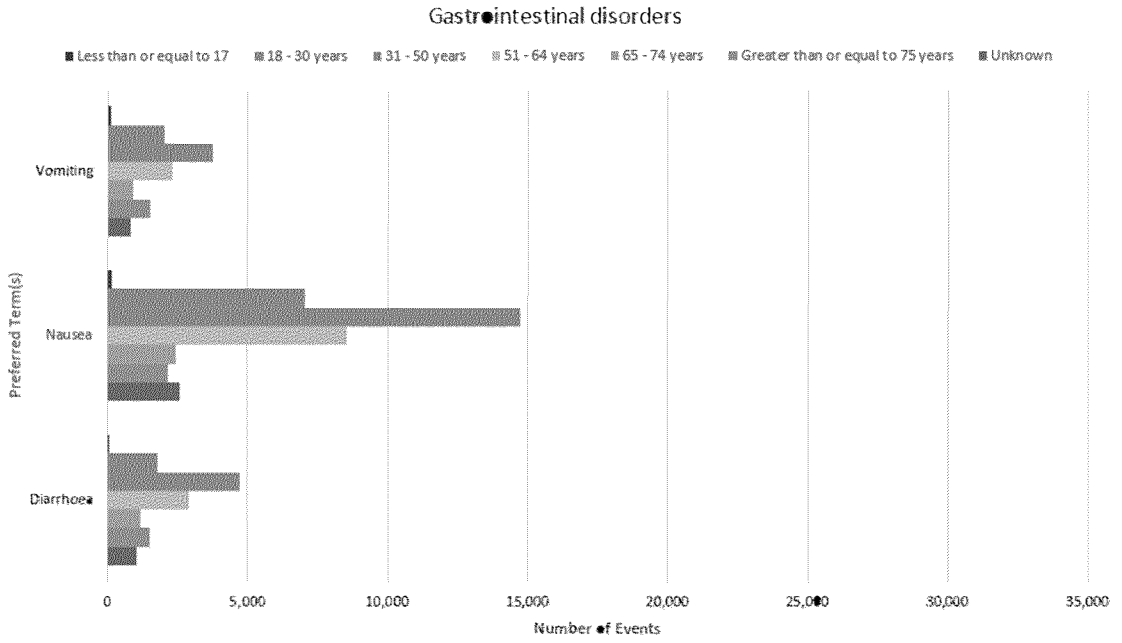
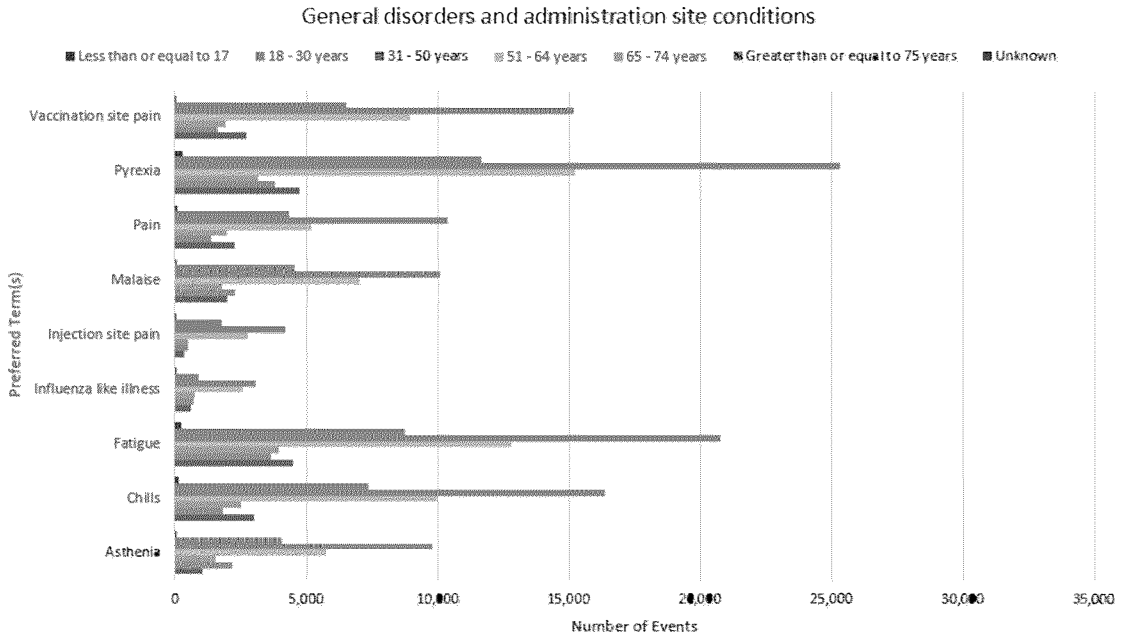
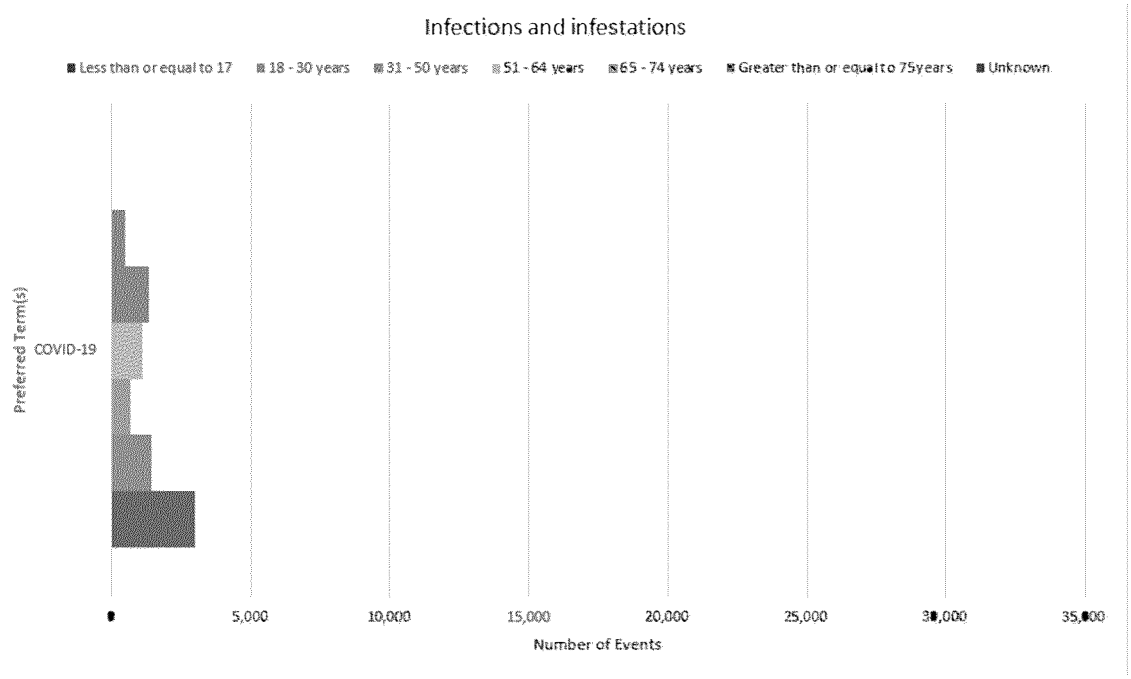


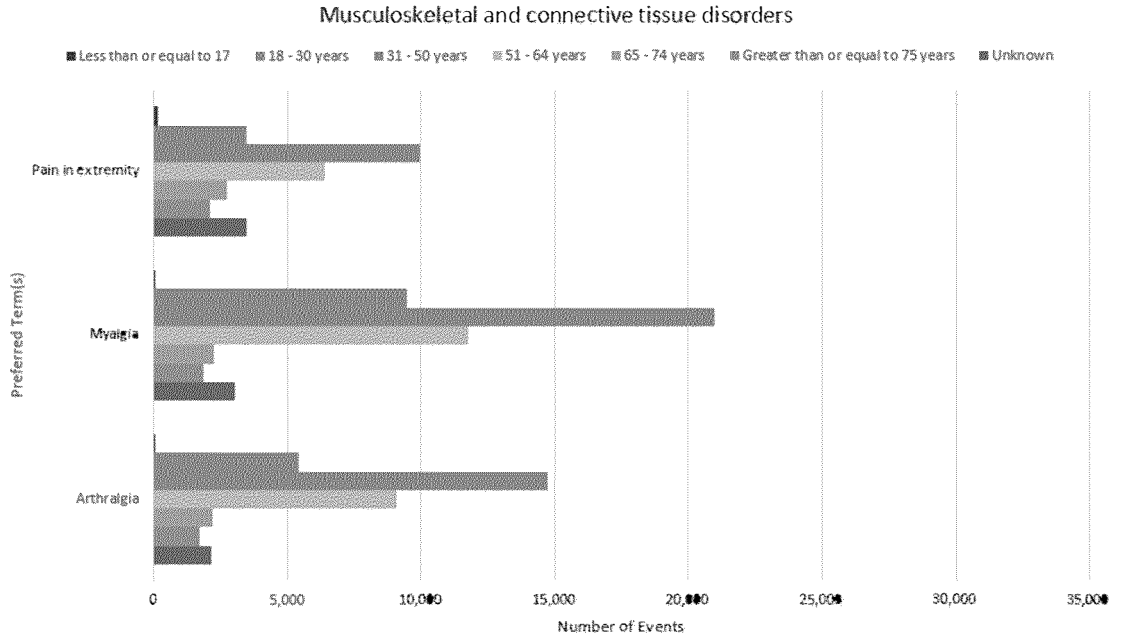
Figure 13. Post-Authorization Data: Events Reported in ≥2% of Cases by SOC and Age Group

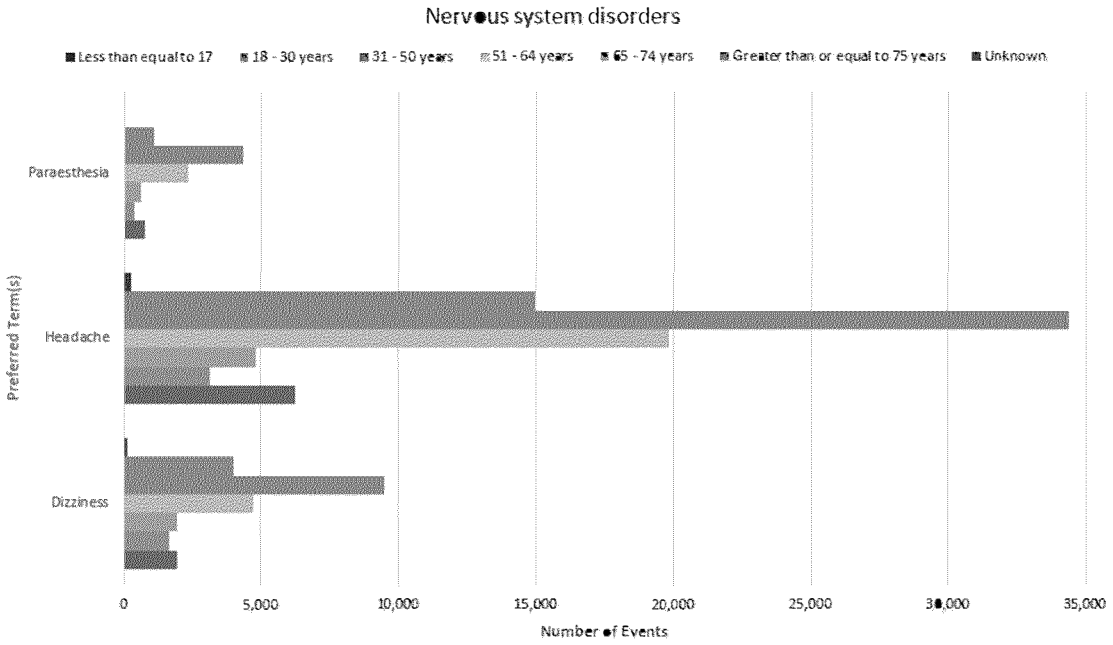


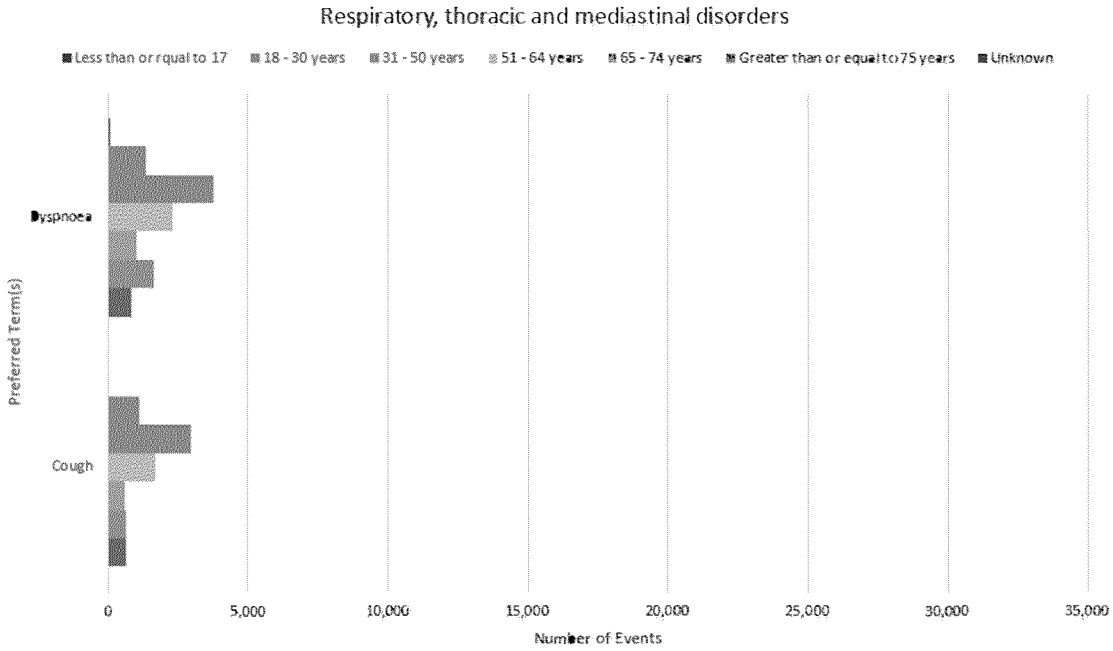












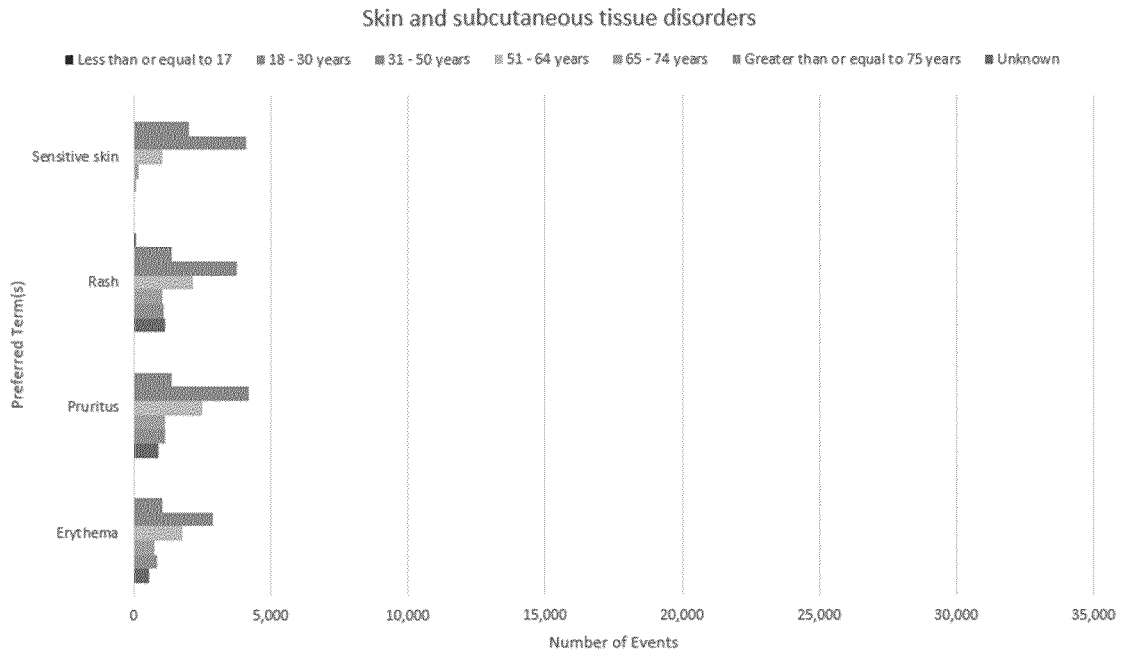
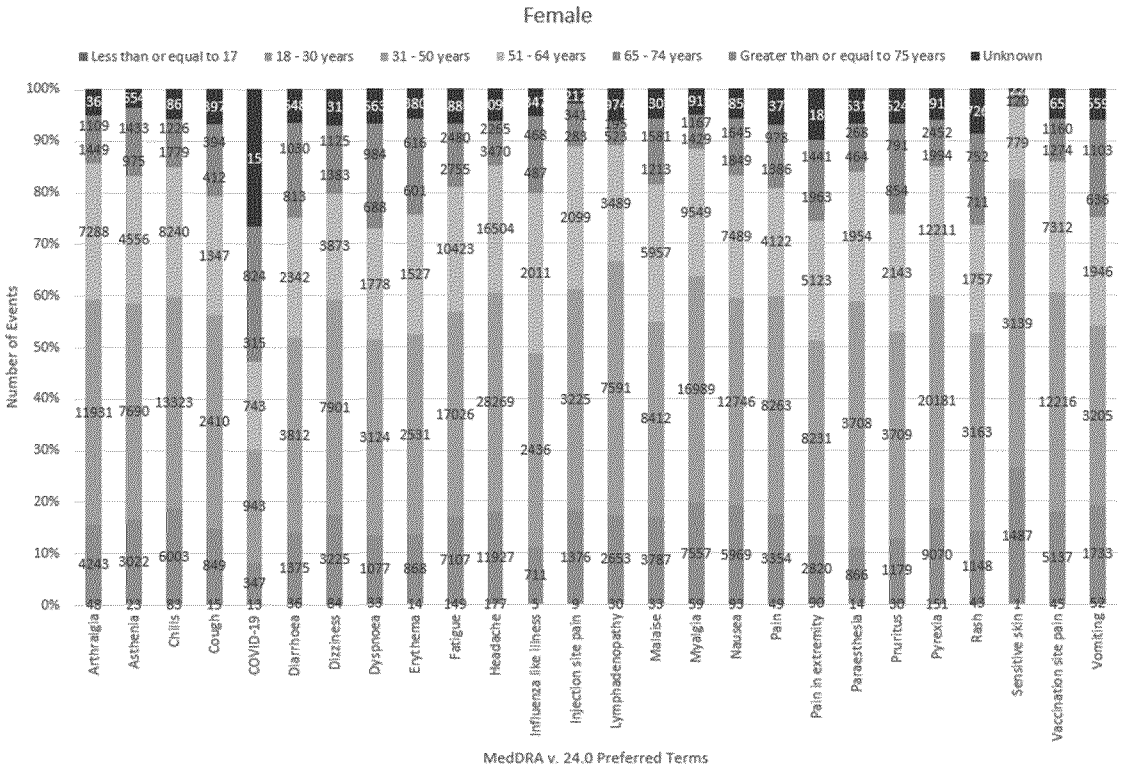
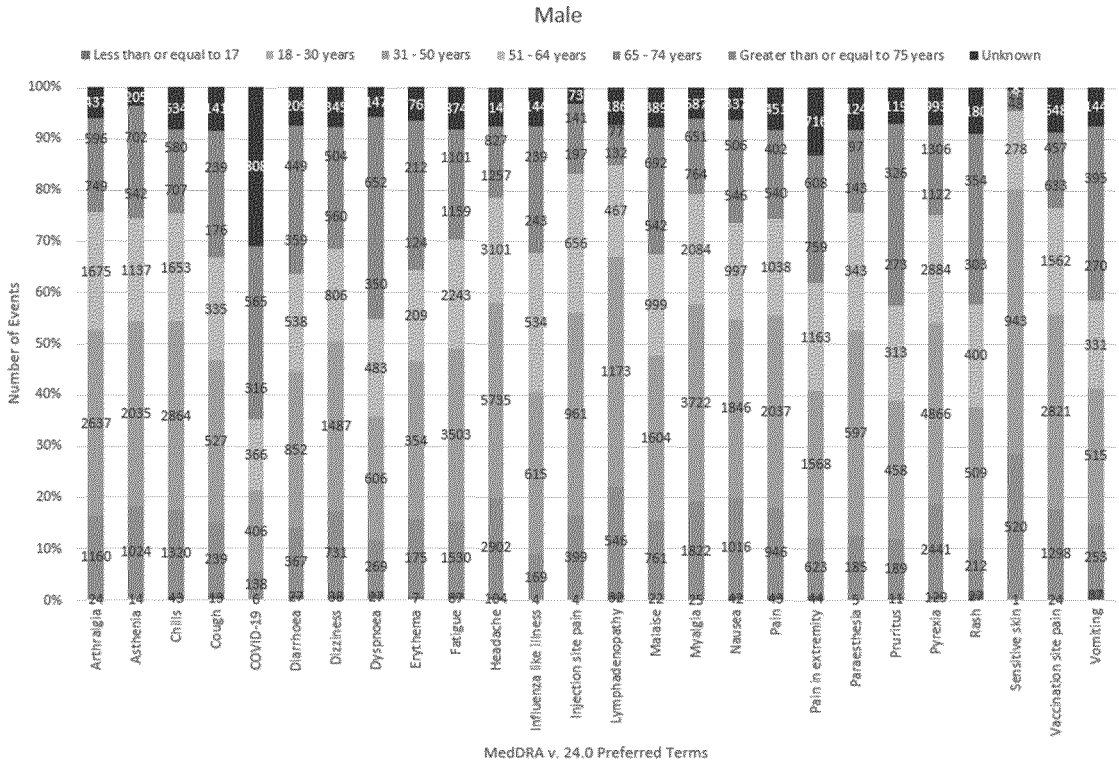


Figure 14. Post-Authorization Data: Events Reported in ≥2% of Cases by Age Group within Gender





The most frequently reported lot numbers in case reports (≥2000 cases) are listed in Table 9 below.

Table 9. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
EL1484	16077
EJ6797	11168
EK9788	10139
EM0477	9214
EJ6136	7034
EJ6134	7029
EJ6795	7010
EJ6796	4942
EJ6788	4421
EL0725	3870
ER1741	3692
EJ6789	3136
EJ6790	2992
ER1749	2762
EP9598	2750
EL1491	2621
EJ3002	2602
EP9605	2461
EK1768	2157

Table 9. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
EL8723	2154
EL0739	2133

Overall, there were no related quality issues identified during investigations of these lot/batch numbers.

Surveillance for any potential product quality issues includes review of quarterly AE/PC reports and monthly SAE/PC reports, and review of weekly AE-batch/lot trending reports. The review of AE and PC reports has as its nexus between Safety and Product Quality and the groups meet on a regular basis. Alerts in the AE/PC reports are reviewed and closed or escalated based on clinical judgement and product knowledge. Any potential signals indicating a potential relationship between a safety issue and a particular batch lot, and that was not already evaluated as part of other signal activities, would undergo evaluation and escalation as per standard procedures.

6.3.1.2.1. Analysis by Dose

Analysis of the occurrences of the AEs by doses[23] for the PM cases is displayed in Table 10. Out of the 327,125 PM cases, the dose was reported in 206,221 distinct cases; in the majority of the cases the events occurred after the first dose.

Table 10. Post-Authorization Cases – Analysis by Dose[a]

	Number of Distinct Cases	Number of AEs
Dose 1	127356	171554
Dose 2	83653	114738
Totals	206221	286292

a. Dose number was evaluated based on the reported Dose number or with availability of both Therapy and Event Onset Dates.

6.3.1.3. Conclusion

Overall, the majority of adverse events were reported for female patients. The greatest number of events occurred in patients in the 31-50 age group. The majority of events were non-serious (non-serious [850,284] vs serious [321,919]), and in most cases the events were resolved or resolving at the time of the report (where outcome was known). Fatal events occurred mainly in patients 75 years of age and older. The proportion of cases with a fatal outcome was higher in cases for which additional comorbidities were reported. The reporting

[23] An analysis by dose was provided for local and systemic reactions as per corePSUR19 guidance. Whenever the number of the cases allowed this analysis, information is provided. An overall evaluation by event and dose is not possible due to technical issues caused by the high number of events.

rates for fatal outcomes were similar for male and female patients, both in the presence and in the absence of comorbidities.

6.3.2. General Overview - Unlocked Cases

A total of 145,825 unlocked[24] case reports (28 from CT and 145,797 from PM) containing 496,718 events fulfilled criteria for inclusion in this PSUR. These 145,825 cases represent 44.5% of the all cases included in the PBRER dataset summarized in Section 6.3.1. Table 11 displays selected characteristics of the unlocked cases at the end of the reporting interval.

Table 11. Selected Case Characteristics - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases	CT No. of Cases[a]	PM No. of Cases
No. of Cases		145,825	28	145,797
Gender	Female	107,027	12	107,015
	Male	32,177	16	32,161
	Unknown/No Data	6621	0	6621
Age (years)	N	126,274	25	126,249
	Min-Max[b]	6 days – 120 years	12 – 81 years	6 days – 120 years
	Mean	50.3	50.7	50.3
	Median	49	52	49
Age group	≤ 17	954	5[c]	949[d]
	18-30	19,735	0	19,735
	31-50	49,102	9	49,093
	51-64	33,242	6	33,236
	65-74	10,819	3	10,816
	≥ 75	12,893	4	12,889
	Unknown	19,080	1	19,079[e]
Country of occurrence (≥2% of all cases)	Italy	32,469	0	32,469
	US	32,265	13	32,252
	France	12,618	0	12,618
	Netherlands	10,732	0	10,732
	UK	9598	0	9598
	Mexico	9196	0	9196
	Spain	8431	0	8431
	Germany	4664	3	4661
	Austria	3531	0	3531
Case Seriousness	Serious	10,576	28	10,548
	Non-serious	135,249	0	135,249
Case Outcome	Resolved/Resolving	85,761	14	85,747
	Resolved with sequelae	890	2	888
	Not resolved	25,480	6	25,474
	Fatal	646	4	642

[24] Unlocked cases are those cases either in the DSU, Primary Review or the Medical Review workflows that are not yet in the Distribution workflow which locks the cases and the system automatically runs reporting rules, schedules and subsequently generates expedited reports as appropriate.

Table 11. Selected Case Characteristics - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases	CT No. of Cases[a]	PM No. of Cases
	Unknown	33,048	2	33,046
Presence of comorbidities	Yes	15,658	8	15,650
	No	130,167	20	130,147

a. BioNTech is the Sponsor of all Clinical Trials; for the following Clinical Trials (C4591001, C4591005, C4591015, C4591017, C4591020), Pfizer acts as lead development party and for the Clinical Trials (BNT162-03, BNT162-06), BioNTech Third Party act as lead development party.
b. Includes only patients to whom BNT162b2 or study therapy was administered directly; does not include exposure during pregnancy or via breastfeeding.
c. Includes 2 cases involving exposure during pregnancy.
d. Includes 26 cases with contradictory demographic information (physical characteristics not matching with the reported age value), 4 cases which upon review were determined not to involve paediatric patients, 27 cases involving exposure during pregnancy, and 133 cases involving exposure via breastfeeding.
e. Includes 234 cases involving exposure during pregnancy and 123 cases involving exposure via breastfeeding.
Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, Frail patients with co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis) described as special populations in Section 16.3.5.5, Section 16.3.5.6 and Section 16.3.5.7, respectively.

6.3.2.1. Clinical Trials Data

The only event reported more than once in clinical trial cases that were unlocked at the end of the reporting interval was coded to the PT Maternal exposure during pregnancy (2 cases).

6.3.2.2. Post-Authorization Data

The overall safety evaluation includes a review of the most frequently reported events by SOC and by PT for events reported in ≥2% of unlocked cases at the end of the reporting interval.

Table 12. Post-Authorization Data: Events Reported in ≥2%* of Unlocked Cases

MedDRA SOC MedDRA PT	AEs (AERP%) N = 145,797
Blood and lymphatic system disorders	
Lymphadenopathy[a]	9073 (6.22%)
Gastrointestinal disorders	
Nausea[a]	17,569 (12.05%)
Diarrhoea[a]	5848 (4.01%)
Vomiting[a]	4667 (3.20%)
General disorders and administration site conditions	
Pyrexia[a]	34,635 (23.76%)
Fatigue[a]	25,066 (17.19%)
Chills[a]	21,564 (14.79%)
Vaccination site pain[a]	17,497 (12.00%)
Pain[a]	11,570 (7.94%)
Malaise[a]	15,001 (10.29%)
Asthenia[a]	13,875 (9.52%)
Injection site pain[a]	9721 (6.67%)

Table 12. Post-Authorization Data: Events Reported in ≥2%* of Unlocked Cases

MedDRA SOC **MedDRA PT**	**AEs (AERP%)** **N = 145,797**
Influenza like illness	4691 (3.22%)

Table 12. Post-Authorization Data: Events Reported in ≥2%* of Unlocked Cases

MedDRA SOC MedDRA PT	AEs (AERP%) N = 145,797
Musculoskeletal and connective tissue disorders	
Myalgia[a]	28,609 (19.62%)
Arthralgia[a]	19,542 (13.40%)
Pain in extremity[a]	11,542 (7.92%)
Nervous system disorders	
Headache[a]	41,883 (28.73%)
Dizziness[a]	9413 (6.46%)
Paraesthesia[a]	3763 (2.58%)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea[b]	3008 (2.06)
Skin and subcutaneous tissue disorders	
Pruritus[a]	4572 (3.14%)
Rash[a]	4231 (2.90%)
Erythema[a]	3212 (2.20%)
Sensitive skin	4758 (3.26%)
Total number of events	**496,671**

a. Listed or consistent with listed AEs in current RSI.
b. Consistent with anaphylactic reactions listed in the current RSI.
* Reporting proportion (% of total cases) at the end of the current reporting period.

6.3.2.3. Conclusion

The data contained in the unlocked cases is consistent with the overall dataset.

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

Appendix 4.2 provides a list of ongoing interventional safety studies. No interventional safety studies were completed during the reporting interval

7.1. Completed Clinical Trials

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

7.2. Ongoing Clinical Trials

During the reporting period, there were 10 ongoing[25] sponsor-initiated clinical trials.

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

- 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*

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

and older 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: there were 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.*
  - C4501007, *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.*
  - 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[26], *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,[26] *Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy subjects: A phase II, randomized, placebo-controlled, observer-blind study.*

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

[26] This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech SE.

Remaining Trials:

- There were 2 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.*

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

7.3. Long-term Follow-up

There is no new safety information beyond 6-months follow-up of clinical trial subjects for this reporting period.

7.4. Other Therapeutic Use of Medicinal Product

There is no relevant information for this reporting period.

7.5. New Safety Data Related to Fixed Combination Therapies

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

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting period, there were 5 ongoing[25] sponsor-initiated non-interventional studies.

Safety Studies (see Appendix 4.4 for a list of ongoing non-interventional safety studies):

- PASS: Non-interventional studies C4591008[27] and C4591012.[28] No clinically important information has emerged from these 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

- There were 3 ongoing non-interventional studies:

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[27] Study C4591008 is a voluntary study; it is included in the US-PVP as post-authorisation safety study addressing the important potential risk of VAED/VAERD.

[28] Study C4591012 is a commitment to the US FDA and is Category 3 commitment in the EU_Risk Management Plan.

- C4591006, *General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).*
- C4591014,[29] *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*

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

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

During the reporting period, the MAH was committed to demonstrating real-world VE through TND study(s) for the BNT162b2 (COVID-19) vaccine as a post-authorization commitment to FDA, EMA and MHRA. To meet this commitment, the MAH is conducting three VE studies at three different study sites. The C4591014 study is a retrospective non-interventional database study (CT24) described above in Section 8 *Findings from Non-Interventional Studies*. In addition, there are two ongoing research collaborations conducting prospective respiratory disease surveillance which have been amended to include BNT162b2 VE objectives. Both studies are low-interventional[30] non-Pfizer sponsored research being conducted in collaboration with Pfizer and are briefly described below.

- **Study WI235284** [31](Emory University Sponsor)
  Study Title: Respiratory Syncytial Virus (RSV) in older adults and pregnant women study (ROAPS) amendment for BNT162b2 post-authorization vaccine effectiveness

  This study is a prospective population-based surveillance study originally conducted to estimate incidence for RSV hospitalizations among older adults and pregnant women (ROAPS), which has been ongoing since October 2018 at 2 hospitals in Atlanta Georgia. The study protocol has been amended to include COVID VE objectives. All patients admitted to the hospitals with acute respiratory illness are screened for eligibility and invited to participate if appropriate. Enrolled patients have a nasopharyngeal swab collected for viral testing, undergo a patient interview for data collection on vaccination history (including BNT162b2), comorbidities, COVID-19 related risk behaviors and other risk factors, and electronic medical record review for hospitalization and outcome data

[29] PAM-MEA-013.

[30] According to article 2 (2)(3) of the Clinical Trials Regulation No 536/2014, the study does not involve any administration of vaccine or other Pfizer products but since a specimen collection procedure is required per protocol, this qualifies this study as 'low-interventional'.

[31] PAM-MEA-024.

collection. No Pfizer products are administered as part of the study protocol. The study aims to enroll approximately 6000 patients.

- **Study WI255886**[32] (Bristol University, UK, Sponsor)
  Study Title: Avon Community Acquired Pneumonia Study (Avon CAP): A pan-pandemic acute lower respiratory tract disease surveillance study

  This is a prospective population-based observational study, including adults aged ≥18 years, admitted to one of two hospitals in Bristol (UK) with symptoms of lower respiratory tract disease. The study has been enrolling participants since mid-2020. The protocol has been amended to include COVID VE objectives. COVID VE will be estimated using a TND analysis, utilizing data on vaccination history (BNT162b2, influenza and pneumococcal vaccinations given as standard of care), comorbidities, pre-admission COVID test and current admitting condition from electronic medical records, and a COVID risk-behaviors questionnaire which will be completed on patient interview.

  No new safety information has emerged from these studies at the time of this report.

During the reporting interval, there was 1 ongoing MAH-sponsored clinical trial, that was not part of the BNT162b2 development program, where BNT162b2 is administered as part of the study drug.

- B7471026: A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when co-administered with a booster dose of BNT162b2 in adults 65 years of age and older.

  No new significant safety finding for BNT162b2 was identified from this study.

During the reporting interval, there was 1 ongoing clinical trial conducted by National Institute of Allergy and Infectious Diseases on delayed heterologous booster doses.

- **Study 21-0012 (NCT04889209)**
  Study Title: A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA Vaccines

  A phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial was designed to assess the safety, reactogenicity and immunogenicity of a delayed (>/=12 weeks) vaccine boost on a range of EUA-dosed COVID-19 vaccines (mRNA-1273, and mRNA-1273.211 manufactured by ModernaTX, Inc.; BNT162b2 manufactured by Pfizer/BioNTech; or Ad26.COV2.S manufactured by Janssen Pharmaceuticals/Johnson & Johnson).

[32] PAM-MEA-025.

During this reporting period, no new safety information from other clinical trial studies was reported about mixed dose schedules, antibody waning, booster dose or revaccination.

9.2. Medication Errors

Cases potentially indicative of medication errors[33] that occurred in the reporting period are summarized below.

From the global safety database, 17,234 cases (5.3% of the total PM dataset) potentially indicative of medication errors were retrieved worldwide up to 18 June 2021.

Of the 17,234 retrieved cases, 6458 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- Off-label use or misuse rather than medication error was reported in 2236 cases;
- Reporting information was no longer consistent to meet medication error criteria in 1752 cases per RSI update;
- Questions about the scheduling of the 2 doses of BNT162b2 and/or information that the second dose may be administered (but it was not administered yet at the time of reporting) or was scheduled outside the prescribed dosing window were reported in 1604 cases;
- Reporting information was not consistent to meet medication error criteria in 72 cases;
- Reporting information was not consistent for paediatric patients (eg, height, weight, clinical details, etc indicative of an adult patient) and did not meet the medication error criteria for Product administered to patient of inappropriate age in 71 cases;
- Medical inquiries only were reported in 614 cases;
- The patient intentionally refuted to be administered or was not able to receive the scheduled BNT162b2 in 98 cases;
- BNT162b2 was administered during breast feeding (not contraindicated) in 3 cases;

[33] Search criteria: MedDRA (version 24.0): *HLTs*: Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR *PTs*: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

– Reporting information on BNT162b2 supply issue in 8 cases.

The potentially relevant medication error cases were 10,776 reporting 27,448 events.

Clinical Trial Data

During the reporting period no serious cases indicative of medication errors were reported.

Post-Authorisation Data

The 10,776 relevant medication error cases originated mostly (≥ 10 occurrences) from the following countries:

Table 13. Most reported Countries for Medication Error Cases

Country	Number of Cases	Country	Number of Cases
US	7,039	Poland	42
UK	1,325	Norway	40
France	556	Finland	35
Germany	392	Greece	26
Italy	147	Austria	25
Belgium	145	Netherlands	23
Canada	114	Puerto Rico	20
Mexico	105	Switzerland	19
Czech Republic	101	Chile	14
Sweden	85	Turkey	13
Romania	80	Croatia	12
Israel	67	Denmark	11
Portugal	60	Hungary	11
Spain	60	Brazil	10
Ireland	54	Panama	10
Japan	46	Singapore	10

There were 4346 females and 2016 male patients, whereas the gender was not specified for 4414 patients. When provided (n = 4421), the age ranged from 10 years to 103 years with a mean age of 52.7 years and a median of 53 years.

Of the 10,776 medication error cases reporting 27,448 events, there were 14,945 relevant medication error events. The most frequently reported (≥2%) medication error PTs were: Poor quality product administered (3414), Product temperature excursion issue (2174), Inappropriate schedule of product administration (1907), Circumstance or information capable of leading to medication error (1131), Product preparation issue (845), Incorrect route of product administration (834), Product preparation error (707), Underdose (594), Product storage error (531), Product dose omission issue (507), Wrong technique in product usage process (455), Incorrect dose administered (302), Product administered at inappropriate site (276), and Wrong product administered (271).

Furthermore, there were 885 cases referred about an overdosage of the vaccine; these cases will be separately discussed in Section 16.3.4.2 *Overdose*.

Of the 14,945 medication error events, 231 were serious and 14,714 were non-serious. The relevant event outcome[34] was reported as fatal (1), resolved/resolving (219), resolved with sequelae (3), not resolved (79), and unknow (14,643). In the fatal case, from EudraVigilance, a 71-year-old female patient received her 1st dose of BNT162b2 on 24 March 2021 (batch/lot number: ET3674). On 31 March 2021 the patient was exposed to COVID-19 and on 02 April 2021, she developed COVID-19 lung failure, further described as COVID-19 pneumonia, pulmonary failure, and breakthrough infection, all with fatal outcome. The medication error PT "Incomplete course of vaccination" was reported with a fatal outcome too, but on review the impossibility to complete the course of vaccination was a consequence of the patient's death rather than a cause of death (see Section 16.3.4.1 *Death*).

During the reporting interval 6 different sets of medication error cases were identified reporting the following medication errors, all no-harm with no co-reported events:

- From the US: in 1095 cases BNT162b2 was stored in the standard freezer for 22 to 35 days, then pulled from the standard freezer, thawed and administered (PTs Product temperature excursion issue, Poor quality product administered).

- From the US: in 225 cases BNT162b2 was stored in a regular freezer for 4 additional days beyond the two weeks period, for a total of 18 days (PTs Poor quality product administered, Product storage error).

- From the US: in 129 cases an incorrect dilution of BNT162b2 with sterile water (instead of the normal saline diluents) was reported. The vaccine was administered to the patients (PTs Product preparation error, Poor quality product administered).

- From France: in 109 cases patients were administered with more than 2 hours thawed vials (about 6 hours), at room ambient temperature before being diluted in NaCl (PTs Poor quality product administered, Product temperature excursion issue).

- From Belgium: 106 cases where the nurse inadvertently used 25-gauge 16mm (also reported as 15 mm) long needles instead of the 25 mm recommended length. The event was reported as subcutaneous administration (PTs Wrong technique in product usage process, Incorrect route of product administration).

- From the US: in 304 cases BNT162b2 was diluted with 1.3 ml rather than 1.8mL (304 patients received this more concentrated dose of the vaccine – see Section 16.3.4.2 *Overdose*, [PTs Overdose, Product preparation issue]).

[34] Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events.

Medication Errors Analysis

Among the relevant medication error cases (9891 cases[35]), the following scenarios, categorized according to the EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014) were described:

- Medication errors associated with harm [ie, resulting in adverse reaction(s)] were reported in 291 cases (2.9% of relevant medication error cases);
- Medication errors without harm [ie, not resulting in adverse reaction(s)][36] were reported in 9487 cases (95.9% of relevant medication error cases), of which 3181 cases involved co-reported AEs;
- Potential medication errors were reported in 107 cases (1.1% of relevant medication error cases);
- Intercepted medication errors were reported in 6 cases (0.1% of relevant medication error cases).

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

Medication errors associated with harm (333 medication errors events in 291 cases)

Cases were mostly (≥10 occurrences) reported from the US (117), the UK (39), Mexico (30), Germany (24), Romania (16), France (13) and Japan (10).

Serious medication errors

In 60 cases (involving 64 medication error events), serious medication errors potentially contributed to the occurrence of SAEs. Cases originated from the UK (23), Romania (16), Germany (6), France, the US (3 each), Belgium, Hungary, Japan, Mexico, the Netherlands, Portugal, Slovakia, Sweden, and Switzerland (1 each).

The serious events indicative of medication error were: Incorrect route of product administration (22), Inappropriate schedule of product administration (16), Product administered at inappropriate site (5), Wrong technique in product usage process (4), Expired product administered (3), Contraindicated product administered, Incorrect dose administered, Poor quality product administered, Product administration error, Product temperature excursion issue, Wrong product administered (2 each), Medication error, and Product dose omission issue (1 each). The most frequently (≥ 5 occurrences) co-reported events were Hyperhidrosis, Hypotension, Syncope (16 each), Bradycardia, Mydriasis, Pallor (15 each),

[35] Relevant medication error cases 9891 (291 harm + 9487 no-harm + 107 potential + 6 intercepted).

[36] AEs may be co-reported in a case, but they are not considered to be a result of the medication error.

Fatigue, Vaccination site pain (11), Headache (10), Pain in extremity, Pyrexia (7 each), Chills, Pain, Paraesthesia (6 each), Asthenia, Myalgia, and Nausea (5 each).

Upon review of medication error serious events:

Vaccine administration errors: (41 cases, 43 serious medication error events). The serious medication error events were Incorrect route of product administration (22), Product administered at inappropriate site (5), Wrong technique in product usage process (4), Expired product administered (3), Contraindicated product administered, Incorrect dose administered, Product administration error, Wrong product administered (2 each), and Medication error (1).

The most frequently (≥ 10 occurrences) co-reported events regardless the seriousness were Hyperhidrosis, Hypotension, Syncope (16 each), Bradycardia, Mydriasis, Pallor (15 each), Fatigue, Vaccination site pain (11 each), and Headache (10).

- *Errors in the route/site of administration*: 32 cases (reporting 34 serious medication error events) mainly described errors in
  - the route of administration of the vaccine other than the intramuscular (intravenous or subcutaneous – PT: Incorrect route of product administration, 22 cases) or
  - the vaccine was administered in the vaccinee's arm, but not in the deltoid muscle (PT: Product administered at inappropriate site, 5 cases) or
  - the use of an incorrect needle or syringe for vaccine administration (PT Wrong technique in product usage process, 4 cases), or
  - unspecified administration technique errors (PT: Product administration error [2 cases], Medication error [3 cases]). In 15 out of 22 cases of Incorrect route of product administration, all from Romania, the reporter (physician) suspected that the co-reported events (Syncope, Bradycardia, Mydriasis, Hyperhidrosis, Pallor, Hypotension) occur due to the penetration into the vascular bed of the needle.
- *Wrong vaccine other than recommended in the RSI administered*: 2 cases involved vaccinees who received (PT Wrong product administered) respectively 1 dose of BNT162b2 vaccine and 1 dose of the Moderna vaccine (co-reported PTs: Pyrexia, Malaise, Fatigue, Headache); 1 dose of BNT162b2 vaccine and 1 dose of Astra Zeneca vaccine (co-reported PTs: Headache, Swelling face, Pyrexia, Paraesthesia, Paraesthesia[37]).
- *Other vaccine administration errors*: In 2 cases the vaccinees received a third dose (PT Incorrect dose administered, co-reported events Hypertension, Pyrexia, Bronchitis, Inflammation, *Escherichia* urinary tract infection, Pyrexia, Atrial fibrillation). The administration of unspecified expired vaccine (PT Expired product administered, co-reported PTs: Vaccination site lymphadenopathy, Hypersensitivity, Palpitations, Chest discomfort, Hypertension, Pain, Fatigue, Bedridden, Vaccination site pain, Back pain)

[37] Paraesthesia reported twice for both, skin and feet/hands.

was reported in 3 cases. In 2 cases BNT162b2 was contraindicated to the vaccinee (PT Contraindicated product administered) due to an ongoing allergy after the first dose of BNT162b2 (co-reported PTs Erythema, Face oedema), or was allergic to BNT162b2 excipient (PEG), (co-reported PTs Throat tightness, Dyspnoea, Anaphylactic reaction, Tonsillar hypertrophy, Pharyngeal swelling).

Vaccine scheduling errors: (16 cases, 16 serious PT Inappropriate schedule of product administration).

The most frequently (≥ 2 occurrences) co-reported events were Fatigue (4), Headache, Nausea, Pain (3 each), Diarrhoea, Dysmenorrhoea, Heavy menstrual bleeding, Myalgia, Pain in extremity, Paraesthesia, Pyrexia, Somnolence (2 each).

- *Incorrect interval between doses (16 cases):* events described errors involving scheduled second dose vaccinations outside the recommended 21 days after the first dose (second dose was scheduled in longer than 21 days after the first dose or shorter than 21 days after the first dose).

Other medication errors (3 cases, 5 serious medication error events): The serious events indicative of medication error were: Poor quality product administered, Product temperature excursion issue, (2 each), and Product dose omission issue (1).

- *Storage issue*: vials were stored at about 9-10 degrees Celsius for 2 days in a normal refrigerator and then administered (1 case), and storage refrigerator had lower temperature (- 2.7 C°) prior to dilution (1 case). Co-reported events were Seizure, Circulatory collapse, Tachycardia, Loss of consciousness, Presyncope, Somatic symptom disorder, Facial paralysis, Hypotension, Vertigo, Paraesthesia, and Hypertensive crisis.

- *Dose omission issue*: appointment for the second dose was cancelled (PT Product dose omission issue) due to SARS-CoV-2 test positive (PTs: Drug ineffective, SARS-CoV-2 test positive).

Non-serious medication errors

In 231 cases (reporting 269 non-serious medication error events), medication errors potentially contributed to the occurrence of the AEs. Most of the cases (≥2 occurrences) originated from the US (114), Mexico (29), Germany (18), the UK (16), France (10), Japan (9), Italy (8), Sweden (4), Czech Republic (3), Ireland, and Poland (2 each).

The events indicative of medication error were: Incorrect route of product administration (59), Product administered at inappropriate site (52), Wrong technique in product usage process (34), Poor quality product administered (20), Product administration error (15), Expired product administered (14), Wrong product administered (13), Product preparation error (12), Incorrect dose administered (10), Inappropriate schedule of product administration, Product temperature excursion issue (7 each), Circumstance or information capable of leading to medication error (6), Underdose (4), Extra dose administered (3), Product dose omission issue, Product preparation issue (2 each), Inadequate aseptic technique

in use of product, Incorrect dosage administered, Incorrect product administration duration, Medication error, Product administered to patient of inappropriate age, Product storage error, Transcription medication error, Wrong dose, and Wrong technique in device usage process (1 each).

The most frequently (≥ 10 occurrences) co-reported events regardless the seriousness were Pain in extremity (50), Headache (45), Vaccination site pain (42), Pyrexia (33), Chills, Pain (30 each), Arthralgia (27), Asthenia (23), Fatigue, Myalgia (20 each), Erythema (19), Nausea (18), Dizziness (17), Vaccination site erythema (15), Body temperature increased, Dyspnoea, Malaise, Paraesthesia, Rash, Sensitive skin (11 each), Hypoaesthesia, and Pruritus (10 each).

Vaccine administration errors (200 cases, 218 non-serious medication error events). The medication error events were Incorrect route of product administration (59), Product administered at inappropriate site (52), Wrong technique in product usage process (34), Expired product administered (14), Product administration error, Wrong product administered (13 each), Incorrect dose administered (9), Poor quality product administered (7), Circumstance or information capable of leading to medication error, Extra dose administered (3 each), Product temperature excursion issue, Underdose (2 each), Inadequate aseptic technique in use of product, Incorrect dosage administered, Incorrect product administration duration, Medication error, Product preparation error, Wrong dose, Wrong technique in device usage process (1 each).

The most frequently (≥ 10 occurrences) co-reported events regardless of seriousness were Pain in extremity (43), Headache (39), Vaccination site pain (37), Pain (29), Arthralgia, Pyrexia (27 each), Chills (25), Asthenia (23), Myalgia (20), Erythema (18), Dizziness (17), Fatigue (16), Nausea (15), Vaccination site erythema (14), Dyspnoea, Paraesthesia, Rash, Sensitive skin (11 each), Body temperature increased, Malaise, and Pruritus (10 each).

- *Errors in the route/site of administration:* 155 cases (reporting 160 medication error events) mainly described errors in route of administration of the vaccine other than the intramuscular (intravenous or subcutaneous, 65 cases), or the vaccine was administered in the vaccinee's arm, but not in the deltoid muscle (80 cases), or the use of an incorrect needle or syringe for vaccine administration (10 cases).

- *Wrong vaccine other than recommended in the RSI administered*: 13 cases (reporting 14 medication error events).

  – 5 cases involved vaccinees who received respectively 1 dose of BNT162b2 vaccine and 1 dose of the Moderna vaccine,

  – 3 vaccinees received 1 dose of BNT162b2 vaccine and 1 dose of AstraZeneca vaccine,

  – 2 vaccinees received 1 dose of BNT162b2 vaccine and 1 dose of Johnson & Johnson vaccine,

  – 1 vaccinee received 1 dose of BNT162b2 and 1 dose of Sputnik vaccine, whereas

  – 2 vaccinees received an unspecified dose of vaccine.

- *Other vaccine administration error*: 32 cases (reporting 44 medication error events).
  - 15 cases reported administration of expired vaccines,
  - 2 vaccinees received a third dose of BNT162b2,
  - 6 vaccinees received 2 or more doses of BNT162b2 at the same time (or the same day).
  - In 8 cases the vaccinees received an incomplete administration of the dose due to administration issues, whereas
  - in 1 case the vaccinee reported other dose administration issues.

Vaccine preparation errors (12 cases, 23 non-serious medication error events). Errors included dilution before use not correctly performed (2 cases), improper dilution with sterile water (6 cases), manually thawed (1 case), and other unspecified preparation error (3 cases).

Vaccine scheduling errors (7 cases, 8 non-serious medication error events). The second dose was scheduled more than 21 days after the first dose (3 cases), and the second dose of the vaccine was scheduled less than 21 days after the first dose (3 cases). There were errors in scheduling second dose administration date (1 case).

Other medication errors (12 cases, 20 non-serious medication error events). These events reported unspecified medication errors (4 cases) and errors in storage (6 cases), and other dose related errors (2 cases).

Medication errors without harm (13,514 medication errors events in 9487 cases)

These medication error PTs describe errors occurring during 1 or more steps of the vaccination process: preparation, administration, or scheduling of second dose.

Among the medication error cases without harm, cases originated mostly (≥ 60 occurrences) from the following countries: US (6090), UK (1245), France (524), Germany (352), Belgium (143), Italy (125), Canada (101), Czech Republic (97), Sweden (78), Romania (63), Mexico (62), and Israel (61).

The most reported (≥ 2% of AERP) medication error events were: Poor quality product administered (3371), Product temperature excursion issue (2163), Inappropriate schedule of product administration (1851), Circumstance or information capable of leading to medication error (1045), Incorrect route of product administration (750), Underdose (589), Product storage error (530), Product preparation error (524), Product dose omission issue (501), Wrong technique in product usage process (407), Product preparation issue (268), Incorrect dose administered (266), Wrong product administered (248), Product administered at inappropriate site (215), and Expired product administered (192). Event seriousness was reported as serious for 140 medication error events.

- *Vaccine preparation errors*[38] (680 cases, 1205 medication error events). Events mainly described errors on volume dilution (other than 1.8 mL), or error on type of solvent (mainly sterile water rather than 0.9% NaCl solution) or error in filling the syringe before the administration.

- *Vaccine administration errors*[39] (2585 cases, 3506 medication error events). Events mainly described errors of accidental exposure to vaccine, errors in administration of vaccine dose not adequately prepared, errors in administration technique, errors in route of administration, errors in the volume or dosage of the vaccine administered, errors in administering the second dose outside the recommended 21 days after the first dose per the RSI, errors of vaccination at the wrong injection site, errors due to a patient medical condition, errors in co-administration of other vaccines and other administration errors.

- *Vaccine scheduling errors*[40] (1848 cases, 1904 medication error events). Events mainly described errors involving scheduled second dose vaccinations outside the recommended 21 days after the first dose.

- *Other medication errors* [41](4374 cases, 6899 medication error events). Events described storage issues[42], unspecified medication errors, vaccination error, and other dose related errors.

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[38] PTs: Product preparation issue, Product preparation error, Intercepted product preparation error, Underdose and Accidental underdose (if associated to other PT indicative of erroneous preparation), Inadequate aseptic technique in use of product, Dose calculation error, Circumstance or information capable of leading to medication error (PT across all 4 subcategories).

[39] PTs: Contraindicated product administered, Counterfeit product administered, Discontinued product administered, Drug administered in wrong device, Expired product administered, Extra dose administered, Incorrect dosage administered, Incorrect dose administered, Incorrect dose administered by device, Incorrect dose administered by product, Incorrect product administration duration, Incorrect product dosage form administered, Incorrect product formulation administered, Incorrect route of product administration, Intercepted product administration error, Lack of vaccination site rotation, Poor quality product administered, Product administered at inappropriate site, Product administered by wrong person, Product administered to patient of inappropriate age, Product administration error, Recalled product administered, Underdose and Accidental underdose (unless other PT indicative of erroneous preparation), Wrong patient received product, Wrong product administered.

[40] PTs: Inappropriate schedule of product administration, Wrong schedule, Product dose omission issue and Product dose omission in error (if there is an associated term indicative of an inappropriate scheduling), Booster dose missed.

[41] PTs: Product temperature excursion issue, Product storage error, Wrong product stored, Accidental exposure to product, Accidental exposure to product, Accidental overdose, Accidental underdose, Drug monitoring procedure incorrectly performed, Exposure via eye contact, Exposure via skin contact, Incomplete course of vaccination, Intercepted medication error, Medication error, Physical product label issue, Product communication issue, Product confusion, Product dispensing error, Product dispensing issue, Product expiration date issue, Product label confusion, Product lot number issue, Product monitoring error, Product prescribing error, Product prescribing issue, Product selection error, Product substitution error, Transcription medication error, Vaccination error, Wrong dose, Wrong drug, Wrong technique in device usage process, Wrong technique in product usage process.

[42] Vast majority of them originated from clusters.

Potential Medication Errors (109 medication errors events in 107 cases)

Cases were from US (94), Mexico (6), UK (3), Colombia, France, Poland and Spain (1 each). Age ranged from 14 to 93 years (n = 43) with a mean of 60 years and a median of 64 years. Patients were female (73), male (21) and unspecified (13).

The relevant medication error events were: Circumstance or information capable of leading to medication error (76), Inappropriate schedule of product administration (15), Counterfeit product administered (4), Incomplete course of vaccination, Product dose omission issue, Wrong technique in product usage process (3 each), Medication error, Product administered at inappropriate site, Product prescribing error, Underdose, and Wrong product administered (1 each), all non-serious.

There were 31 cases reporting events not associated to the potential medication errors. The most frequently (≥2 occurrences) events include: Fatigue (7), Pain in extremity, Suspected counterfeit product (4 each), Arthralgia, Headache, Myalgia, Pain (3 each), Chills, Influenza like illness, and Pyrexia (2 each), all non-serious.

Events mainly described, potential errors on scheduling the second dose, questions about potential drug-drug interactions, scheduling, vaccine dosing, counterfeit vaccines, concurrent treatment/procedures, and potential AEs.

Intercepted Medication Errors (8 medication error events in 6 cases)

Cases originated from France, the US (2 each), Norway and Romania (1 each). There were 2 female patients whereas for 4 cases the gender was not reported; all cases were non serious. The relevant reported events were, Intercepted medication error (3), Intercepted product preparation error, Product preparation issue (2 each), and Intercepted product administration error (1).

Intercepted medication error: an insulin needle was removed from the syringe and another needle suitable for intramuscular injection was used (1 event); the patient received notification for 1st and 2nd dose at the same day (1 event) and "felt unwell" (PT Malaise) for this error on scheduling; the vial was mixed with 2.6 mL (1 event) of saline solution and not 1.8 mL (PT Product preparation issue) and was not used.

Intercepted product preparation error: A vial, reconstituted with a larger volume of diluent (2.2 mL), was not used (1 event); a physician asked to mark the syringes at 0.3 mL of volume (1 event).

Intercepted drug administration error: probably due to vacuum effect during the aspiration the pharmacist withdrawn less (PT Product preparation issue) than 0.3 mL (about 0.22 mL) and did not administered the dose (1 event).

Conclusion

Overall, among the 9891 relevant medication error cases, 333 cases (0.1% of the total interval cases, 3.4% of total relevant medication error cases) were considered harmful, 60 of which

(0.6% of total relevant cases) were serious and most of them originated from vaccine administration issues (41 cases on 60 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.

10. NON-CLINICAL DATA

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

11. 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 9 studies that presented important new safety findings for BNT162b2.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Frail subjects
1	***Grupper A, Sharon N, Finn T, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol 2021; doi: 10.2215/CJN.03500321.*** Background and objectives: Coronavirus disease 2019 (COVID-19) is associated with higher morbidity and mortality in patients on maintenance hemodialysis. Patients on dialysis tend to have a reduced immune response to infection or vaccination. The aim of the study was to assess, for the first time to the best of our knowledge, the humoral response following vaccination with the BNT162b2 vaccine in patients on maintenance hemodialysis and the factors associated with it. Design, setting, participants, & measurements: The study included 56 patients on maintenance hemodialysis (dialysis group) and a control group composed of 95 health care workers. All participants had received two doses of the BNT162b2 (Pfizer-BioNTech) vaccine. The serology testing was done using Quant II IgG anti-Spike severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) assay by Abbott a median of 30 days after receipt of the second dose of the vaccine. Results: All subjects in the control group developed an antibody response compared with 96% (54 of 56) positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; interquartile range, 1128–5651) were significantly lower than in the control group (median, 7401; interquartile range, 3687–15,471). A Mann–Whitney U test indicated that this difference was statistically significant (U=1238; P <0.001). There was a significant inverse correlation of age and IgG levels in both groups. The odds of being in the lower quartile were significantly higher for older individuals (odds ratio, 1.11 per year of age; 95% confidence interval, 1.08 to 1.20; P=0.004) and for the dialysis group compared with the control group (odds ratio, 2.7; 95% confidence interval, 1.13 to 7.51; P=0.05). Within the dialysis group, older age and lower lymphocyte count were associated with antibody response in the lower quartile (odds ratio, 1.22 per 1-year older; 95% confidence interval, 1.13 to 1.68; P=0.03 and odds ratio, 0.83 per 10-e^3/µl-higher lymphocyte count; 95% confidence interval, 0.58 to 0.97; P=0.05). Conclusions: Although most patients on maintenance hemodialysis developed a substantial humoral response following the BNT162b2 vaccine, it was significantly lower than controls. Age was an important factor in the humoral response, regardless of chronic medical conditions.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
2	***Goupil R, Benlarbi M, Beaubien-Souligny W, et al. Short-term antibody response after 1 dose of BNT162b2 vaccine in patients receiving hemodialysis. Canadian Medical Association Journal 2021; 193 (22) E793-E800; DOI: https://doi.org/10.1503/cmaj.210673.*** Background: Patients receiving in-centre hemodialysis are at high risk of exposure to SARS-CoV-2 and death if infected. One dose of the BNT162b2 SARS-CoV-2 vaccine is efficacious in the general population, but responses in patients receiving hemodialysis are uncertain. Methods: Serial plasma from patients receiving hemodialysis and health care worker controls before and after vaccination with 1 dose of the BNT162b2 mRNA vaccine, as well as convalescent plasma from patients receiving hemodialysis who survived COVID-19 were obtained. Anti-RBD IgG levels and stratified groups by evidence of previous SARS-CoV-2 infection were measured. Results: This study included 154 patients receiving hemodialysis (135 without and 19 with previous SARS-CoV-2 infection), 40 controls (20 without and 20 with previous SARS-CoV-2 infection) and convalescent plasma from 16 patients. Among those without previous SARS-CoV-2 infection, anti-RBD IgG was undetectable at 4 weeks in 75 of 131 (57%, 95% confidence interval [CI] 47% to 65%) patients receiving hemodialysis, compared with 1 of 20 (5%, 95% CI 1% to 23%) controls ($p < 0.001$). No patient with nondetectable levels at 4 weeks developed anti-RBD IgG by 8 weeks. Results were similar in non-immunosuppressed and younger individuals. Three patients receiving hemodialysis developed severe COVID-19 after vaccination. Among those with previous SARS-CoV-2 infection, median anti-RBD IgG levels at 8 weeks in patients receiving hemodialysis were similar to controls at 3 weeks ($p = 0.3$) and to convalescent plasma ($p = 0.8$). Interpretation: A single dose of BNT162b2 vaccine failed to elicit a humoral immune response in most patients receiving hemodialysis without previous SARS-CoV-2 infection, even after prolonged observation. In those with previous SARS-CoV-2 infection, the antibody response was delayed. The patients receiving hemodialysis should be prioritized for a second BNT162b2 dose at the recommended 3-week interval.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

<table>
<tr><th>No.</th><th>Citation/Abstract</th></tr>
<tr><td>3</td><td>
Ali H, Aribi A, Arslan S, et al. Safety and Tolerability of SARS-CoV-2 Emergency-Use Authorized Vaccines Allogeneic Hematopoietic Stem Cell Transplant Recipients. Transplant Cell Ther 2021; S2666-6367(21)01073-3. doi: 10.1016/j.jtct.2021.07.008

Background and Objectives: It was a retrospective study performed to identify the incidence of adverse events following SARS-CoV-2 and the incidence of a new onset GVHD or worsening of existing GVHD after EUA vaccine administration and the incidence of SARS-CoV-2 positivity in vaccinated HCT patients.

Study design: The authors retrospectively reviewed 113 HCT patients who received at least one dose of EUA vaccine to describe the safety/tolerability, any impact on GVHD, and incidence of SARS-CoV-2 PCR positivity after vaccination. Patients received either Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines. Patients were included if they were 18 years or older and had received at least one dose of vaccine in the post HCT setting.

Results: The incidence of lymphopenia occurred at 8.8% as summarized in the table below.

Table. Clinical Laboratory Adverse Effects after COVID-19 Vaccination
<table>
<tr><th>Lymphopenia, n (%)</th><th>10 (8.8)</th></tr>
<tr><td>Grade 1</td><td>3</td></tr>
<tr><td>Grade 2</td><td>3</td></tr>
<tr><td>Grade 3</td><td>4</td></tr>
</table>
All patients with Grade 3 lymphopenia had prior baseline lymphopenia prior to receiving vaccine. Both mRNA vaccines, BNT162b2 and mRNA-1273, were found to be safe and efficacious in the general population.

Conclusions: This study provides preliminary data that both EUA mRNA vaccines were generally safe and well tolerated in an allogeneic HCT population despite some limitations.
</td></tr>
<tr><td>4</td><td>
Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021; 137(23):3165-73.

Abstract: Patients with CLL have an increased risk for severe COVID-19 disease and mortality. The goal of this study (NCT04746092) was to determine the efficacy of COVID-19 vaccine in patients with CLL. We evaluated humoral immune responses to BNT162b2 mRNA COVID-19 vaccine in patients with CLL and compared responses with those obtained in age-matched healthy controls. Patients received two vaccine doses, 21 days apart, and antibody titers were measured using Elecsys Anti-SARS-CoV-2S assay after administration of the second dose. In a total of 167 patients with CLL the antibody response rate was 39.5%. A comparison between 52 patients with CLL and 52 sex- and aged-matched healthy controls, revealed a significantly reduced response rate among patients (52% vs 100%, respectively; adjusted odds ratio=0.010, 95% CI 0.001-0.162; p<0.001). Response rate was highest in patients who obtained clinical remission after treatment (79.2%), followed by 55.2% in treatment-naive and 16% only in patients under treatment at the time of vaccination. In patients treated with either BTK inhibitors or venetoclax +/- anti-CD20 antibody, response rates were considerably low (16.0% and 13.6%, respectively). None of the patients exposed to anti-CD20 antibodies <12 months prior to vaccination responded. In a multivariate analysis, the independent predictors of response were younger age, females, lack of currently active treatment, IgG levels >=550 mg/dL and IgM levels >=40mg/dL. In conclusion, antibody-mediated response to BNT162b2 mRNA COVID-19 vaccine in patients with CLL is markedly impaired and affected by disease activity and treatment.
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</table>

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Pregnancy and Lactation
5	***Collier A-RY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. JAMA 2021; 325(23):2370-80.*** Abstract: Pregnant women are at increased risk of morbidity and mortality from COVID-19 but have been excluded from the phase 3 COVID-19 vaccine trials. Data on vaccine safety and immunogenicity in these populations are therefore limited. Objective: To evaluate the immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women, including against emerging SARS-CoV-2 variants of concern. Design, Setting, and Participants: An exploratory, descriptive, prospective cohort study enrolled 103 women who received a COVID-19 vaccine from December 2020 through March 2021 and 28 women who had confirmed SARS-CoV-2 infection from April 2020 through March 2021 (the last follow-up date was 26 March 2021). This study enrolled 30 pregnant, 16 lactating, and 57 neither pregnant nor lactating women who received either the mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines and 22 pregnant and 6 nonpregnant unvaccinated women with SARS-CoV-2 infection. Main Outcomes and Measures: SARS-CoV-2 receptor binding domain binding, neutralizing, and functional non-neutralizing antibody responses from pregnant, lactating, and nonpregnant women were assessed following vaccination. Spike-specific T-cell responses were evaluated using IFN-gamma enzyme-linked immunospot and multiparameter intracellular cytokine-staining assays. Humoral and cellular immune responses were determined against the original SARS-CoV-2 USA-WA1/2020 strain as well as against the B.1.1.7 and B.1.351 variants. Results: This study enrolled 103 women aged 18 to 45 years (66% non-Hispanic White) who received a COVID-19 mRNA vaccine. After the second vaccine dose, fever was reported in 4 pregnant women (14%; SD, 6%), 7 lactating women (44%; SD, 12%), and 27 nonpregnant women (52%; SD, 7%). Binding, neutralizing, and functional non-neutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in pregnant, lactating, and nonpregnant women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Binding and neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants. Conclusion and Relevance: In this exploratory analysis of a convenience sample, receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.
6	***Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Efficient maternofetal transplacental transfer of anti-SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis 2021: ciab266. doi: 10.1093/cid/ciab266. (Accepted manuscript).*** Maternal and cord blood sera were collected from 20 parturients who received the BNT162b2 vaccine. All women and infants were positive for anti S- and anti-RBD-specific IgG. Cord blood antibody concentrations were correlated to maternal levels and to time since vaccination. Antenatal SARS-CoV-2 vaccination may provide maternal and neonatal protection.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
7	***Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest 2021; 131(13):e150319.*** Background: The significant risks posed to mothers and fetuses by COVID-19 in pregnancy have sparked a worldwide debate surrounding the pros and cons of antenatal SARS-CoV-2 inoculation, as we lack sufficient evidence regarding vaccine effectiveness in pregnant women and their offspring. We aimed to provide substantial evidence for the effect of BNT162b2 mRNA vaccine versus native infection on maternal humoral, as well as transplacentally acquired fetal immune response, potentially providing newborn protection. Methods: A multicenter study where parturients presenting for delivery were recruited at 8 medical centers across Israel and assigned to three study groups: vaccinated (n = 86); PCR confirmed SARS-CoV-2 infected during pregnancy (n = 65), and unvaccinated non-infected controls (n = 62). Maternal and fetal blood samples were collected from parturients prior to delivery and from the umbilical cord following delivery, respectively. Sera IgG and IgM titers were measured using Milliplex MAP SARS-CoV-2 Antigen Panel (for S1, S2, RBD and N). Results: BNT162b2 mRNA vaccine elicits strong maternal humoral IgG response (Anti-S and RBD) that crosses the placenta barrier and approaches maternal titers in the fetus within 15 days following the first dose. Maternal to neonatal anti-COVID-19 antibodies ratio did not differ when comparing sensitization (vaccine vs. infection). IgG transfer rate was significantly lower for third-trimester as compared to second trimester infection. Lastly, fetal IgM response was detected in 5 neonates, all in the infected group. Conclusions: Antenatal BNT162b2 mRNA vaccination induces a robust maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
8	***Kelly JC, Carter EB, Raghuraman N, et al. Anti-SARS-CoV-2 antibodies induced in breast milk after Pfizer-BioNTech/BNT162b2 vaccination: Am J Obstet Gynecol. 2021: S0002-9378(21)00211-8. doi: 10.1016/j.ajog.2021.03.031.*** Objective: In December 2020, 2 lipid nanoparticle-formulated, nucleoside-modified messenger RNA–based vaccines received emergency use authorization by the US Food and Drug Administration, after their trials demonstrated 94% to 95% efficacy in preventing COVID-19. Although no lactating people were included in the vaccine trials, national organizations support vaccination of this population, suggesting potential infant protection by passive transfer of maternal antibodies. The authors sought to characterize breast milk levels of anti–SARS-CoV-2 antibodies in lactating people undergoing COVID-19 vaccination. Study Design: Participants were prospectively recruited during phase IA rollout of the COVID-19 vaccine at a tertiary care center, after institutional review board approval. Inclusion criteria included lactation and planned vaccination with the Pfizer-BioNTech BNT162b2 vaccine. After obtaining informed consent, participants provided frozen breast milk samples at the following time points of vaccination: before, within the first 24 hours, and the following week. Samples were assessed for SARS-CoV-2 RNA by quantitative real-time polymerase chain reaction and antispike IgG and IgA by an enzyme-linked immunosorbent assay. Results: A total of 5 subjects and 29 human milk samples were included in the analysis. All prevaccine milk samples tested negative for SARS-CoV-2 RNA, as defined by the cycle threshold value of >40 for the N1 target. Antispike IgG and IgA levels were significantly elevated relative to the prevaccine baseline at all time points. Antispike protein IgG remained sustained at a significant elevation beginning at 20 days after the first dose compared with the prevaccine baseline (P=.0061), through the final milk sample (day 30–39 P=.0095, >40 days P=.0040. Levels of antispike protein IgA were significantly elevated from baseline, starting 2 weeks after the first dose (P=.0286) through to the final sample (day 20–29 P=.0121, day 30–39 P=.0095, >40 days P=.0040); however, individual level data suggest a possible gradual decline in antispike IgA in human milk over time after the second dose. Conclusions: The Authors characterized longitudinal breast milk levels of antispike IgG/A following Pfizer-BioNTech BNT162b2 vaccination, demonstrating sustained elevation of IgG/IgA levels. This response is similar to previous studies on maternal vaccination, which have shown high levels of breast milk IgA/G production for up to 6 months after vaccination for influenza and pertussis. A concurrent decrease in infant respiratory illness rates suggest that maternal vaccination confers protection against infection in breastfed infants. Thus, the Pfizer-BioNTech/BNT162b2 vaccination may also confer protection against COVID-19 to breastfed infants as well. Our study is limited by a small number of participants, but we report data that suggest a potential immune benefit to infants of lactating people up to 80 days after COVID-19 vaccination. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination.

Table 14. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Thrombosis and Intracranial Haemorrhage
9	***Shimazawa R, Ikeda M. Potential adverse events in Japanese women who received tozinameran (BNT162b2, Pfizer-BioNTech). Journal of Pharmaceutical Policy and Practice 2021: 14(1)*** Reports of CVST and intracranial haemorrhage (ICH) following the administration of coronavirus vaccines have raised concerns regarding their safety. Although no regulatory authority has recognized ICH as an adverse event associated with tozinameran (BNT162b2, Pfizer-BioNTech), fatal and non-fatal cases have been reported. In Japan, 10 fatal cases (five men and women) have been reported to date. Four of the five women died of ICH and the other died of aspiration pneumonia, whereas all five men died of causes other than stroke. This imbalance is incompatible with the mortality data on cardiovascular diseases in the National Statistics, which show no apparent disparity between sexes or between haemorrhagic and ischemic stroke. Cumulatively, our analysis reveals a disproportionately high incidence of death by ICH in Japanese women who received tozinameran, suggesting a potential association of ICH with the vaccine. Although we understand that the benefits of tozinameran still outweigh the risks, we believe that a causal link with the vaccine is not proven but possible and warrants further analysis.

Interval data about the use of BNT162b2 in:

- Frail subjects are summarized in Section 16.3.5.7 *Use in Frail Patients with Co-Morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis)*. Use in frail subjects is described in Section 5.1 *Pharmacodynamics properties* of the RSI;
- Pregnancy and during breastfeeding are summarized in Section 16.3.5.3 *Use in Pregnant/Lactating Women.* Use in pregnancy and lactation is described in Section 4.6 *Fertility pregnancy and lactation* of the RSI.
- For Lymphopenia (Section 15.1) and Thromboembolic events (Section 16.2.1) no additional risks minimizations activities are warranted at this time.

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.

12. 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.

A complete list of SMSRs prepared and submitted by the MAH is provided below.

SMSR Number	Reporting Period
1	01 December 2020 through 31 December 2020
2	01 January 2021 through 31 January 2021
3	01 February 2021 through 28 February 2021
4	01 March 2021 through 31 March 2021
5	01 April 2021 through 29 April 2021
6	30 April 2021 through 31 May 2021

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

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

14. LATE-BREAKING INFORMATION

After the DLP, based on the Signal of Myocarditis and pericarditis for COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY (EPITT No. 19712) - EMA/PRAC/325882/2021 recommendation dated 08 July 2021, the MAH updated the RSI (CDS version 5.0 dated 14 July 2021) and EU-SmPC to include information about myocarditis and pericarditis following vaccine administration and has distributed a DHPC to address these findings. The DHPC was distributed starting from 19 July 2021 to all EU member states where the respective vaccines are authorised. The EU-RMP was accordingly updated (version 2.3) and was submitted to EMA on 06 August 2021. With respect to approved version 2.0, the list of safety concerns was updated with the inclusion of myocarditis and pericarditis as important identified risk and the Pharmacovigilance plan was consequently updated.

After DLP, Immune thrombocytopenia was closed and categorized as no risk, Trigeminal neuralgia and Hypertensive crisis with intracranial haemorrhage were closed as non-validated signals.

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

Signals that were detected for BNT162b2 and are ongoing or closed during the reporting interval are presented in Table 15. Appendix 3 provides a summary of the safety signals that were ongoing or closed during the reporting interval. See Section 16.2.1 for evaluation of signals that were closed during the reporting interval and Section 16.3 for evaluation of new information for known risks not considered to constitute a newly identified signal.

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Anaphylaxis	Closed	Inquiry from a competent authority	Important Identified risk	EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Hyperhidrosis	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Night sweats	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Asthenia	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Lethargy	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Decreased appetite	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia)[a]	Closed	Routine Pharmacovigilance, Inquiry from a competent authority	Identified risk[b]	EMEA/H/C/005735/II/0038/G, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Diarrhea	Closed	Clinical study data, Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Pain in extremity (arm)	Closed	Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Vomiting	Closed	Clinical study data, Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Hypersensitivity, other than anaphylaxis	Closed	Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Seizure	Closed, Refuted	Inquiry from a competent authority	No risk	-
Thromboembolic events	Closed, Refuted	Inquiry from a competent authority	No risk	-
Delayed skin reaction	Closed, Refuted	Scientific Literature, Inquiry from a competent authority	No risk	-

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Delayed syncope	Closed, Refuted	Inquiry from a competent authority	No risk	-
Eye pain and eye swelling	Closed, Refuted	Inquiry from a competent authority	No risk	-
Herpes zoster, including ophthalmic herpes zoster	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Appendicitis	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Hearing loss and Tinnitus	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Extensive swelling of the limbs	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002.3
Reaction associated with dermal fillers	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/SDA/023 (EPITT ref. 19674), EMEA/H/C/005735/MEA/002.2
Injection site pruritus	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1
Insomnia	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Overdose[d]	Closed, Refuted	Routine Pharmacovigilance	No risk	-
Deaths (including elderly or frail individuals)[e]	Closed, Refuted	Inquiry from a competent authority	No risk	-
Facial nerve palsy	Closed, Refuted	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Immune thrombocytopenia[f]	Ongoing	Inquiry from a competent authority	Not yet determined	PAM-SDA-034 (EPITT No.: 19680).

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Trigeminal neuralgia[g]	Ongoing	Inquiry from a competent authority	Not yet determined	-
Myocarditis and pericarditis[h]	Ongoing	Inquiry from a competent authority	Not yet determined	EMA/PRAC/325882/2021 PAM-SDA-032 (EPITT No. 19712)
Hypertensive crisis with intracranial haemorrhage[i]	Ongoing	Inquiry from a competent authority	Not yet determined	-

a. In Appendix 3, Dizziness, Tachycardia and Paraesthesia appear as individual signals determined to be risk.
b. Added to CDS and local labels as potential symptom of Vaccination stress-related response in the Warnings and Precautions section (not ADR section). Identified risk for the process of vaccination rather than the vaccine substrate. CDS, Section 4.4 updated to enhance the providers understanding to take precautions and to differentiate stress/anxiety related reactions versus anaphylaxis reactions.
c. No risk in the CDS; identified risk in the EU-SmPC.
d. Interval reporting period data are summarized in Section 16.3.4.2 *Overdose*.
e. Interval reporting period and cumulative data are summarized in Section 16.3.4.1 *Death* and in Section 16.3.4.1.1 *Death Review by Age Group*.
f. Closed after the PSUR DLP on 04 August 2021 as no risk.
g. Closed after the PSUR DLP on 02 July 2021 as non-validated signal.
h. Closed after the PSUR DLP on 30 June 2021 as Important identified risk.
i. Closed after the PSUR DLP on 30 June 2021 as non-validated signal.

Post-approval regulatory requests (worldwide)

According to the corePSUR19 guidance[43]

- Safety reviews requested by health authorities in the context of the SMSRs and considered as non-validated signals (hypoglycaemia and serious hypertension) or as safety topics (lymphopenia and haemophagocytic syndrome) are in Appendix 6A.1 through Appendix 6A.4. The HA requests, the search criteria and the conclusions are noted below for convenience of review.[44]

- Additional safety reviews requested in the context of any other regulatory procedure or for which the MAH committed to closely monitor (immune thrombocytopenia, hearing loss and tinnitus, serious arrhythmias, acute pancreatitis, acquired haemophilia and menstrual disorders) are in Appendix 6B.1 through Appendix 6B.6.[45]

Continued monitoring or a cumulative review was requested by a competent authority or in a previous SMSR of the following unlisted events/topics that a competent authority did not consider a signal and were also determined to not be a safety signal by the MAH.

Factors that were considered in coming to this conclusion included one or more of the following:

- Whether the AE is new for the product;

- Seriousness, severity, increased frequency or medical significance of the data;

- High or rapidly increasing statistical disproportionality score;

- Potential public health impact;

- Factors suggestive of a relationship to the drug when considering disease knowledge, biological plausibility, mechanism of action of the vaccine or the vaccine class, alternative etiologies based on clinical and scientific experience, and temporal clustering of events.

15.1. Lymphopenia

In the final AR of the 2nd SMSR (01 January 2021 – 31 January 2021), the MAH was requested to "provide a cumulative review of lymphopenia (including cases from post-

[43] https://www.ema.europa.eu/en/documents/scientific-guideline/consideration-core-requirements-psurs-covid-19-vaccines_en.pdf

[44] PBRER criteria applied.

[45] Search by generic name.

marketing experience, clinical trial data, as well as relevant literature). Based on this review, the need for a PI update should be discussed."

- Search Criteria: PT Lymphopenia.

See Appendix 6A.1 for details.

Conclusion

Transient lymphopenia is an expected association with immunization due to migration of lymphocytes from the bloodstream to lymphoid tissues as part of the expected immune response to the vaccine.[46] Upon review of the fatal and non-fatal cases, a transient decrease in lymphocytes was reported in 38 out of 73 cases however, most cases involved patients with underlying conditions (such as thrombocytopenia, urinary tract infection, COVID-19), malignancies (prostate cancer), and/or other chronic diseases (arthritis, rheumatoid arthritis, atrial fibrillation, arterial hypertension), which should be taken into account. Based upon review of the available information from non-clinical, clinical phase 1 and post-authorization, no new significant safety information has emerged. No additional change to the RSI is warranted at this time. Safety surveillance will continue.

15.2. Immune thrombocytopenia

The MAH reviewed this topic in the 3rd SMSR (01 February 2021 – 28 February 2021), and committed to review of this topic again in the upcoming PSUR.

Assessed under the regulatory procedure PAM-SDA-034 (EPITT No. 19680).

- Search criteria: HLT Thrombocytopenias.

See Appendix 6B.1 for details.

Conclusion

This review of thrombocytopenia consists of clinical study data, post-authorization 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. 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

[46] Vogel AB, Kanevsky I, Che Y, et al. BNT162b vaccines protect rhesus macaques from SARS-CoV-2. Nature 2021;592(7853):283-9. doi: 10.1038/s41586-021-03275-y. Epub 2021 Feb 1. PMID: 33524990.

totality of the data, thrombocytopenia is not determined to be a causally associated adverse effect of the vaccine. Routine pharmacovigilance will continue.

15.3. Hearing Loss and Tinnitus

The MAH reviewed these topics in the 3rd SMSR (01 February 2021 – 28 February 2021), and committed to review of this topic again in the upcoming PSUR. In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), considering the report raised recently by UMC on this issue for COVID-19 vaccines, the number of cases that are being received occurring soon after vaccination, and some positive rechallenges after the second dose, a review is expected in the upcoming PSUR.

- Search criteria: HLT: Hearing loss and PT Tinnitus

See Appendix 6B.2-1 and Appendix 6B.2-2 for details.

Conclusion

Hearing loss, including deafness and sudden hearing loss, have been reported following vaccination with BNT162b2 vaccine.

Out of a total of 980 cases, most spontaneous cases of hearing loss are confounded by a medical history reporting a pre-existing ear disorder or other significant clinical risk factors (as acoustic neurinoma, tympanoplasty, autoimmune disorder and cancer). A bucket of 124 cases reported hearing loss in the context of other adverse events that may explain the symptomatology (eg, cerebrovascular accident, encephalitis, infections).

A total of 2499 subjects reported tinnitus. Among these cases there were 558 reports confounded by a medical history reporting a pre-existing ear and/or autoimmune/infection disorder (tinnitus, deafness, acoustic neurinoma, COVID infection, autoimmunity, etc) and additional 638 cases describing tinnitus in the context of different diseases known to be associated with tinnitus (as cerebrovascular accident, facial paralysis, migraine, blood pressure issues etc). All other cases reported insufficient information to perform a meaningful assessment.

Clinical study results do not demonstrate an imbalanced number of events between placebo and vaccine. At this time, statistical signal detection in the safety database has not shown a signal of disproportionate reporting for hearing losses and tinnitus. Further, O/E analysis does not suggest an increased rate for these topics.

Given the totality of the available information, a causal association with the vaccine is unlikely for hearing loss and for tinnitus and changes to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable.

15.4. Hypoglycaemia

In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested to "discuss hypoglycaemia not only limited in patients with diabetes type 1 after vaccination with Comirnaty."

- Search Criteria: SMQ Hypoglycaemia (Narrow).

See Appendix 6A.2 for details.

Conclusion

Upon review of the fatal and non-fatal cases, most cases involved patients with underlying conditions including other chronic diseases (such as diabetes mellitus- type 1 and type 2, hypothyroidism, disease risk factor, chronic kidney disease, cardiac failure and, hypoglycaemia), which should be taken into account. Based upon review of the available information, no new significant safety information has emerged. No additional change to the RSI is warranted at this time. Safety surveillance will continue.

15.5. Serious Hypertension

In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested "to perform a cumulative review focused on serious hypertension, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of any plausible mechanisms, the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable. Any findings from the MAH's review of stress/anxiety related reactions should be taken into account, if relevant."

- Search Criteria: HLT Accelerated and malignant hypertension (Primary Path).

See Appendix 6A.3 for details.

Conclusion

There is no plausible mechanism to explain any sustained elevated serious hypertension caused by BNT162b2. The topic of serious hypertension has emerged as a concern for some COVID-19 vaccines and is being carefully monitored for BNT162b2. In 32% of the post-marketing cases, events indicative of anxiety stress related reactions was co-reported and coded to the PTs Dizziness, Dyspnoea, Paraesthesia, and Tachycardia. No other safety signals have emerged based on a review of these cases and of the O/E analysis performed. No labelling change is needed at this time. Surveillance will continue.

15.6. Haemophagocytic Syndrome

In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested "to provide a review of cases suggestive of Haemophagocytic syndrome (aka macrophage activation syndrome). Upon evaluation of the causative role alternative aetiologies such as genetic predisposition, viral infections (e.g. EBV, SARS-CoV2), concomitant medication should be taken into account."

- Search Criteria: PT Haemophagocytic lymphohistiocytosis.

See Appendix 6A.4 for more details.

Conclusion

Soy M, et al.[47] indicated that haemophagocytic syndrome or haemophagocytic lymphohistiocytosis is an acute and rapidly progressive systemic inflammatory disorder characterized by cytopenia, excessive cytokine production, and hyperferritinemia. It may be triggered by genetic conditions, infections including COVID-19, malignancies, autoimmune-autoinflammatory diseases, and some drugs. Upon review of these 10 cases, most cases involved patients with poor underlying conditions, including viral infection (such as herpes zoster, mononucleosis, EBV, COVID-19), malignancies (such as B lymphoma, breast cancer), and/or other chronic diseases, which should be taken into account. No new significant safety information has emerged. Safety surveillance will continue.

15.7. Serious Arrhythmias

In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), the MAH was requested to perform a cumulative review focused on serious arrythmia, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable.

- Search criteria: PT Arrythmia.

See Appendix 6B.3 for details.

Conclusion

The MAH has reviewed cases reported and conducted unadjusted O/E analyses for spontaneous reports on Arrythmia as of 18 June 2021 stratified by various risk windows. Serious arrythmias events, occurred in patients with an underlying heart-rhythm conduction disorder such as medical history of tachycardia, bradycardia, extrasystole, cardiac pacemaker insertion atrial flutter etc and/or concomitant medication such as amlodipine, atorvastatin, levothyroxine in over one third of the cases reported (289 out of 777 cases). Arrythmia has not been identified as a signal and routine monitoring will continue.

15.8. Acute Pancreatitis

In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), the MAH was requested to perform a cumulative review focused on serious acute pancreatitis, including details of any underlying condition(s) (including COVID-19), time to onset, duration and outcome, together with an assessment of the causal relationship with the vaccine and a discussion on the need to update the product information, if applicable. The MAH should also make every effort to document such cases as the lack of information could preclude concluding on the causal relationship between the vaccine and pancreatitis.

[47] Soy M, Atagündüz P, Atagündüz I, et al. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. Rheumatology International 2021, 41: 7- 18

- Search criteria: PT Pancreatitis acute.

See Appendix 6B.4 for details.

Conclusion

Pancreatitis has been spontaneously reported following vaccination with BNT162b2 in the post-authorization setting. Of the total 65 cases as of 18 June 2021, 27 reported relevant medical history of alcoholism, pancreatitis, biliary pathologies, hypercholesterolaemia, HIV infection, intraductal papillary mucinous neoplasm, suspected COVID-19 infection, and diabetes mellitus possibly contributing to the development of pancreatitis. Additionally, seven (7) cases reported pancreatitis in the context of other diagnoses: cholelithiasis, increased bilirubin, unspecified infections, COVID-19, and hypertriglyceridaemia. Eight (8) cases reported the concomitant medications which may also contribute to pancreatitis. Four cases of pancreatitis were reported on the same day; 1 case within 5 minutes and 3 cases within few hours. Sixteen cases reported negative COVID-19 test results, three cases reported positive COVID-19 test results, while, majority of cases did not provide COVID-19 testing.

The totality of the reviewed information does not support a causal association between the vaccine and pancreatitis for the following reasons: there is not a clear mechanism of action to explain why vaccinated individuals may have an increased risk for pancreatitis and there is a lack of literature linking any vaccination to the occurrence of pancreatitis, there are a relatively low number of reports of pancreatitis in the context of about 642 million of BNT162b2 doses administered in the post-authorization setting and no imbalance in reporting of pancreatitis between vaccine and placebo groups in Study C4591001. The benefit risk profile of the vaccine remains favorable. Routine signal detection activities will continue.

15.9. Acquired Haemophilia

In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), it was stated that several cases of Acquired haemophilia have been reported: 3 in France and 1 in Ireland. In the literature, 1 case has also been described at day 9 of vaccination with Comirnaty vaccine in a 69-year-old patient. Four other cases have also occurred in other countries (global data via Vigibase, as well as UK data via Vigibase). Considering that this is a very rare and serious event, and that the role of the vaccine in the occurrence of these autoantibodies to factor VIII ("acquired haemophilias") cannot be excluded, the MAH is requested to review this in the upcoming PSUR.

- Search criteria: HLT Coagulation factor deficiencies.

See Appendix 6B.5 for details.

Conclusion

The search of the safety database identified 11 cases, all reported as serious. Seven of the 11 reports included details in the medical history regarding medical conditions and diseases under treatment that could predispose to AHA (cancer, rheumatoid arthritis, chronic kidney

failure, nephroangiosclerosis, diabetes mellitus and hypothyroidism). One case reported pruritus evolving long before the administration of the vaccine, and the two cases from non-interventional studies had insufficient information on patient's medical history, background diseases, and concomitant medications. In the remaining case, it is unclear whether there was a history of prolonged bleeding prior to vaccination.

In aggregate, all the cases (except 1 case with age not reported) occurred in elderly patients greater than 65 years, who are the most predisposed to AHA, with the majority of these patients having associated comorbidities.

The O/E ratio did not exceed 1 over either risk window for either endpoint.

Overall, the analysis does not support a causal association between vaccination and acquired hemophilia. Routine monitoring will continue.

15.10. Menstrual Disorders

In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), it was stated that a number of queries have been received about menstrual disorders, especially menorrhagia. This issue merits further investigation in the upcoming PSUR which, may be a matter of concern for young women, a review is expected in the upcoming PSUR.

In the preliminary AR of the 7th SMSR (01 June 2021 – 30 June 2021) this additional request is reported.
In accordance with the LoQ of the 5th MSSR, the MAH will provide a review on Menstrual disorders in the PSUR to be submitted in August 2021. The MAH is requested to include in this PSUR review a separate 'post-marketing cases evaluation' of the cases reporting a menstrual disorder, which should also include a sub-analysis of cases divided between post-menopausal cases and menstrual disorder cases. Causality assessment should be provided per case for at least the serious cases. SmPC and/or RMP changes with regards to menstrual disorders should also be discussed, supported with clinical data and data from literature. In addition, an O/E analysis, with sensitivity analysis to compensate for backlog cases, for Menstrual disorders, including an age-stratified analysis which separates females of childbearing age from post-menopausal aged women, should also be performed by the MAH. The MAH should use a cut-off date after the DLP of the PSUR, as accurate as possible, in order to provide properly above requested data in the PSUR.

- Search criteria: HLGT of Menstrual cycle and uterine bleeding disorders (Primary path).

See Appendix 6B.6 for details.

Conclusion

Recent studies have demonstrated that a sizable proportion of women have experienced menstrual cycle disturbances because of the COVID-19 pandemic. In one study, almost half of the women reported periods that were heavier and painful compared to before the pandemic. These are likely to be associated with psychological distress and stress related to

the pandemic, weight gain, longer working hours, and dietary changes. Stress and stress hormones have an inhibitory effect on the GnRH release from the hypothalamus.[48]

A review of adverse events reported during the blinded placebo-controlled follow-up period in the pivotal clinical trial did not reveal any imbalance in the incidence of reporting of menstrual cycle and uterine bleeding disorders between participants receiving BNT162b2 and those receiving placebo.

Many of the cases retrieved from the search of the safety database were significantly confounded by their past/concurrent medical conditions or lack of reported clinical information with which to assess a potential relationship. In aggregate, most of the reports (n = 1886, 77.7%) occurred in women between 18 and 50 years of age, with most of these cases reporting a prior history of suppressed lactation, contraceptive usage, or previous history of menstrual abnormality.

Analysis of serious cases showed that 3.4% of all serious cases reported menstrual irregularities that resulted in hospitalization. The majority of these few cases were confounded by relevant medical history while others had limited information.

The few numbers of cases of thrombocytopenia associated with menorrhagia suggests that thrombocytopenia, regardless of etiology, is not a commonly co-reported event with metrorrhagia following COVID-19 vaccination with BNT162b2.

Overall, this analysis does not support a causal association between vaccination and menstrual alteration in women. There is compelling alternative explanation for menstrual irregularity during these pandemic times, as is supported by the lack of imbalance in a large placebo-controlled clinical trial with over 42000 participants, where approximately half were women. Additionally, there is neither significant literature nor post marketing data that supports a causal association. Routine monitoring will continue.

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 16 summarizes the important risks and missing information for BNT162b2 at the beginning of the reporting interval.

Table 16. 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. COPD, diabetes, chronic neurological disease, cardiovascular disorders)

[48] Phelan N, Behan LA, Owens L. The impact of the COVID-19 pandemic on women's reproductive health. Front Endocrinol 2021;12:642755. doi: 10.3389/fendo.2021.642755.

Table 16. Ongoing Safety Concerns

Missing information (Cont'd)	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

As per EU RMP ver. 1.0 (dated 21 December 2020).

Proposed changes to the safety concerns are detailed in Section 16.4 *Characterisation of Risks*.

16.2. Signal Evaluation

Please refer to Table 15 for signals that were ongoing and closed during the reporting interval.

16.2.1. Evaluation of Closed Signals

16.2.1.1. Evaluation of Closed Signals During the Reporting Interval Assessed under any Regulatory Procedure

- **Signals Determined to be Important Identified Risks**

Anaphylaxis (EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

- **Signals Determined to be Identified Risks (Not Categorized as Important)**

Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia) (EMEA/H/C/005735/II/0038/G, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

Diarrhoea (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

Pain in extremity (arm) (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

Vomiting (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

Asthenia, lethargy, decreased appetite, hyperhidrosis, night sweats (EMEA/H/C/005735/II/0036)

Hypersensitivity (other than anaphylaxis) (EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

- **Signals Determined Not to be Risks**

Extensive swelling of the vaccinated limb[49] (EMEA/H/C/005735/MEA/002.3)

Insomnia (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

Reaction associated with dermal fillers [EMEA/H/C/005735/SDA/023 (EPITT ref. 19674), EMEA/H/C/005735/MEA/002.2]

Injection site pruritus (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1)

Facial nerve palsy (EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2)

16.2.1.2. Evaluation of Closed Signals During the Reporting Interval not Assessed as part of any Regulatory Procedure

Signals that were evaluated and closed as refuted during the reporting interval are updated to the end date of the PSUR reporting period and summarized below.

- **Signals Determined to Not be Risks**

1) Seizure
   a) Evaluation
      i) Source

      Seizure was triggered as a safety signal as a result of a) a PRAC request for review of topic for the monthly SMSR, b) a request by the Saudi Arabia HA to review this topic as a safety signal, and c) request by the MHRA to review this as a safety topic. An evaluation was included in the 5th SMSR. The evaluation concluded that a causal association between the COMIRNATY vaccine and seizure could not be established, and that it would continue to be monitored.

      ii) Data

      Cumulatively (through 18 June 2021) there were a total of 1879 cases from the MAH safety database that reported events contained in the MedDRA SMQ (v. 24.0) "Generalised convulsive seizures following immunisation", narrow search. The most frequently reported PTs (> 9 %) were as follows:

SOC	Preferred Term	n/ (%)
Nervous system disorders	Seizure	1174/ (62.48%)
Nervous system disorders	Epilepsy	424/ (22.57%)
Nervous system disorders	Headache	318/ (16.92%)

[49] This wording reflects the CHMP Rapporteur's AR; the signal is reported in Table 15 as Extensive swelling of the limbs.

SOC	Preferred Term	n/ (%)
General disorders and administration site conditions	Pyrexia	277/ (14.74%)
General disorders and administration site conditions	Fatigue	203/ (10.80%)
Nervous system disorders	Dizziness	193/ (10.27%)
Nervous system disorders	Loss of consciousness	192/ (10.22%)
Nervous system disorders	Generalised tonic-clonic seizure	175/ (9.31%)

Most cases were reported from the UK (25.7% [482)]), followed by the US (15.1% [284]), Mexico (8% [150]), France (6.5% [122]) and Japan (6.3% [119]).

There were 1107 females, 698 males and for 74 subjects the gender was not reported. Age ranged between 1 to 107 years with a mean age of 50.7 years. There were 46 subjects ≤ 17 years of age, 1144 subjects from 18 to 64 years and 519 subjects 65 years and above. In 170 subjects the age was unknown.

In 1464 cases the relevant event was reported after a single dose, as follows: after Dose 1 in 944 cases, after Dose 2 in 519 cases and after Dose 4 in 1 case. In 42 cases the relevant event was reported after both vaccine doses.

Time to onset of the relevant event was reported as follows: unspecified time following vaccination (1115 cases), ≤ 1 day (565 cases), 1 to 7 days (24 cases), >7 days to < 1 month (23 cases), > 1 month to < 6 months (14 cases) and unknown (664 cases). In 112 cases the event was reported pre-therapy.

In 337 cases a nervous system disorder was reported as a medical history including 1050 events. Most frequently reported was epilepsy (or related events) (398), a form seizure (156), a dementia type disorder (84), a cerebrovascular accident or disorder (57), and stroke-type of events (54).

The O/E analyses (cumulative through 18 June 2021) of clinical trial and spontaneously reported seizures/convulsion/seizure disorders (inc. febrile) was 0.099 (95% CI: 0.094, 0.104) for the 14-day risk window and 0.069 (95% CI: 0.065, 0.072) for the 21-day risk window.

Statistical signal detection in the safety database has not shown a signal of disproportionate reporting for Seizure.

iii) Outcome

Overall, based on review of the totality of the available information (through 18 June 2021), the conclusions of the previous in-depth evaluation of seizure remain unchanged in that there is insufficient evidence to establish association between the vaccine and seizure and related events. The event will continue to be monitored and re-evaluated as warranted. The benefit risk profile of the vaccine remains favourable.

2) Thromboembolic events

a) Evaluation

i) Source

This signal was extensively reviewed in the 4th SMSR (01 March 2021 – 31 March 2021) and concluded not to be a risk caused by BNT162b2. It should be noted that the major types of thromboembolic events, such as stroke (ischemic and hemorrhagic), myocardial infarction and pulmonary embolism are AESI and are each reviewed independently.

ii) Data

The MedDRA version 24.0 search strategy used was: SMQ Embolic and Thrombotic Events (narrow).

In the placebo-controlled Phase 2/3 portion of Study C4591001 (data-lock date 13 March 2021), the table below shows subjects who reported thromboembolic events. Overall, there was no significant imbalance in these events between the vaccine and placebo groups.

Thromboembolic Preferred Term	Subjects receiving BNT162b2 (N = 21,926)	Subjects receiving Placebo (N = 21,921)
Acute myocardial infarction	3	2
Myocardial infarction	0	4
Amaurosis fugax	0	1
Retinal artery occlusion	0	1
Vascular stent occlusion	1	0
Cerebrovascular accident	3	0
Ischaemic stroke	1	1
Transient ischaemic attack	2	0
Cerebellar infarction	0	1
Cerebral infarction	0	1
Haemorrhagic stroke	0	1
Penile vein thrombosis	0	1
Pulmonary embolism	3	5
Deep vein thrombosis	5	3

Source: Data from Interim Clinical Study Report Protocol C4591001

The safety database was searched for BNT162b2 reports using the above search strategy cumulatively through 18 June 2021. There were 9088 cases reported, 106 from clinical studies, 8966 from spontaneous sources, 13 from other solicited sources and 3 from medical literature. Two percent of the cases were non-serious and 98% were serious. Of the 9088 cases, 5874 were from sources considered medically confirmed (eg, HCP or regulatory agencies), and 3214 were not medically confirmed.

The cases were comprised of 5162 (56.8%) females and 3723 (41.0%) males. Three of the cases were reported in very young paediatric subjects (7 days, 5 months and 15 months). These cases were individually reviewed.

1. A [redacted] old infant report described a [redacted] born to a mother who had received vaccine approximately 1 month before [redacted] birth. The [redacted] was reported to have been diagnosed with a left sylvian stroke < 3 days after delivery, however the circumstances of the pregnancy and delivery are not reported.

2. A 5-month-old breastfeeding boy whose mother received dose 2 the day before, developed a rash, refusal to eat, fever and elevated liver enzymes and was diagnosed with TTP. The child died an unspecified time later and no further information was provided.

3. Five (5) days following vaccination of [redacted] mother with dose 1, a [redacted] old breastfeeding [redacted] was noted to have decreased movement of [redacted] left hand and a downward turning of the left corner of [redacted] mouth. An extensive workup including brain MRI/MRA, abdominal ultrasound, echo and EEG failed to find an explanation. [redacted] was diagnosed with a TIA. Thrombocytopenia was also reported but no platelet count provided. The outcome of the hand and corner of the mouth was unknown while the other events resolved.

Excluding these 3 reports from age calculations, the remaining ages ranged from 13 to 102 years (mean 67.8, median 72). The youngest vaccinated person was a 13-year-old girl who reported "warm spots" on various areas of her arms and legs at an unspecified time after dose 1. She also complained of forgetfulness. There were no details to support the presence of a thromboembolic event in this individual.

Countries reporting >10% of the cases were: UK (1480, 16.3%), US (1291, 14.2%) and France (1177, 13.0%). The remaining countries in decreasing order of reports were Germany, Italy, Netherlands, Spain, Sweden, Japan and Norway. Case outcomes were fatal in 986 (10.8%) cases, unknown in 1341 (14.8%), not resolved in 2607 (28.7%) and resolved/resolving/resolved with sequela in 4154 (45.7%).

The 9088 cases contained 32,543 adverse events. The thromboembolic events most commonly reported were: Pulmonary embolism (19.6% of all AEs in the 9088 cases), Cerebrovascular accident (13.4%), Deep vein thrombosis (13.3%), Thrombosis (11.4%), Myocardial infarction (7.1%), Transient ischemic attack (5.8%), Ischaemic stroke (4.7%), Cerebral infarction (4.5%), Hemiparesis (3.8%), Thrombophlebitis superficial (2.3%) and Hemiplegia (2.0%).

The table below shows the thromboembolic events with an elderly to non-elderly occurrence ≥1.

Thromboembolic events (Preferred Term)	Number of cases with PT in Elderly	Number of cases with PT in non-Elderly
Splenic infarction	10	4
Acute myocardial infarction	189	87

Thromboembolic events (Preferred Term)	Number of cases with PT in Elderly	Number of cases with PT in non-Elderly
Coronary artery stenosis	11	5
Intracardiac thrombus	16	7
Myocardial infarction	405	196
Amaurosis	5	1
Retinal artery thrombosis	7	1
Retinal vascular occlusion	2	1
Retinal vascular thrombosis	11	5
Intestinal ischaemia	15	3
Vascular stent thrombosis	4	1
Hepatic infarction	4	1
Portosplenomesenteric venous thrombosis	3	1
Arteriovenous fistula thrombosis	3	1
Basal ganglia infarction	4	1
Basal ganglia stroke	4	1
Basilar artery occlusion	4	1
Basilar artery thrombosis	10	3
Carotid artery occlusion	14	4
Carotid artery stenosis	9	2
Carotid artery thrombosis	12	3
Cerebellar stroke	5	2
Cerebral artery embolism	14	5
Cerebral artery occlusion	10	3
Cerebral artery thrombosis	13	3
Cerebral infarction	335	57
Cerebral ischaemia	55	15
Cerebral small vessel ischaemic disease	2	1
Cerebral thrombosis	60	27
Cerebrovascular accident	808	325
Cerebrovascular disorder	19	2
Embolic cerebral infarction	9	2
Embolic stroke	33	6
Haemorrhagic stroke	56	11
Haemorrhagic transformation stroke	8	1
Hemiplegia	114	60
Ischaemic cerebral infarction	49	9
Ischaemic stroke	356	73
Lacunar infarction	16	6
Paraplegia	6	2
Quadriplegia	5	1
Thalamic infarction	11	3
Thalamus haemorrhage	5	1
Thrombotic stroke	13	3
Transient ischaemic attack	362	142
Vertebrobasilar stroke	2	1
Renal artery thrombosis	2	1
Pulmonary artery thrombosis	10	2
Pulmonary embolism	1181	524
Thrombolysis	2	1
Arterial occlusive disease	11	6
Arterial thrombosis	16	7

Thromboembolic events (Preferred Term)	Number of cases with PT in Elderly	Number of cases with PT in non-Elderly
Deep vein thrombosis	731	414
Embolism arterial	7	1
Haemorrhagic infarction	4	1
Infarction	21	3
Ischaemia	14	4
Obstructive shock	2	1
Pelvic venous thrombosis	14	6
Peripheral embolism	12	5
Peripheral ischaemia	16	6
Vena cava thrombosis	6	3
Venous thrombosis limb	70	32

iii) Outcome

The well controlled and randomized clinical trial did not demonstrate a signal for thrombotic events causally associated with the vaccine. As expected, the thromboembolic events that are most common in the worldwide population (eg, PE, DVT, MI, stroke) are the events most often reported. Likewise, many common adverse events can be expected to occur co-incidental to vaccination by chance alone. Many thromboembolic events are also AESI and, as such, they are monitored closely and are subject to more specific review and evaluation (eg, MI, Stroke, PE, DVT). Less commonly reported embolic and thrombotic events are monitored routinely and specifically when co-reported with thrombocytopenia, as part of surveillance for TTS. Based on this review, thromboembolic events are not identified as a causally associated risk for BNT162b2

3) Delayed skin reaction

a) Evaluation

i) Source

The safety topic was identified through scientific literature and per the MHRA question on 06 March 2021: "We have become aware of some reports internationally of delayed onset skin reactions with the mRNA vaccines. Having reviewed our own data there is only a limited amount of cases with an onset 7 days or more from vaccination, however, it would be helpful to have an idea of whether there is any further data from Pfizer/BioNTech which would be relevant to this, including any spontaneous reporting of delayed onset skin reaction or relevant AEs from the clinical trials with a delayed onset."

ii) Data

Delayed skin reactions were not a safety signal identified in the controlled clinical studies for BNT162b2.

The spontaneous BNT162b2 reports were searched cumulatively through 18 June 2021 for PTs within HLT Vaccination site reactions and latency per event reported from day 4 to day 8 post any dose. There were 1283 cases retrieved. In these 1283 cases the following relevant PTs were identified: Extensive swelling of

vaccinated limb, Shoulder injury related to vaccine administration, Vaccination site abscess, Vaccination site bruising, Vaccination site cellulitis, Vaccination site coldness, Vaccination site discharge, Vaccination site discolouration, Vaccination site discomfort, Vaccination site eczema, Vaccination site erosion, Vaccination site erythema, Vaccination site extravasation, Vaccination site granuloma, Vaccination site haematoma, Vaccination site haemorrhage, Vaccination site hypersensitivity, Vaccination site hypoaesthesia, Vaccination site induration, Vaccination site infection, Vaccination site inflammation, Vaccination site injury, Vaccination site irritation, Vaccination site joint discomfort, Vaccination site joint erythema, Vaccination site joint inflammation, Vaccination site joint movement impairment, Vaccination site joint pain, Vaccination site joint swelling, Vaccination site lymphadenopathy, Vaccination site macule, Vaccination site mass, Vaccination site movement impairment, Vaccination site necrosis, Vaccination site nodule, Vaccination site oedema, Vaccination site pain, Vaccination site papule, Vaccination site paraesthesia, Vaccination site pruritus, Vaccination site pustule, Vaccination site rash, Vaccination site reaction, Vaccination site recall reaction, Vaccination site swelling, Vaccination site thrombosis, Vaccination site urticaria, Vaccination site vesicles, Vaccination site warmth.

These 1283 cases that resulted from the search were reported from day 4 to day 8 post any dose.

The most commonly co-reported PTs in these cases were reactogenicity related events (eg, Headache, Fatigue, Myalgia, Pyrexia, etc).

When reported, the relevant events occurred post dose 1 in 576 cases and post dose 2 in 196 cases.

The AE duration per relevant event was not reported for events in 1094 cases. When reported, the duration was: from hours to 2 days for events in 74 cases, from > 2 days to 7 days for events in 99 cases, and >7 days to 31 days (1 month) for events in 20 cases; and longer than 1 month for events in 1 case.

When reported, the most commonly reported clinical outcome per the relevant event was Resolved/Resolving in 635 cases.

Based on the data reported, considering millions of doses of the vaccine administered, the majority of delayed skin reactions that occurred from 4 to 8 days after dosing, delayed skin reactions is not a signal at this time. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

4) Delayed syncope

a) Evaluation

i) Source

The signal of delayed syncope was reviewed in the 3rd SMSR based on a request from FDA CBER.

ii) Data

Clinical Trial C4591001, the Pfizer clinical database was searched for BNT162b2 adverse event reports from the safety data package (DLP 14 November 2020) used for the EUA, which is the last source of unblinded information available, containing PTs Loss of consciousness and Syncope (MedDRA v 23.1). Events that occurred on the day of vaccination (Day 1) were excluded as they are likely related to the vaccine or the blood draw procedure and do not address the question of delayed Syncope. Instead, events occurring between Day 2 and beyond after vaccination Dose 1 or 2 were identified. The data were analyzed as occurring between Day 2 to Day 7 and after day 7 for completeness.

The spontaneous BNT162b2 reports were searched cumulatively through 18 June 2021 for PTs Syncope and Loss of consciousness (LOC). There were 4930 cases retrieved. Cases with latency of 1 day and later were the focus of the review. This resulted in a total of 2390 cases. There were a total of 1430 cases reporting Syncope and 1137 cases reporting LOC (some cases reported both PTs). When reported, the relevant events occurred post dose 1 in 1176 cases and post dose 2 (with a latency of 1 day or later after dosing) in 852 cases.

The most commonly co-reported PTs in these cases were reactogenicity related events (eg, Dizziness, Headache, Nausea, Pyrexia, etc).

For the events of Syncope and LOC regardless of which dose of vaccine was received, the following is a breakdown on a total number of cases with Latency per the relevant event reported as 1 day and later:

- 1 day: 1465 cases;
- Days 2-5: 560 cases;
- Days 6-10: 167 cases
- Days 11-31: 174 cases;
- After day 31: remaining cases.

The largest of these datasets (latency 1 day = 1465 cases) was further analyzed for information on AE duration and AE outcome: the largest set was for unknown duration of the relevant event (in 1121 cases). The most commonly reported outcome was reported as resolved/resolving for relevant AEs in 1100 cases.

iii) Outcome

Based on the data reported, the majority of reports of syncope and loss of consciousness were reported one day following vaccination. Considering the totality of data, the signal of delayed syncope does not appear to be a risk and a causal association between the vaccine and these events cannot be confirmed. Routine PV monitoring will continue, and the signal will be re-opened if new relevant information becomes available.

5) Eye pain and Eye swelling

a) Evaluation

i) Source

The safety topic was reviewed following a request by the PRAC in the Assessment Report of the 1st SMSR (01 December 2020 through 31 December 2020) to assess if cases of eye swelling and eye pain were reported as single AEs or in the context of hypersensitivity reactions.

ii) Data

The safety database was searched for all reports using MedDRA 24.0 for the following search criteria: PTs: Eye pain, Eye swelling through 18 June 2021. The search criteria retrieved 2564 cases. There were 2007 females and 477 males and 80 cases where gender was not reported. Age ranged between 12 years to 100 years (mean: 47.4). Medical history was reported for 1419 cases. The vast majority of cases reported eye pain and/or eye swelling in the context of allergic reaction, anaphylaxis and/or angioedema. Many cases reported were co-reported with different reactogenicity events as pyrexia, headache, pain, swelling. A few cases reported eye pain and/or eye swelling associated with high blood pressure, facial paresis and/or paralysis, dermal filler reaction or associated with conjunctivitis.

iii) Outcome

Overall, no new safety signal has been identified. Eye swelling is considered listed in the context of angioedema/allergic reaction/anaphylaxis.

The analysis of this safety topic does not suggest a causal association as an independent event with BNT162b2 vaccine and no changes to the CDS are warranted.

6) Herpes zoster (including ophthalmic HZ)

a) Evaluation

i) Source

The topic of herpes zoster including ophthalmic herpes zoster has been closely monitored through the clinical studies and in the post-authorization period. In April 2021, SwissMedic requested a review of the topic and discussion as to whether product information needed to be adjusted.

ii) Data

The spontaneous BNT162b2 reports in the safety database were searched cumulatively through 18 June 2021 using the MedDRA version 24.0 for the following PTs: Herpes zoster; Herpes zoster infection neurological; Varicella zoster virus infection; Herpes zoster cutaneous disseminated; Herpes zoster oticus; Ophthalmic herpes zoster; Herpes zoster reactivation. There were 3450 cases retrieved.

Age ranged from 19 to 103 years (mean. 62.7 years). There were 2251 females, 1047 males and in 153 cases in which gender was not reported. Time to onset ranged

between the day of vaccination up to 109 days after vaccination. Duration, when reported, ranged between 1 day up to > 3 months after vaccination.

A total of 1578 cases did not provide any medical history. Of the remaining subjects, relevant medical history was reported for 1033 cases and included various conditions that may suppress or negatively affect one's immune status: previous herpes zoster infection, varicella infection, immunodeficiency, auto-immune diseases (diabetes, rheumatoid arthritis, hypothyroidism, cancer, previous confirmed or suspected COVID-19 infection). Case outcome was reported as resolved/resolving/resolved with sequel in 1657 cases, not resolved at the time of reporting in 1204 cases, unknown in 583 cases and fatal in 6 cases. In none of the fatal cases was the cause of death attributed to HZ infection or reactivation.

A signal of disproportionality (EB_{05}>2) was not noted during the weekly routine signal detection for BNT162b2 and herpes zoster.

iii) Outcome

In most cases, the information reported was not sufficient to perform a meaningful assessment and most cases did not report any performed evaluation to confirm the diagnosis. There were no signals of disproportionality for herpes zoster in routine signal detection. The upper limit of the 95% confidence interval for the O/E ratio did not exceed 1. An estimated 642 million of doses of BNT162b2 were administered globally through 18 June 2021.

In the final AR of the 7th SMSR (01 June 2021 – 30 June 2021), the MAH was requested to provide an updated age-stratified O/E analysis of Herpes zoster, with a sensitivity analysis to account for the backlog cases. The MAH is also requested to discuss possible mechanism that could underpin Herpes zoster reactivation following vaccination (MS1/MS4).

The MAH finds that there were 3426 processed cases (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*) and 766 unprocessed cases that comprise the PTs utilized for the observed number of herpes zoster cases (Herpes zoster, Ophthalmic herpes zoster, Herpes zoster reactivation, Herpes zoster infection neurological, Herpes zoster oticus, Herpes zoster cutaneous disseminated, Varicella zoster virus infection), for a total of 4192 cases used in the sensitivity analyses. Applying a background rate of 414.21/100,000 PY (Study C4591004), and assuming PY= 26,429,571, the O/E during a 21-day risk window remains less than <1 (O/E = 0.038, 95% CI [0.037, 0.039]). Age-specific O/E are not provided for this PSUR because age-specific background rates are not available in ACCESS. The MAH will look for other sources with this detail and will provide age-specific O/E in next monthly report as background rates allow.

Varicella zoster virus reactivation has been reported coincident with cases of COVID-19. It is theorized that lymphopenia associated with the infection may induce a reactivation (of herpes zoster) by affecting the T-cells' ability to mobilize a response to control varicella zoster virus. Following immunization for COVID-19, it could be

hypothesized that the humoral and cell-mediated immune responses stimulated by BNT162b2 vaccination, result in an alteration of the balance of T-cells with the end result being an inability to keep the infection in check and therefore, reactivation occurs.[50] 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. Routine signal detection activities will continue.

7) Appendicitis

a) Evaluation

i) Source

The safety topic was followed closely in C4591001 and reviewed in the post-authorization setting following a request by a regulatory agency following a reported assessment by the WHO Uppsala Monitoring Center dated April 2021.

ii) Data

The safety database was searched cumulatively through 18 June 2021 for all BNT162b2 vaccine spontaneous and literature reports and serious clinical trial reports reporting the PT Appendicitis (MedDRA version 24.0).

A total of 145 cases have been retrieved using the criteria mentioned above. There were 94 females, 45 males and for 6 cases gender was not reported. Age was reported as ranging from 13 to 89 years (mean: 45.8). A total of 6 cases were reported in paediatric subjects less than or equal to 17 years of age, 104 cases were reported in adults (≥ 18 to <65), 25 cases were reported by elderly (≥ 65) and for 10 cases age was not reported. Latency from vaccination to onset of appendicitis was provided in 126 cases and ranged from day of vaccination to 225 days after vaccination. Ninety-three (93) cases occurred within one week after vaccination whereby in eleven (11) of these cases appendicitis occurred on the same day as vaccination; (1 case within 15 minutes and 2 cases within 5 hours and 12 hours).

Medical history was reported for 74 cases. A relevant medical history was reported for 44 cases: 7 cases reported appendicitis/appendix disorder; 8 cases reported Covid-19 infection; 6 cases reported Type 1 and 2 diabetes mellitus diabetes; 1 case reported mixed connective tissue disease / Sjogren's syndrome; 1 case reported cutaneous lupus erythematosus and Sjogren's syndrome; 4 cases reported cancer; 1 case reported diverticulitis; 1 case reported Hodgkin's disease and sarcoidosis; 2 case of endometriosis; 2 reported diarrhea/gastrointestinal disorder; 2 reported constipation; 4 reported infections; 2 reported unspecified surgery; and 3 reported abdominal pain.

[50] Psichogiou M, Samarkos M, Mikos N, et al. A reactivation of varicella zoster virus after vaccination for SARS-CoV-2. Vaccines 2021; 9(6):572. https://doi.org/10.3390/vaccines9060572.

Of the 145 cases, 4 cases reported positive SARS-COV-2 test results, 53 cases reported negative COVID-19 test results, 1 reported pending COVID-19 test result, and 87 cases did not provide COVID-19 testing information.

Case outcome was reported as resolved in 41 cases, resolving in 66 cases, resolved with sequelae in 9 cases, not resolved at time of reporting in 10 and unknown in 19 cases.

A signal of disproportionality (EB_{05}>2) for term indicative of appendicitis was not noted on 18 June 2021 for BNT162b2 during routine PV monitoring activities. A literature review did not identify a specific signal for BNT162b2 vaccine associated appendicitis. The O/E ratio was below 1 for both the 21-day risk window and no risk window

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.

iii) Outcome

Appendicitis has been spontaneously reported following vaccination with BNT162b2 vaccine. Most reports are in adult patients, consistent with the age populations targeted for vaccination in most regions. Forty-four (44) cases reported relevant medical conditions that may have predisposed to GI inflammation and/or appendicitis. Review of the literature review did not identify a significant safety information for vaccine associated appendicitis. The O/E ratio was below 1 in the epidemiology signal detection analyses.

The totality of the reviewed information does not indicate a causal association between the vaccine and appendicitis for the following reasons: there is not a clear mechanism to explain why vaccinated individuals may have an increased risk for appendicitis, there was no indication identified from the literature linking vaccination to the occurrence of appendicitis, and given the relatively low number of reports of appendicitis in the context of more than half a billion BNT162b2 vaccine doses administered. The benefit risk profile of the vaccine remains favorable. Routine signal detection activities will continue.

8) Hearing loss and Tinnitus (see Section 15.3, Appendix 6B.2-1 and Appendix 6B.2-2).

16.2.2. Signal Evaluation Plan for Ongoing Signals

The table below provides the evaluation plan for signals in which the evaluation was still ongoing (i.e. not closed) at the cut-off date of this PSUR.

Table 17. Signal Evaluation Plan for Ongoing Signals

Signal	Evaluation Plan
Trigeminal neuralgia [a]	A cumulative review of the safety database, clinical database and search the published literature.
Immune thrombocytopenia [b]	A review of thrombocytopenia is included in Appendix 6B.1.
Myocarditis and Pericarditis [c]	Monitoring and assessment as per BC Criteria as well as O/E analyses stratified by age and gender. In addition, post-authorization observational studies ongoing and planned will better characterize the occurrence in vaccinees versus non-vaccinated individuals.
Hypertensive crisis with intracranial haemorrhage [a]	A cumulative review of the safety database, clinical database and search of the published literature.

a. Signal closed after DLP as non-validated signal.
b. Signal assessed under the regulatory procedure PAM-SDA-034 (EPITT No.: 19680). Signal closed after DLP and categorised as no risk.
c. Signal assessed under the regulatory procedure SDA 032. After DLP the signal was closed and determined to be a Risk. The EU-SmPC has been updated after DLP by adding Myocarditis and Pericarditis in Section 4.4 Special warnings and precautions for use and in Section 4.8 Undesirable Effects.

16.3. Evaluation of Risks and New Information

Evaluation of new information for recognized important identified and important potential risks, other risks (not categorized as important), special situations, and special patient populations for BNT162b2 is provided below in Section 16.3.1, Section 16.3.2, Section 16.3.3, Section 16.3.4 and Section 16.3.5, respectively.

Follow-up Questionnaires

As per the coreRMP19 guideline, for those events for which follow-up questionnaires are implemented (e.g. anaphylaxis, VAED/VAERD) the MAH should provide process data (e.g. response rate, need for corrective actions) and reassess the need for continuing this routine pharmacovigilance activity in the PSURs.

The MAH's procedures related to the follow-up questionnaires are described below:

As per internal case processing procedures, in each and every case for which a questionnaire/DCA is available for a specific event, this information is captured in the safety database to ensure that the questionnaire is sent out for completion by the reporter in all cases where FU is allowed.

Two DCAs and a Follow-up Questionnaire have been created for COVID-19 vaccine.

- The first DCA is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced in a vaccinated individual, particularly in relation to potential cases of vaccine lack of effect or VAED. The DCA was implemented on 07 December 2020 based on MHRA, EMA and FDA commitments and remains in use.

- The second DCA is intended to enable the retrieval of clinical details about potential anaphylactic reactions experienced by an individual following administration of BNT162b2. The DCA was implemented on 23 December 2020 and based on MHRA, and EMA commitments and remains in use.

- Additionally, a Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire is used for all other reports and, is intended to capture more specific information about vaccine administration details, facility where vaccine was provided, any prior vaccinations received, medical and family history, adverse events and relevant medical tests (eg, Platelet Factor IV antibody in cases of thromboembolic events with thrombocytopenia). This Follow-up Questionnaire was implemented on 15 February 2021 and to be used for all reports not meeting the DCA criteria above.

1. Follow-up for COVID-19 Vaccine Cases Received Through Eudravigilance

For cases received through Eudravigilance, the DSU case reviewer requests follow-up information from the owner of the case (eg, National Competent Authority [NCA]), when applicable and for all cases with a suspect COVID-19 vaccine as follows:

Table 18. Follow-up for COVID-19 Vaccine Cases Received through Eudravigilance

Case type	As per process implemented on 10 March 2021	As per process implemented on 17 May 2021
All serious cases meeting DCA criteria	1st follow-up performed within 10 calendar days from SRD applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No second attempt performed.	No change
Non-serious cases identified by SSRM and meeting DCA criteria	1st follow-up performed within 10 calendar days from notification applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No second attempt performed.	No change
Any other non-serious case not identified by SSRM and meeting DCA criteria	1st follow-up performed within 10 calendar days from notification applying only the appropriate Pfizer-BioNTech COVID-19 DCA. No follow-up attempts are performed	1st follow-up performed within a maximum of 60 calendar days from SRD applying only the appropriate Pfizer-BioNTech COVID-19 DCA No second attempt performed.
All other serious and non-serious cases not meeting DCA criteria	No follow-up attempts are performed	No change
ICH Invalid	1st follow-up attempt within 10 calendar days from book-in. No second attempt performed.	No change

Abbreviations: International Conference on Harmonisation (ICH); Safety Receipt Date (SRD); Safety Surveillance Risk Management (SSRM).

In compliance with the criteria mentioned above, the local DSU case reviewer or case reviewer acting on their behalf (eg, a DSU case reviewer from one of the Platforms) is responsible for evaluation of follow-up requirements and setting appropriate action items within the global safety database. Execution of action items is performed by the DSU case reviewers within the relevant local DSU.

For those NCAs that either prohibit the request of follow up information from Pfizer or that have communicated to Pfizer that they automatically request follow-up from the original reporter, the DSU case reviewer enters a contact log entry in the case to document how follow-up activities are managed by the NCA.

2. Follow-up for COVID-19 Vaccine Cases Received Outside of the Eudravigilance Process

For all COVID-19 vaccine cases that are not received through Eudravigilance, the DSU case reviewer requests follow-up information directly from the HCP reporter, if possible, as follows:

Table 19. Follow-up for COVID-19 Vaccine Cases Received Outside of the Eudravigilance Process

Case type	As per process implemented on 10 March 2021	As per process implemented on 17 May 2021
All serious cases	1st follow-up performed within 10 calendar days from SRD applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.	No change
Non-serious cases identified by SSRM	1st follow-up performed within 10 calendar days from notification applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.	No change
Any other non-serious case not identified by SSRM	No follow-up attempts are performed.	1st follow-up performed within a maximum of 60 calendar days from SRD applying the Pfizer-BioNTech COVID-19 DCA or the Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire, as applicable to the events involved in the case. No second attempt performed.
ICH Invalid	1st follow-up attempt within 10 calendar days from book-in. No second attempt performed.	No change

Abbreviations: International Conference on Harmonisation (ICH); Safety Receipt Date (SRD); Safety Surveillance Risk Management (SSRM).

In compliance with the criteria mentioned above, the local DSU case reviewer or case reviewer acting on their behalf (eg, a DSU case reviewer from one of the Platform) is responsible for evaluation of follow-up requirements and setting appropriate action items within the global safety database. Execution of action items is performed by the DSU case reviewers within the relevant local DSU.

For consumer cases, the DSU case reviewer sends the Pfizer BioNTech COVID-19 Vaccine Follow-up Questionnaire to the consumer and requests to provide it to his/her HCP for appropriate completion. The consumer is requested to complete the questionnaire to the best of his/her knowledge if unable to provide it to the HCP. Only one attempt is performed with the consumer; an additional attempt is performed with the HCP if the contact details are provided.

3. Follow-up Via Emergency Phone Calls

The DSU case reviewer performs emergency phone calls requesting follow-up only for HCP reporters, if the phone number of the HCP is available and contact can be made. The phone call is performed only for the following events:

Serious allergic reactions – events of anaphylaxis, anaphylactoid reaction, or anaphylactic shock.

The DSU case reviewer pursues follow up information of all available clinical details immediately with HCP reporters, applying the Pfizer-BioNTech COVID-19 DCA on vaccine anaphylactic reactions.

If no response is received via the phone contact, the DSU case reviewer sends the Pfizer-BioNTech COVID-19 DCA.

If response is received via the phone contact, there is no need to send the DCA unless specifically requested by the reporter.

DSU case reviewers perform follow-up activities with reporter(s), as described above and document in the contact log when the follow-up activities are not possible.

Product Safety Surveillance and Reporting Individual Case Safety Reports case reviewers confirm that follow-up activities have been initiated or closed before completing the cases under their process. If follow-up activities have not been appropriately tracked, they notify the relevant DSU. No additional queries are asked during case assessment, as follow-up is being conducted by use of the applicable COVID DCAs or AEM01-GSOP-MEC01-RF01 Pfizer-BioNTech COVID-19 Vaccine Follow-up Questionnaire.

Analysis of the incremental data are provided for Anaphylaxis in Section 16.3.1 and for VAED/VAERD in Section 16.3.2.

16.3.1. Evaluation of Important Identified Risks

Evaluation of incremental data for the important identified risk Anaphylaxis is provided below.

Table 20. Evaluation of Important Identified Risks

Important Identified Risk: Anaphylaxis *Search criteria[a]: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock*
Clinical Trial Data: Number of cases: 1 (0.6% of 702 cases of the total CT dataset; 1 BNT162b2). In 1 case received from [redacted] a 17-year-old female subject with medical history of asthma, drug hypersensitivity, eczema, food allergy, seasonal allergy received 1st dose of blinded therapy (BNT162; placebo) on 20 November 2020 at 17:04 and 2nd dose on 15 December 2020 at 15:16 and subsequently received 3rd dose of study vaccine (BNT162b2) on 25 January 2021 at 16:50 (all via intramuscular route in left deltoid as single doses for COVID-19 immunization). On 27 January 2021 at 10:30 (2 days after receiving BNT162b2 injection on her left arm) the subject started developing hives on her left arm (PT Anaphylactoid reaction) and used her epinephrine pen (self-administered) at 10:54 and developed shortness of breath shortly at 11:00. The hives resolved at 11:04 and the shortness of breath resolved at 11:24. Ongoing concomitant medications included salbutamol, epinephrine, cetirizine, loratadine, and triamcinolone. There were no concomitant vaccines administered on same date of study vaccine and no prior vaccinations (within 4 weeks prior to the first administration date of study drug). Outcome of the event anaphylactoid reaction was reported as resolved. On 05 March 2021, (40 days after vaccination 3), subject received a 2nd dose of BNT162b2 and on 16 March 2021, subject reported to site that there was no reaction to BNT162b2 dose given 05 March 2021. The investigator reported that there was a reasonable possibility that the event anaphylactoid reaction was related to dose 3 of the study vaccine (BNT162b2), but not related to dose 1 and dose 2 of blinded therapy (BNT162; placebo), concomitant drugs or clinical trial procedure.
Post-Authorization Data: • Number of cases: 3829. Upon review, 2 cases were determined to be non-contributory and are not included in the discussion for the following reason: • These 2 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route). • Number of relevant cases 3827 (1.2% of 327,125 cases, the total PM dataset). • MC cases (3326), NMC cases (501). • Country of incidence: Japan (1700), US (459), UK (426), Germany (161), Italy (132), Australia (102), France (77), Spain (73), Mexico (58), Canada and Sweden (56 each). The remaining 527 cases were distributed among 42 countries. • Subjects' gender: female (3184), male (454) and unknown (189). • Subjects' age in years (n = 3431), range: 12-104, mean 45.6, median 44. • Medical history (n = 2330): the most frequently (≥2%) reported medical conditions included Asthma (555), Food allergy (538), Drug hypersensitivity (358), Hypertension (275), Seasonal allergy (258), Hypersensitivity (224), Anaphylactic reaction (190), Urticaria (110), Dermatitis contact (96), Contrast media allergy (85), Rhinitis allergic (81), Rubber sensitivity (73), COVID-19 (72), Diabetes mellitus (70), Suppressed lactation (67), Allergy to animal (65), Dermatitis atopic (62), Allergy to arthropod sting, Allergy to chemicals (57 each), and Mite allergy (52). • COVID-19 Medical history (n = 101): COVID-19 (72), Suspected COVID-19 (23), SARS-CoV-2 test positive (3), COVID-19 pneumonia (2), COVID-19 immunisation (1). • Co-suspects (n = 60): Relevant co-suspects included beclomethasone, perindopril arginine (2 each), roxithromycin, macrogol, Hib vaccine conj, amifampridine, amfetamine, amoxicillin clavulanic acid, tetanus vaccine toxoid, bendamustine, budesonide, loxoprofen, methylprednisolone sodium succinate, polio vaccine inact 3v (vero), rizatriptan, tacrolimus, ciclesonide, tiotropium bromide, cisplatin, amfetamine sulfate, citalopram, hepatitis B vaccine rhbsag (yeast), hydrocortisone sodium succinate,

Table 20. Evaluation of Important Identified Risks

COVID-19 AstraZeneca vaccine, indapamide, desogestrel, loxoprofen, dexamfetamine saccharate, mepolizumab, dexamfetamine sulfate, mycophenolate mofetil, diphtheria vaccine toxoid, paroxetine hydrochloride, epinephrine, pertussis vaccine acellular 3-component, epinephrine hydrochloride, polyethylene glycol microspheres, erythromycin, riboflavin sodium phosphate, ethinylestradiol, roflumilast, fesoterodine, salbutamol, fexofenadine hydrochloride, testosterone cipionate, fluorouracil, thiamine mononitrate, fluoxetine, tofacitinib citrate, adalimumab, glucurolactone, glycine (1 each).

- Number of relevant events: 3919.
- Relevant event seriousness: serious (3873), non-serious (46).
- Reported relevant PTs: Anaphylactic reaction (3418), Anaphylactic shock (421), Anaphylactoid reaction (75), Anaphylactoid shock (5).[51]
- Time to event onset (n = 3288), range:<24 hours to 180 days, median 0 days.
  - <24 hours: 3030 events;
  - 1 day: 138 events;
  - 2-7 days: 84 events;
  - 8-14 days: 20 events;
  - 15-30 days: 9 events;
  - 31-181 days: 6 events.
- Duration of relevant events (n = 891 out of 2246 occurrences with outcome of resolved/resolved with sequelae), range: 10 seconds to 114 days, median 0 day.
  - <24 hours: 473 events;
  - 1 day: 242 events;
  - 2-7 days: 145 events;
  - 8-14 days: 20 events;
  - 15-30 days: 7 events;
  - 31-181 days: 3 events.
- Relevant event outcome: fatal (28), resolved/resolving (2,961), resolved with sequelae (56), not resolved (173), unknown (704).
- Lot/Batch Number if relevant. The lot/batch numbers which reported ≥3% of cases reporting anaphylaxis are: EP9605 (380), EW4811 (198), ER7449 (179), ER2659 (153), ER9480 (137), EY2173 (122).

Analysis by age group

- PM: Paediatric (23), Adults (3021), Elderly (395) and Unknown (388).
- No significant difference observed in the reporting proportion of anaphylaxis relevant PTs between adult and elderly population. However, a higher reporting proportion of event coded to the PTs Anaphylactic shock was observed in paediatric population when compared to adult or elderly population (48.8.% in paediatrics vs 11.0% in adults vs 11.9% in elderly).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 1055 (27.6% of the cases reporting anaphylaxis).
- The reporting proportion of anaphylaxis related events with fatal outcome (1.7%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.3% of events with fatal outcome), but this is expected considering that underlying comorbidities are likely to be contributory to individual's death and delayed recovery. The reporting proportion of anaphylaxis related events with outcome not resolved (4.5%) is comparable in individuals

[51] Of note, 15 cases reported that the patients were either allergic to PEG or interaction with PEG was reported (PTs Reaction to excipient (12), Drug interaction, Reaction to preservatives, Contraindicated product administered (1 each).

Table 20. Evaluation of Important Identified Risks

with comorbid conditions when compared to the reporting proportion (4.3%) observed in the individuals without comorbidities.
Literature Data: During the reporting interval, there were no new significant data received from literature sources.
Risk Assessment of New Information: Based on the interval data, no new safety information was identified pertaining to the risk of anaphylaxis with BNT162b2. This risk is communicated in the BNT162b2 CDS, Section 4.4, General recommendations, which includes information on appropriate action to be taken, as follows: "As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine. The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness." This risk is also listed in the CDS Section 4.8, Undesirable effects, Appendix A, Appendix B. This risk will continue to be monitored through routine pharmacovigilance.

a. Search criteria have evolved since EU-RMP first written due to MedDRA changes and refinements to searches. The initial search criteria included the Anaphylactic reaction SMQ (Narrow and Broad); these criteria were then updated in the EU-RMP v 2.0 to Anaphylactic reaction SMQ (Narrow and Broad, with the MedDRA algorithm applied), with relevant cases assessed according to BC criteria. Based on the preliminary PRAC Assessment Report; EMEA/H/C/005735/MEA/002.4 of the 5th SMSR, the search criteria were updated to the following PTs Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock.

Follow-up Questionnaires - Analysis of Data during the Reporting Interval

During the PSUR interval there were 3830 initial cases of anaphylaxis; of these the MAH received both significant and not significant FU information or did not receive any additional information; the table below summarizes the numbers of significant FU reports and the number of reports that did not receive any FU information, by country and by all case report types.

Of the 3830 initial cases there were 1695 (44.3%) that received a significant FU; and 1764 cases (46.1%) with no FU received.

Table 21. All Report Types[a] - Number of Anaphylaxis Cases

Country Where Event Occurred	FU Significant	No FU
Australia	11	68
Austria	11	12
Bahrain		2
Belgium	11	26
Bulgaria	1	
Canada	27	25
Chile	3	
Colombia	3	1
Costa Rica	2	
Croatia	4	1
Cyprus	2	
Czech Republic	10	10
Denmark	15	14
Estonia	1	

Table 21. All Report Types[a] - Number of Anaphylaxis Cases

Country Where Event Occurred	FU Significant	No FU
Finland	8	35
France	14	43
Germany	39	69
Greece	16	16
Hong Kong	4	4
Hungary	8	
Iceland		2
Ireland	8	3
Israel	4	1
Italy	104	11
Japan	893	744
Latvia	2	1
Lebanon	1	
Lithuania	2	2
Luxembourg		2
Malaysia		
Malta	7	1
Mexico	6	52
Netherlands	19	15
New Zealand		6
Norway	15	18
Panama		3
Poland	3	34
Portugal	11	20
Qatar		1
Romania	10	22
Saudi Arabia	1	
Serbia	1	
Singapore	7	
Slovakia	1	1
Slovenia	1	1
South Africa		2
Spain	15	57
Sweden	10	30
Switzerland	11	9
Turkey	3	
United Arab Emirates		
UK	91	313
US	279	87
Grand Total	**1695 (44.3%)**	**1764 (46.1%)**

a. Spontaneous MC or NMC, Regulatory Authority, Licensee, Literature sources and NIS

Of note, in certain circumstances: 1) follow-up with the reporter is not permitted by local regulatory authorities and/or by local regulations; 2) follow-up with the reporter is not possible because cases are received via a Regulatory Authority and the RA does not accept requests for follow-up from a pharmaceutical company; or 3) where follow-up must be discontinued, ie, where the reporter states “no additional information will be available” or the reporter refuses further contact or wants to remain anonymous.

Based on the above note, the MAH performed the same calculation by selecting case reports received by RA only and to verify especially the percentage of cases that did not receive FU information; accordingly, there were:

Cases with no FU from Regulatory Authority	Cases with no FU from all case report types
1458 (38.1%)	1764 (46.1%)

Therefore, removing the RA cases with no FU from the total count, the number of remaining cases with no FU received during the period decreases to 306 (8.0%), thus confirming the RA circumstances described above.

Table 22. Regulatory Authority Reports – Number of Anaphylaxis Cases

Country Where Event Occurred	FU Significant	No FU
Australia	11	68
Austria	8	12
Bahrain		2
Belgium	11	25
Bulgaria		
Canada		1
Croatia	4	1
Cyprus	2	
Czech Republic	9	9
Denmark	13	12
Estonia	1	
Finland	7	35
France	13	42
Germany	16	46
Greece	9	14
Hong Kong	3	4
Hungary	2	
Iceland		2
Ireland	8	3
Israel		
Italy	92	9
Japan	754	617
Latvia	2	1
Lithuania	1	2
Luxembourg		2
Malta	4	1
Mexico	2	42
Netherlands	19	13
New Zealand		6
Norway	14	18
Panama		3
Poland	1	32
Portugal	10	20
Romania	8	15
Serbia	1	
Singapore	3	
Slovakia		1
Slovenia	1	1

Table 22. Regulatory Authority Reports – Number of Anaphylaxis Cases

Country Where Event Occurred	FU Significant	No FU
South Africa		1
Spain	14	55
Sweden	6	27
Switzerland	9	9
UK	76	307
US	5	
Grand Total	**1139 (29.7%)**	**1458 (38.1%)**

Conclusion

The percentage of significant follow-up information received from all case report types for anaphylaxis-related PTs is around 30%; this relatively low percentage is due, in part, to the fact that many reports are from Regulatory Authorities.

Direct follow-up by MAH is severely limited due to the vast number of reports under mass vaccination processes that are provided directly by regulatory authorities. The MAH consider the use of the DCA a useful source when the reporters choose to respond and no corrective actions are warranted at this time; the MAH will re-evaluate the efficiency of these tools at the next PBRER.

16.3.2. Evaluation of Important Potential Risks

Evaluation of incremental data for the important potential risk VAED/VAERD is provided below.

Table 23. Evaluation of Important Potential Risks

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Search criteria:[a]
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.
VAED is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection.[52]

[52] Flor M Munoz, et al. Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Brighton Collaboration. September 2020, Vaccine Journal Draft Manuscript.

Table 23. Evaluation of Important Potential Risks

As noted by the Brighton Collaboration, there is currently no uniformly accepted definition of VAED (or VAERD) and the BC working group considers that a definitive case of VAED (Level 1 diagnostic certainty) cannot be ascertained with current knowledge of the mechanisms of pathogenesis of the condition; they have provided guidance on levels of diagnostic certainty of VAED cases based on various laboratory and clinical findings. No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful O/E analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continue to accrue. The search criteria utilised to identify potential cases of VAED/VAERD for this PSUR include the PTs Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease[53] or other PTs indicating a lack of effect of the vaccine and medical disorders chosen because they are PTs potentially indicative of severe or atypical COVID-19. Of note, there were no cases reporting the PTs Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease.
Clinical Trial Data: There were no cases reporting COVID-19 infection associated to one of the PTs utilized to identify potential severe or atypical cases of COVID-19.
Post-Authorization Data: Of the 631[54] cases retrieved based on search strategy, 47 cases were determined to be non-contributory and are not included in the discussion because the subjects developed SARS-CoV-2 infection during the early days from the 1st dose (days 1 – 13); therefore, the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable, even if severe, cannot be considered a potential case of enhanced disease. **Overview** • Number of cases: 584 (0.2% of the total PM dataset). • MC cases (438), NMC cases (146). • Country of incidence: UK (112), US (101), France (89), Italy (53), Germany (31), Austria (30), Spain (28), Hungary (22), Mexico (14), Belgium (13); Czech Republic (10); the remaining 81 cases originated from 29 different countries. • Patients' gender: female (298), male (268), and unknown (18). • Patients' age in years (n = 553), range: 17 – 103, mean 70.3, median 77. • Relevant event seriousness: 1261 serious. • Reported relevant PTs by organ system: – Respiratory system PTs (500): Dyspnoea (180), COVID-19 pneumonia (179), Respiratory failure (52), Pulmonary embolism (33), Hypoxia (24), Tachypnoea (17), and Acute respiratory distress syndrome (15).

[53] New PTs introduced with MedDRA version 24.0.

[54] Note: 3 additional cases retrieved with this search strategy were excluded from the discussion for the following reasons: 2 cases, where the PT Drug ineffective was coded, reported that the patients developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine; in 1 case the PT Therapeutic product effect decreased did not refer to BNT162b2 vaccine.

Table 23. Evaluation of Important Potential Risks

- Gastrointestinal (188): Diarrhoea (111), Vomiting (50), Abdominal pain (27); Cardiovascular system (60): Cardiac failure (25), Arrhythmia (13), Myocarditis (7), Acute myocardial infarction (5), Deep vein thrombosis (4), Cardiogenic shock, Vasculitis (2 each), Peripheral ischaemia, and Shock (1 each);
- Nervous system (29): Cerebrovascular accident (12), Seizure (10), Altered state of consciousness (6), and Encephalopathy (1);
- Renal and urinary system (33): Acute kidney injury (20), and Renal failure (13);
- Blood and lymphatic system (16): Thrombocytopenia (16);
- Other PTs (17): Multiple organ dysfunction syndrome (15), and Meningitis (2).

- Case outcome: fatal (160), not resolved (169), resolved/resolving (182), resolved with sequelae (7), unknown (66).

COVID-19 positivity and severity of events

- Suspected COVID-19 infection: 159 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (154 cases) or to Vaccination failure (5 cases)][55];
- Confirmed COVID-19 infection: 425 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (240 cases) or Vaccination failure (185 cases)].
- Seriousness criteria for the total 584 cases:
  - Medically significant: 221 (of which 10 serious also for disability);
  - Hospitalization required (non-fatal/non-life threatening): 166 (of which 115 serious also for medically significant and/or disability);
  - Life threatening: 37 (of which 24 also serious also for hospitalization);
  - Death: 160.

Seriousness criteria: medically significant (221)

- In 137 of 221 cases where the seriousness criterion was "medically significant", the subjects had a confirmed COVID-19 infection after vaccination, while 84 subjects had unconfirmed suspected COVID-19 infection. These 84 subjects did not require hospitalisation.
- Among the 137 confirmed COVID-19 cases, subjects' age ranged from 18 to 103 years (n = 127, mean 56.7, median 51) (87 adults, 41 elderly, 9 unknown); gender was reported as female (99), male (32) and unknown (6).
- Time to event onset of COVID 19 infection was reported for 112 of these 137 cases:
  - Day 14 to 73 after dose 1 (22 cases);
  - Day 4 to 120 after dose 2 (67 cases);
  - Day 0 to 44 after vaccination [dose number not reported] (23).
- The commonly reported (>2 occurrences) relevant PTs[b] in these 137 cases were: Drug ineffective (82), Dyspnoea (56), Vaccination failure (55), Diarrhoea (44), COVID-19 pneumonia (20), Abdominal pain (15), Vomiting (13), Arrhythmia (6), Tachypnoea (5), Hypoxia, Myocarditis, and Thrombocytopenia (3 each);
- The outcome of the COVID-19 infection related events[c] reported in these 137 cases was: resolved/resolving (84), not resolved (25), and unknown (71).

[55] In these 5 cases COVID-19 infection was clinically confirmed.

Table 23. Evaluation of Important Potential Risks

Seriousness criteria: hospitalisation (non-fatal, non-life threatening) (166)

- Hospitalization occurred in 166 subjects, for 40 of them COVID-19 infection was not confirmed.
- In the 126 COVID-19 confirmed cases, subjects' age (n = 121) ranged from 30 to 100 years, (mean 77.1, median 82) (20 adult, 102 elderly, 4 unknown); gender was reported as female (54), male (70), unknown (2).
- Time to event onset of COVID-19 infection was reported for 111 of these 126 cases.
  - Day 11 to 48 after dose 1 (22 cases)
  - Day 1 to 94 days after dose 2 (83 cases)
  - Day 0 to 37 after vaccination [dose number not reported] (6 cases).
- The commonly reported (>2 occurrences) relevant PTs[b] in these 126 cases were: Vaccination failure (64), Drug ineffective (62), COVID-19 pneumonia (47), Dyspnoea (38), Pulmonary embolism (16), Diarrhoea (14), Respiratory failure (11), Vomiting (8), abdominal pain (6), Hypoxia (5), Tachypnoea (4), Arrhythmia, Multiple organ dysfunction syndrome, Seizure, and Thrombocytopenia (3 each).
- The outcome of the COVID-19 infection related events[c] reported in these 126 cases was: resolved/resolving (73), not resolved (39), resolved with sequelae (5), and unknown (49).

Seriousness criteria: life-threatening (non-fatal) (37)

- Hospitalisation occurred in 20 of the 37 cases characterised as life-threatening; COVID-19 was confirmed in 30 subjects.
- In these 30 confirmed COVID-19 cases, subject's age ranged from 35 to 97 years (n = 28), (mean 72.6 years, median 75 years), (6 adult, 22 elderly, 2 unknown); gender was reported as female (17), male (12), unknown (1).
- Time to event onset of COVID-19 infection was reported for 27 of these 30 cases.
  - Day 14 to 71 after dose 1 (8 cases);
  - Day 3 to 65 after dose 2 (9 cases);
  - Day 0 to 30 after vaccination [dose number not reported] (10 cases).
- The commonly reported (>2 occurrences) relevant PTs[b] in these 30 cases were: Drug ineffective (22), COVID-19 pneumonia (13), Dyspnoea Vaccination failure (8 each), Pulmonary embolism (5), Hypoxia, and Respiratory failure (3 each);
- The outcome of the COVID-19 infection related events[c] reported in these 30 cases was: resolved/resolving (18), not resolved (14), resolved with sequelae (1), and unknown (7).

Seriousness criteria: death (160)

- One hundred thirty-two (160) subjects died; of these, COVID-19 was not confirmed in 28 cases; the remaining 132 confirmed cases are described below.
  - Age in years (n = 131), range: 17 – 100, mean 82.0, median 85, (1 adolescent, 7 adults, 123 elderly, 1 unknown);
  - Gender: female (47), male (84), unknown (1);
  - Country of incidence: France (35), UK (15), Germany, Hungary (12 each), Austria (10), Italy, US (8 each), Malta (7), Spain (5); the remaining 20 cases originated from 15 different countries.
  - Medical history (n = 114 cases) included PTs (reported more than twice) in the following SOCs:
    - Vascular disorders - 66 cases (50%): Hypertension (55), Deep vein thrombosis Peripheral venous disease (5 each), and Varicose vein (4);

Table 23. Evaluation of Important Potential Risks

- Cardiac disorders - 64 cases (48.5 %): Atrial fibrillation (65), Cardiac failure (13), Myocardial ischaemia (12), Coronary artery disease (8), Cardiac disorders (5), Cardiac failure congestive, Myocardial infarction (4 each), Acute myocardial infarction, Angina pectoris, Arrhythmia, Atrial flutter, and Hypertensive heart disease (3 each).
- Metabolism and nutrition disorders - 53 cases (40.2%): Type 2 diabetes mellitus (24), Obesity (12), Diabetes mellitus (10,), Dyslipidaemia, Hypercholesterolaemia, and Hyperuricaemia (3 each);
- Nervous system disorders - 45 cases (34.1 %): Dementia (8), Cerebrovascular accident, Cognitive disorder (7 each), Dementia Alzheimer's type (5), Vascular dementia (4), Ischaemic stroke, and Parkinson's disease (3 each).
- Respiratory, thoracic and mediastinal disorders - 41 cases (31.1%): Chronic obstructive pulmonary disease (13), Pulmonary embolism (6), Asthma (4), Bronchitis chronic, and Sleep apnoea syndrome (3 each).
- Surgical and medical procedures - 39 cases (29.5 %): Cholecystectomy, Haemodialysis (4 each), Appendicectomy, Coronary arterial stent insertion, Hospitalisation, and Prostatectomy (3 each);
- Renal and urinary disorders: 32 cases (24.2%): Chronic kidney disease (21), and Renal failure (7);
- Infections and Infestations – 32 cases (24.2%): COVID-19 (12), and Pneumonia (4);
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) - 24 cases (18.2%): Prostate cancer (6), and Prostatic adenoma (3);
- Other medical histories were reported under the following SOCs: Social circumstances (24 cases,), Musculoskeletal and connective tissue disorders (23 cases), Gastrointestinal disorders (18 cases), Psychiatric disorders (17 cases), Injury, poisoning and procedural complications (15 cases), Endocrine disorders (14 cases), Hepatobiliary disorders (12), Eye disorders (11), General disorders and administration site conditions (7 cases), Immune system disorders (7 cases), Reproductive system and breast disorders, Skin and subcutaneous tissue disorders (6 cases each), Investigations (5 cases), Congenital familial and genetic disorders (4 cases), Blood and lymphatic system disorders, and Ear and labyrinth disorder (3 each).

- Time to event onset of COVID-19 occurrence was reported in 116 of the 132 cases:
  - 14 days to 42 days after dose 1 (30);
  - 0 days to 109 days after dose 2 (72);
  - 0 days to 41 days after vaccination [dose number not reported] (14).
- The most frequently reported (≥2%) causes of death (n = 130) were: COVID-19 (64), COVID-19 pneumonia (55), Drug ineffective (46), Vaccination failure (35), Respiratory failure (18), Dyspnoea (10), Cardiac failure (9), Pulmonary embolism (7), Acute respiratory syndrome, Hypoxia (6 each), Acute respiratory failure, Multiple organ dysfunction syndrome, Pneumonia, Pyrexia, Renal failure (5 each), Acute kidney injury, Asthenia, Cerebrovascular accident, Cough, Sepsis (4 each), Atrial fibrillation, and Septic shock (3 each).
  - In 61 fatal cases, vaccination failure was reported (see Section 16.3.4.5 *Lack of Therapeutic Efficacy*):
    - Fifty-six (56) of these cases involved elderly subjects [aged 65 to 74 years (7) or greater than 75 years (49)], including 54 subjects with underlying medical history of clinical significance.
    - The remaining 5 cases involved subjects between 36 and 63 years of age; 4 of them had concurrent medical histories that could impact the severity and evolution of the COVID-19 infection, including but not limited to obesity (2), kidney diseases (3), hypertension (2), atrial fibrillation (1), type 2 diabetes mellitus (1), and epilepsy(1). The fifth case involved a healthy 36-year-old male who was vaccinated although he had previously had an asymptomatic

Table 23. Evaluation of Important Potential Risks

COVID-19 infection (date not provided). He had a vaccination failure approximately 3 weeks after the second vaccine dose and died due to systemic inflammatory response syndrome and sepsis. VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 425 subjects with confirmed COVID-19 following one or both doses of the vaccine; 290 of the 425 cases were severe, resulting in hospitalisation, disability, life-threatening consequences or death. None of the 290 cases could be definitively considered as having VAED/VAERD. Conclusion: In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.
Literature Data: During the reporting interval, there were no new significant data received from literature sources.
Risk Assessment of New Information: Based on the data, no new safety information pertaining to the risk VAED/VAERD with BNT162b2 use was identified. The risk of VAED/VAERD will continue to be monitored through routine pharmacovigilance and ongoing clinical study data.

a. Search criteria have evolved since EU-RMP first written due to MedDRA changes and refinements to searches.
b. PTs included in the search strategy.
c. Outcome for Drug ineffective and Vaccination failure are not included. Please note that 1 case may report more than 1 COVID-19 related event.

Follow-up Questionnaires - Analysis of Data during the Reporting Interval

During the PSUR interval there were 631 initial cases of VAED/VAERD; as per the same exercise performed for anaphylaxis above, the table below summarizes the numbers of significant FUs received and the numbers of reports that did not receive any FU information, by country and by all case report types.

Of the 631 initial cases, 336 (53.2%) received a significant FU and 212 (33.6%) with no FU received.

Table 24. All Report Types [a] - Number of VAED/VAERD Cases

Country Where Event Occurred	FU significant	NO FU[b]
Austria	14	12
Belgium	2	10
Bulgaria	1	1
Canada	2	
Chile	1	
Colombia	1	1
Costa Rica	2	
Croatia	1	3
Cyprus	2	
Czech Republic	7	3
Denmark	2	
Estonia	2	2
France	32	45
Germany	22	14

Table 24. All Report Types [a] - Number of VAED/VAERD Cases

Country Where Event Occurred	FU significant	NO FU[b]
Greece		2
Hungary	9	11
India	1	
Ireland		
Israel	3	1
Italy	42	5
Jordan	1	
Kuwait		1
Lebanon	1	
Lithuania	1	2
Malta	4	2
Mexico	5	12
Netherlands	4	2
Norway	2	3
Peru	1	
Philippines		1
Poland	6	
Portugal	2	2
Romania	1	
Serbia	1	
Slovakia		1
Slovenia	1	
Spain	11	15
Sweden	3	3
Switzerland	2	1
UK	49	46
US	95	11
Grand Total	**336 (53.2%)**	**212 (33.6%)**

a. Spontaneous MC or NMC, Regulatory Authority, Licensee, Literature sources and NIS.
b. Of note, in certain circumstances: 1) follow-up with the reporter is not permitted by local regulatory authorities and/or by local regulations; 2) follow-up with the reporter is not possible because cases are received via a Regulatory Authority and the RA does not accept requests for follow-up from a pharmaceutical company; or 3) where follow-up must be discontinued, ie, where the reporter states "no additional information will be available" or the reporter refuses further contact or wants to remain anonymous.

Considering the number of cases received from RA, that usually prevent any FU information, the number of cases that did not receive FU information was 182, therefore removing them from the total count (212) the percentage of no FU decreased to 30 (4.8%).

Conclusion

Direct follow-up by MAH is severely limited due to the vast number of reports under mass vaccination processes that are provided directly by regulatory authorities. Based on the percentage of significant follow-up information received (53.2%) for VAED/VAERD-related PTs the MAH consider the DCA a useful source of information when reporters choose to

respond; no corrective actions are warranted at this time. The MAH will reevaluate the use of these tools at the next PBRER.

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

Other risks were classified as listed adverse events in which a SMSR or SMSR assessment report recommended/requested continued monitoring in future PSURs and/or risks not categorized as important in which new information has become available during the reporting interval that allows further characterisation of a previously recognized risk.

16.3.3.1. Adverse Events of Special Interest (AESIs)

16.3.3.1.1. Anaphylactic AESIs

Please refer to the Risk 'Anaphylaxis' in Section 16.3.1.

16.3.3.1.2. 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: 33 (4.7% of 702 cases, the total CT dataset; 20 were blinded therapy, 10 BNT162b2, 3 were placebo).
- Country of incidence: US (25), Argentina (3), Germany, Turkey (2 each), Brazil (1).
- Subjects' gender: female (4), and male (29).
- Subjects' age in years (n = 33), range: 36-79, mean 62.7, median 63.0.
- Medical history (n = 30): the reported relevant medical conditions included hypertension (20), hypercholesterolaemia (10), obesity, type 2 diabetes mellitus (9 each), coronary artery disease (8), cardiac disorder, hyperlipidaemia (5 each), coronary artery bypass, tobacco user (4 each), blood cholesterol increased, dyslipidaemia (3 each), angina pectoris, diastolic dysfunction, myocardial infarction, tobacco abuse, transient ischaemic attack (2 each), acute myocardial infarction, angiopathy, aortic arteriosclerosis, aortic valve repair, blood pressure increased, cardiovascular disorder, chest pain, coronary arterial stent insertion, diabetes mellitus, ex-tobacco user, hypertriglyceridaemia, mitral valve prolapse, myocardial ischaemia, overweight, peripheral arterial occlusive disease, and ventricular extrasystoles (1 each).
- There were no cases that reported medical history of COVID-19.
- There were no cases that reported co-suspect medications.
- Reported relevant PTs: Acute myocardial infarction (15), Myocardial infarction (11), and Coronary artery disease (7).

- BNT162b2 related event coded to the PT: Myocardial infarction (1). Time to onset of event 2 months 8 days and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-Authorization Data

- Number of cases: 8398 (2.6% of 327,125 cases, the total PM dataset).
- MC cases (6451), NMC cases (1947).
- Country of incidence: Mexico (2078), Italy (1063), France (952), UK (797), US (677), Germany (505), Japan (386), Spain (248), Netherlands (215), Greece (127); the remaining 1350 cases were distributed among 50 countries.
- Subjects' gender: female (6221), male (2018) and unknown (159).
- Subjects' age in years (n = 8000), range: 12 – 104, mean 50.9, median 47.
- Medical history (n = 4138): the most frequently (≥2%) reported relevant medical conditions included hypertension (900), atrial fibrillation (282), diabetes mellitus (197), cardiac failure (184), hypothyroidism (183), type 2 diabetes mellitus (170), obesity (129), arrhythmia (122), myocardial infarction (120), myocardial ischaemia (102), dyslipidaemia (95), coronary artery disease (86), anxiety (81).
- COVID-19 Medical history (n = 449): the most frequently (≥2%) reported medical conditions included COVID-19 (309), Suspected COVID-19 (89), SARS-CoV-2 test positive (13).
- Co-suspects (n = 79 cases). Frequently (>5 occurrences) reported relevant co-suspect was adalimumab (6).
- Number of relevant events: 8616.
- Relevant event seriousness: serious (4195), non-serious (4422).
- Most frequently reported relevant PTs (≥2%): Tachycardia (6238), Arrhythmia (775), Myocardial infarction (635), Cardiac failure (489), Acute myocardial infarction (265).
- Time to event onset (n = 7087),[56] range: <24 hours to 118 days, median <24 hours.
  - <24 hours: 3965 events (69 fatal events);
  - 1 day: 1415 events (90 fatal events);
  - 2-7 days: 1136 events (206 fatal events);

[56] This number does not include 9 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- 8-14 days: 287 events (52 fatal events);
- 15-30 days: 201 events (39 fatal events);
- 31-181 days: 83 events (16 fatal events).

- Duration of relevant events (n = 1176 out of 3672 occurrences with outcome of resolved/resolved with sequelae), range: 1 second to 63 days, median 1 day.

  - <24 hours: 343 events;
  - 1 day: 398 events;
  - 2-7 days: 346 events;
  - 8-14 days: 57 events;
  - 15-30 days: 28 events;
  - 31-181 days: 4 events.

- Relevant event outcome:[34] fatal (638), resolved/resolving (4699), resolved with sequelae (123), not resolved (890), unknown (2276).

  - In the 593 cases (reporting 638 relevant events with a fatal outcome), the reported cause of death (>20 occurrence) were coded to PTs Myocardial infarction (186), Cardiac failure (182), Acute myocardial infarction (79), Cardiac arrest, Dyspnoea (43 each), Cardiac failure acute, Cardiogenic shock (39 each), Arrhythmia (38), Tachycardia (32), Pyrexia (24), and Cardio-respiratory arrest (23). Of note, in 12 cases limited information regarding the cause of death was provided (PT Death [5], Unknown [7]). Most (511 of 593 cases) of the fatal cases involved elderly subjects. When the medical history was provided (496 cases), significant medical conditions included hypertension, atrial fibrillation, cardiac failure, myocardial ischaemia, type 2 diabetes mellitus, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, renal failure, myocardial infarction, and coronary artery disease.

Analysis by age group

- CT: Adults (19), and Elderly (14).

  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (19), Adults (6100), Elderly (1961) and Unknown (317).

  - Higher reporting proportion of events coded to the PTs Acute myocardial infarction, Arrhythmia, Cardiac failure, and Cardiac failure acute was reported in elderly population when compared to adult and paediatric population (Acute myocardial infarction [1.4% in adults vs 0% in paediatrics vs 9.2% in elderly], Arrhythmia [6.7% in adults vs 5.3% in paediatrics vs 16.6% in elderly], Cardiac failure [0.6% in adults vs 0% in paediatrics vs 22.6% in elderly], Cardiac failure acute [0.05% in adults vs 0% in paediatrics vs 3.2% in elderly], and Myocardial infarction [3.1% in adults vs 5.3% in paediatrics vs 20.3% in elderly]). Higher reporting proportion of events coded to the PTs Tachycardia was reported in the adult and paediatric population

when compared to the elderly population ([88.9% in adults vs 84.2% in paediatrics vs 29.6% in elderly]). Higher reporting proportion of event coded to the PT Postural orthostatic tachycardia syndrome was reported in the paediatric population when compared to the adult and elderly population ([0.5% in adults vs 10.5% in paediatrics vs 0.1% in elderly]).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 1832 (0.6% of 327,827 cases, the total dataset).
- The reporting proportion of cardiovascular AESIs with fatal outcome (8.9%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (2.9% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute myocardial infarction; Arrhythmia; Heart failure (PTs: Cardiac failure; Cardiac failure acute); Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No cardiovascular signals have emerged from the review of post-authorisation data. The review of cases and O/E analysis does not raise new concerns. Safety surveillance will continue.

16.3.3.1.3. 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: 18 (2.6% of 702 cases, the total CT dataset; 15 were blinded therapy, 2 BNT162b2, and 1 placebo).
- Country of incidence: US (12), Argentina (2), Brazil, Germany, South Africa, and Turkey (1 each).
- Subjects' gender: female (9), and male (9).
- Subjects' age in years (n = 18), range: 32 - 81, mean 57.9, median 59.5.

[57] CT and PM data pooled.

- Medical history (n = 15 cases): the reported relevant medical conditions included Hypertension (9), Obesity (4), Asthma, Type 2 diabetes mellitus (2 each), Chronic obstructive pulmonary disease, Diabetes mellitus, HIV infection, Hypoxia, Lung neoplasm malignant, Pulmonary fibrosis, Asthma exercise induced (1 each).

- COVID-19 Medical history: None.

- There were no cases that reported co-suspect.

- Reported relevant PTs: COVID-19 (14), COVID-19 pneumonia (4). None of the events were related to BNT162b2 or blinded therapy.

Post-Authorization Data

Number of cases: 12,059. Upon review, 1 case was determined to be non-contributory and is not included in the discussion since this case involved a baby who was indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 12,058 (3.7% of 327,125 cases, the total PM dataset).

- MC cases (6915) NMC cases (5143).

- Country of incidence: US (4332), UK (1702), France (897), Italy (840), Germany (812), Portugal, Spain (272 each), Mexico (267), Austria (247), Romania (236); the remaining 2181 cases were distributed among 62 countries.

- Subjects' gender: female (6876), male (3692) and unknown (1490).

- Subjects' age in years (n = 8127), range: 3 - 104, mean 57.8, median 56.0.

- Medical history (n = 4237): the most frequently (≥2%) reported relevant medical conditions included Hypertension (955), Diabetes mellitus (295), Asthma (290), Type 2 diabetes mellitus (217), Obesity (174), Chronic obstructive pulmonary diseases (144).

- COVID-19 Medical history (n = 1001): the most frequently (≥2%) reported medical conditions included COVID-19 (452), Suspected COVID-19 (291), Exposure to SARS-CoV-2 (151), Occupational exposure to SARS-CoV-2 (33), SARS-CoV-2 test positive (29).

- Co-suspects (n = 83 cases). Frequently (>5 occurrences) reported relevant co-suspect was COVID-19 AstraZeneca (11)

- Number of events: 13,209.

- Relevant event seriousness: serious (8633), non-serious (4576).

- Most frequently reported relevant PTs (≥2%): COVID-19 (8154), Ageusia (1135), Anosmia (924), Suspected COVID-19 (910), SARS-CoV-2 test positive (677), Asymptomatic COVID-19 (567), COVID-19 pneumonia (324).

- Time to event onset (n = 8692),[58] range: <24 hours to 132 days, median 8 days.

  - <24 hours: 612 events (12 fatal events);
  - 1 day: 910 events (16 fatal events);
  - 2-7 days: 2524 events (112 fatal events);
  - 8-14 days: 1823 events (115 fatal events);
  - 15-30 days: 1267 events (102 fatal events);
  - 31-181 days: 1556 events (83 fatal events).

- Duration of relevant events (n = 894 out of 2221 occurrences with outcome of resolved/resolved with sequelae), range: 1 hour to 68 days, median 9 days:

  - <24 hours[59]: 13 events;
  - 1 day[60]: 109 events;
  - 2-7 days: 261 events;
  - 8-14 days: 332 events;
  - 15-30 days: 158 events;
  - 31-181 days: 21 events.

- Relevant event outcome:[34] fatal (658), resolved/resolving (3312), resolved with sequelae (70), not resolved (2001), unknown (7174).

  - In 595 cases (reporting 658 relevant events with a fatal outcome), the reported cause of death (>20 occurrence) were coded to PTs COVID-19 (458), Drug ineffective (169), COVID-19 pneumonia (111), Vaccination failure (87), Respiratory failure (33), Pyrexia (28), Dyspnoea (25), Pneumonia, and SARS-CoV-2 test positive (24 each). Of note, in 13 cases limited information regarding the cause of death was provided (PT Death [8], Unknown [5]). Most (439 of 595 cases) of the fatal cases involved elderly subjects. When the medical history was provided (462 cases), significant medical conditions included hypertension, type 2 diabetes mellitus, COVID-19, chronic obstructive pulmonary disease, and diabetes mellitus.

[58] This number does not include 17 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[59] Majority of the events for which duration was reported as same day, included ageusia and anosmia.

[60] Majority of the events for which duration was reported as one day included ageusia, anosmia, and suspected COVID-19.

Analysis by age group

- CT: Adults (10), and Elderly (8)
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (33), Adults (5179), Elderly (3143).
  - No significant difference observed in the reporting proportion of frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population.

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 2086 (0.6% of 327,827 cases, the total dataset).
- The reporting proportion of COVID-19 AESIs with fatal outcome (13.1%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (2.9% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Ageusia and Anosmia (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No safety signals have emerged based on the review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.4. 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: 178 (0.05% of 327,125 cases, the total PM dataset).
- MC cases (112), NMC cases (66).
- Country of incidence: UK (69), France (24), US (22), Japan (16), Italy (14), Netherlands (6), Poland (4), Finland (3); the remaining 20 cases were distributed among 14 countries.
- Subjects' gender: female (119), male (54) and unknown (5).

- Subjects' age in years (n = 163), range: 16-92, mean 53.1, median 53.
- Medical history (n = 92): the most frequently (≥2%) reported medical conditions included Hypothyroidism (11), Chillblains, Food allergy (7 each), Drug hypersensitivity (6), Erythema multiforme (2).
- COVID-19 Medical history (n = 16): the medical conditions included COVID-19 (8), Suspected COVID-19 (7), and SARS-CoV-2 antibody test positive (1).
- Co-suspects (n = 2). COVID-19 AstraZeneca vaccine, zonisamide (1 each).
- Number of events: 178.
- Relevant event seriousness: serious (99), non-serious (79).
- Most frequently reported relevant PTs Chillblains (98); Erythema multiforme (80).
- Time to event onset (n = 139), range: <24 hours to 41 days, median 4 days.
  - <24 hours: 19 events;
  - 1 day: 23 events;
  - 2-7 days: 54 events;
  - 8-14 days: 23 events;
  - 15-30 days: 17 events;
  - 31-181 days: 3 events.
- Duration of relevant events (n = 16 out of 33 occurrences with outcome of resolved/resolved with sequelae), range: 3 days to 1 month, median 10 days:
  - 2-7 days: 5 events;
  - 8-14 days: 5 events;
  - 15-30 days: 6 events.
- Relevant event outcome:[34] fatal (1), resolved/resolving (74), resolved with sequelae (4), not resolved (68), unknown (32).
  - There was 1 case reporting 1 relevant PT Erythema multiforme with a fatal outcome. The cause of death was reported as abdominal pain lower; anuria; arteriosclerosis; cervical spinal stenosis; contusion; cyanosis; erythema multiforme; hypotonia; intervertebral disc protrusion; metabolic acidosis; paralysis; paraparesis; respiratory failure; spinal cord compression; swelling.

Analysis by age group

- PM: Paediatric (1), Adults (112), Elderly (52) and Unknown (13).

– 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. Higher reporting proportion of event erythema multiforme was reported in elderly population (5.8%) compared to adult population (0.9%).

Analysis by presence of comorbidities[22]

- Number of subjects reporting comorbidities: 42 (23.6% of the cases reporting dermatological AESIs)

- Due to low volume of cases with fatal outcome, a meaningful comparison between subjects with and without comorbidities is not possible.

O/E Analysis

O/E analysis was performed for Chillblains and Erythema multiforme (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No safety signals have emerged based on the review of these cases, or of the Observed versus Expected analysis. Safety surveillance will continue.

16.3.3.1.5. 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.

Post-Authorization Data

Number of cases: 2576. Upon review, 184 cases were excluded from further discussion. These 184 cases are not cases of peripheral facial nerve palsy (BC Category 5) because they reported also other disorders (cerebral haemorrhage, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral venous sinus thrombosis, cerebrovascular accident, ischaemic cerebral infarction, ischaemic stroke, lacunar infarction or transient ischaemic attack).

- Number of relevant cases: 2392 (0.7% of 327,125 cases, the total PM dataset).

- MC cases (1386), NMC cases (1006).

- Country of incidence: UK (511), US (495), France (197), Italy (183), Germany (155), Spain (93), Japan (64), Hong Kong (48), Sweden (45), Israel (44), Mexico (41), Ireland (40); the remaining 476 cases were distributed among 42 countries.

- Subjects' gender: female (1458), male (831), and unknown (103).

- Subjects' age in years (n = 2124), range: 16 – 100, mean 57.5, median 52.

- Medical history (n = 1,166 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (298), Diabetes mellitus (102), Bell's palsy (77), Type 2 diabetes mellitus (68), Hypothyroidism (60), Obesity (38), Cerebrovascular accident (31), Blood cholesterol increased (27), and Facial paralysis (26). Of note, more than 1 medical history was reported in some cases.

- COVID-19 Medical history (n = 81 cases): Reported medical conditions include COVID-19 (50), Suspected COVID-19 (23), COVID-19 pneumonia (5), SARS-CoV-2 test positive (3), Asymptomatic COVID-19 (2), and Coronavirus infection (1). Of note, more than 1 medical history was reported in some cases.

- Co-suspects: 5 cases. Relevant co-suspects were botulinum toxin type A and lithium (1 each).

- Number of relevant events:[61] 2392.

- Relevant event seriousness:[62]: serious (2268) and non-serious (131).

- Reported relevant PTs: Bell's palsy (998), Facial paralysis (1054), Facial paresis (337), and Oculofacial paralysis (3).

- Time to event onset (n = 1908 events),[63] range: <24 hours to 109 days, median 3 days.

  - <24 hours: 425 events;
  - 1 day: 274 events;
  - 2-7 days: 545 events;
  - 8-14 days: 293 events;
  - 15-30 days: 248 events;
  - 31-181 days: 123 events.

- Duration of of relevant events (n = 239 out of 481 occurrences with outcome of resolved/resolved with sequelae), range: 15 seconds to 72 days, median 2 days.

  - <24 hours: 46 events;
  - 1 day: 58 events;

[61] If a case included both PT Facial paresis and PT Facial paralysis, only the PT Facial paralysis was considered in the descriptions of the events as it is most clinically important and if a case included both PT Bell's palsy and PT Facial paralysis, only the PT Bell's palsy was considered in the descriptions of the events as it is most clinically important.

[62] Multiple episodes of the same PT event were reported with a different seriousness within 1 case hence the sum of the events seriousness exceeds the total number of PT events.

[63] This number does not include I event for which partial administration and/or event onset date was reported.

- 2-7 days: 60 events;
- 8-14 days: 26 events;
- 15-30 days: 33 events;
- 31-181 days: 16 events.

- Relevant event outcome:[34] fatal (1), resolved/resolving (979), resolved with sequelae (31), not resolved at the time of reporting (884), and unknown (504).

  - In the single fatal case, the cause of death was coded to the PTs Asthenia, Facial paralysis, Hypothermia, Septic shock, and Slow speech. The case involved a 98-year-old subject with a medical history of atrial fibrillation, hypertension, and colon neoplasm.

- Lot/Batch Number: The lot/batch numbers which reported ≥2% of cases reporting facial paralysis are: #EL1484 (55 cases) and #EM0477 (51 cases). No quality issues identified during investigations of the impacted lot/batch numbers.

Analysis by age group

- PM: Paediatric (5), Adults (1516), Elderly (616) and Unknown (255).

  - There was no significant difference observed in the reporting proportion of facial paralysis events between age groups.

Analysis by presence of comorbidities[22]

- Number of subjects with comorbidities: 570 (23.8% 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) (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

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 (eg, C4591008, C4591010) and secondary data collection studies (eg, C4591009, C4591011, C4591012, C4591021).

16.3.3.1.6. 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: 19 (2.7% of 702 cases, the total CT dataset; 7 cases involved BNT162b2, 11 cases involved blinded therapy, and 1 case involved placebo).
- Country of incidence: US (14), Brazil (2), Germany (2), and Argentina (1).
- Subjects' gender: female (5) and male (14).
- Subjects' age in years (n = 19 cases), range: 24-78, mean 59.8, median 64.
- Medical history (n = 19 cases): the relevant subjects' medical conditions reported more than twice were coded to the PTs Hypertension (7), Type 2 diabetes mellitus and Hyperlipidaemia (4 each).
- There were no cases that reported medical history of COVID-19.
- There were no cases that reported co-suspect.
- Number of relevant events: 19.
- Reported relevant PTs (≥2 occurrences): Gastrointestinal haemorrhage (4), Lower gastrointestinal haemorrhage and Subdural haematoma (2 each). None of the SAEs were assessed as related to BNT162b2 or blinded therapy or placebo.

Post-Authorization Data

Number of cases: 9435. Upon review, 5 cases were determined to be non-contributory and are not included in the discussion since these 5 cases involved babies/foetus who were indirectly exposed to BNT162b2 (either trans-mammary or transplacental route).

- Number of relevant cases: 9430 (2.9% of 327,125 cases, the total PM dataset).
- MC cases (4109), NMC cases (5321).
- Country of incidence: UK (3054), US (1845), Netherlands (696), France (671), Italy (552), Japan (348), Germany (293), Spain (267), Mexico (210), Sweden (161), Norway (129), Canada (119), Australia (104); the remaining 981 cases were distributed among 48 countries.
- Subjects' gender: female (7112), male (2069), and unknown (249).

- Subjects' age in years (n = 8427 cases), range: 1[64]-115, mean 56.5, median 51.

- Medical history (n = 5652 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (879), Disease risk factor (472), Diabetes mellitus (229), Atrial fibrillation, Hypothyroidism (219 each), and Type 2 diabetes mellitus (155). Of note, more than 1 medical history was reported in some cases.

- COVID-19 Medical history (n = 627 cases): Medical conditions reported more than once were coded to the PTs COVID-19 (308), Suspected COVID-19 (307), SARS-CoV-2 test positive (13), COVID-19 pneumonia (9), Exposure to SARS-CoV-2 and SARS-CoV-2 antibody test positive (4 each). Of note, more than 1 medical history was reported in some cases.

- Co-suspects: 248 cases. Frequently (≥10 occurrences) reported relevant co-suspects were apixaban (47), acetylsalicylic acid (27), clopidogrel (13), rivaroxaban and warfarin (10 each).

- Number of relevant events: 10,935.

- Relevant event seriousness: serious (5816) and non-serious (5119).

- Most frequently reported relevant PTs (≥2%): Epistaxis (1267), Contusion (1251), Heavy menstrual bleeding (881), Vaccination site haematoma (699), Thrombocytopenia (537), Haemorrhage (509), Vaccination site bruising (472), Vaginal haemorrhage (414), Petechiae (382), Haematoma (354), Intermenstrual bleeding (292), Haematochezia (221), Vaccination site haemorrhage (219), Immune thrombocytopenia (201), and Purpura (195).

- Time to event onset (n = 7719 events),[65] range: <24 hours to 125 days, median 2 days.

  - <24 hours: 1926 events (12 of which had a fatal outcome);
  - 1 day: 1842 events (32 of which had a fatal outcome);
  - 2-7 days: 2364 events (65 of which had a fatal outcome);
  - 8-14 days: 733 events (23 of which had a fatal outcome);
  - 15-30 days: 573 events (20 of which had a fatal outcome);
  - 31-181 days: 281 events (9 of which had a fatal outcome).

[64] There were 2 cases reporting age as 1 year old. Of which, 1 case reported PT Product administered to patient of inappropriate age and included for age analysis. The other case received from the UK Health Authority presented contradictory information (reported medical history for 3 years) and hence the age of this case was not included for age analysis alone.

[65] This number does not include 29 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- Duration of relevant events (n = 1342 out of 2909 occurrences with outcome of resolved/resolved with sequelae), range: 30 seconds to 88 days, median 3 days.
  - <24 hours: 89 events;
  - 1 day: 343 events;
  - 2-7 days: 624 events;
  - 8-14 days: 166 events;
  - 15-30 days: 86 events;
  - 31-181 days: 34 events.

- Relevant event outcome[34]: fatal (241), resolved/resolving (4780), resolved with sequelae (104), not resolved (2596), and unknown (3286).
  - In 189 cases (reporting 241 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Thrombocytopenia (30), Gastrointestinal haemorrhage (18), Haematemesis (15), Dyspnoea (14), Cardiac arrest (13), Contusion (11), and Vomiting (10). Of note, in 21 cases limited information regarding the cause of death was provided (PT Death) or not reported the cause of death. Most (127 of 189 cases) of these fatal cases involved subjects who were ≥75 years of age. When the medical history was provided (150 cases), significant medical conditions included atrial fibrillation, cardiac failure, cerebral infarction, cerebrovascular accident, chronic kidney disease, chronic obstructive pulmonary disease, haemorrhagic stroke, renal failure and various malignancies. Of note, few patients received anticoagulants or nonsteroidal anti-inflammatory agents as concomitant medications.

- The lot/batch number which reported ≥2% of cases reporting immune mediated/autoimmune AESIs is: #EJ6795 (211 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT: Adults (10) and Elderly (9).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (61), Adults (5870), Elderly (2600) and Unknown (899).
  - A significantly higher reporting proportion of events coded to the PTs Vaginal haemorrhage and Intermenstrual bleeding was observed in adult population when compared to elderly population (Vaginal haemorrhage [5.7% in adults vs 0.8% in elderly] and Intermenstrual bleeding [4.1% in adults vs 0.2% in elderly]. It is expected that the women of reproductive age will have more bleeding than the elderly population. In paediatric population, vaginal haemorrhage and intermenstrual bleeding was reported in 1 case each. While the reporting proportion of PT Vaccination site haemorrhage was significantly higher in paediatric population (9.8%)

when compared to adults and elderly population (1.8% and 2.3% in adults and elderly population, respectively).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 3136 (33.2% of the CT and PM cases reporting haematological AESIs).

- The reporting proportion of haematological AESIs with fatal outcome (3.8%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.0%).

O/E Analysis

O/E analysis was performed for Haemorrhage, Immune thrombocytopenia, and Thrombocytopenia (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No signals for the hematological AESIs have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.7. Hepatic AESIs

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

Clinical Trial Data

- Number of cases: 1 (0.1% of 702 cases, the total CT dataset; the case involved BNT162b2).

- A 62-year-old male subject in [redacted] received BNT162b2 and reported relevant events coded to the PTs Alanine aminotransferase increased and Aspartate aminotransferase increased (1 each). Time to onset of events was recorded as 74 days. The events were assessed as unrelated to BNT162b2 by the investigator and the Sponsor.

Post-Authorization Data

Number of cases: 551. Upon review, 1 case was determined to be non-contributory and is not included in the discussion since this case involved a baby who was indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 550 (0.2% of 327,125 cases, the total PM dataset).

- MC cases (391), NMC cases (159).

- Country of incidence: US (113), UK (94), France (66), Japan (62), Germany (30), Italy (24), Netherlands, Spain (18 each), Austria, Israel, Sweden (10 each), Belgium, Canada, Denmark, Greece, Hungary (7 each), Czech Republic (6); the remaining 54 cases were distributed among 22 countries.

- Subjects' gender: female (335), male (199), and unknown (16).

- Subjects' age in years (n = 483), range: 16 – 104, mean 57.2, median 59.

- Medical history (n = 368 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Type 2 diabetes mellitus (21), Diabetes mellitus, Hypothyroidism (17 each), Hyperlipidaemia, Obesity (12 each), Cholecystectomy (10), Dyslipidaemia (9), Alcohol use and Hypercholesterolaemia (8 each). Of note, more than 1 medical history was reported in some cases.

- COVID-19 Medical history (n = 42 cases). Medical conditions reported more than once were coded to the PTs COVID-19 (24), Suspected COVID-19 (14), COVID-19 pneumonia (3), Asymptomatic COVID-19 and SARS-CoV-2 antibody test positive (2 each). Of note, more than 1 medical history was reported in some cases.

- Co-suspects: 25 cases. Relevant co-suspects reported more than once were paracetamol, atorvastatin (3 each), adalimumab, amoxicillin-clavulanic acid, apixaban, and palbociclib (2 each).

- Number of relevant events: 714.

- Relevant event seriousness: serious (359) and non-serious (355).

- Most frequently reported relevant PTs (≥2%): Alanine aminotransferase increased (99), Hepatic enzyme increased (66), Aspartate aminotransferase increased (62), Hepatic function abnormal (60), Liver function test abnormal (52), Transaminases increased (49), Hepatic pain (47), Gamma-glutamyltransferase increased (46), Liver function test increased (41), Blood bilirubin increased (37), Blood alkaline phosphatase increased (29), Liver injury (23), Hepatic enzyme abnormal and Hepatomegaly (16 each).

- Time to event onset (n = 438 events)[66], range: <24 hours to 83 days, median 5 days.

  - <24 hours: 47 events (2 of which had a fatal outcome);
  - 1 day: 64 events;
  - 2-7 days: 166 events (4 of which had a fatal outcome);
  - 8-14 days: 76 events;
  - 15-30 days: 64 events;

[66] This number does not include 3 events for which partial administration or event onset dates were reported.

- 31-181 days: 21 events (1 of which had a fatal outcome).

- Duration of relevant events (n = 44 out of 109 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 37 days, with a median of 7 days.
  - 1 day: 9 events;
  - 2-7 days: 16 events;
  - 8-14 days: 5 events;
  - 15-30 days: 11 events;
  - 31-181 days: 3 events.

- Relevant event outcome: fatal (12), resolved/resolving (203), resolved with sequelae (8), not resolved at the time of reporting (119), and unknown (372).
  - In 12 cases (reporting 12 relevant events with a fatal outcome), the cause of death (≥3 occurrences) were coded to the PTs General physical health deterioration (4), Liver function test abnormal and Renal failure (3 each). When the medical history was provided (11 cases), the subject's medical condition included alcoholism, breast cancer, cholecystitis, ischaemic cardiomyopathy, liver disorder, renal failure. Eight (8) of the 12 cases involved subjects who were ≥80 years of age.

- The lot/batch number which reported ≥2% of cases reporting hepatic events is: #EM0477 (14 cases), #ET3674 (13 cases), and #EJ6788 (11 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT: Adult (1)

- PM: Paediatric (3), Adults (284), Elderly (201) and Unknown (62).
  - Among the frequently (≥2%) reported relevant hepatic events, PT Hepatic pain was reported significantly higher in adult population when compared to elderly population (13% in adult vs 3% in elderly). No cases reported events coded to the PT Hepatic pain in the paediatric population. Upon further review, the majority of the events (hepatic pain) was assessed as non-serious in adult population (25 of 37 events).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 202 (36.7% of the CT and PM cases reporting hepatic AESIs).

- The reporting proportion of hepatic AESIs with fatal outcome (2.1%) is slightly higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.1%)

O/E Analysis

O/E analysis was performed for Acute liver injury/Liver injury (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Hepatic events were a safety topic determined not to be validated signals. No other safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.8. Immune-mediated/autoimmune AESIs

- Search Criteria: SMQ Immune-mediated/autoimmune disorders (Broad and Narrow) OR HLGT (All Path) Autoimmune disorders OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity.

Clinical Trial Data

- Number of cases: 15 (2.1% of 702 cases, the total CT dataset; 7 cases involved BNT162b2/BNT162b1 and 8 cases involved blinded therapy).
- Country of incidence: US (14) and China (1).
- Subjects' gender: female (9) and male (6).
- Subjects' age in years (n = 15), range: 33 – 82, mean 53.5, median 51.
- Medical history (n = 13 cases): the relevant subjects' medical conditions reported more than once were coded to the PTs Type 2 diabetes mellitus (4), Hypothyroidism (3), and Seasonal allergy (2). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history: None.
- Co-suspects: 4. The co-suspects reported were calcium folinate, fluorouracil, irinotecan, and oxaliplatin (1 each).
- Reported relevant PTs (15): Diabetic ketoacidosis (4), Pancreatitis (3), Colitis, Enterocolitis, Eosinophilic oesophagitis, Hypersensitivity, Hyperthyroidism, Myasthenia gravis, Pericarditis, and Polymyalgia rheumatica (1 each). Of the above SAEs, Polymyalgia rheumatica (time to onset of event: 58 days; with event outcome resolving) and Hyperthyroidism (time to onset of event: 218 days; with event outcome resolving) were assessed as related to BNT162b2 and BNT162b1, respectively. All the other SAEs were assessed as not related to blinded therapy.

Post-Authorization Data

Number of cases: 6906. Upon review, 4 cases were determined to be non-contributory and are not included in the discussion since these 4 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 6902 (2.1% of 327,125 cases, the total PM dataset).
- MC cases (3898), NMC cases (3004).
- Country of incidence: US (1587), UK (1461), France (532), Italy (459), Germany (420), Japan (349), Israel (229), Spain (186), Sweden (117), Mexico (115), Netherlands (114); the remaining 1333 cases were distributed among 50 countries.
- Subjects' gender: female (4735), male (1863), and unknown (304).
- Subjects' age in years (n = 6057), range: 12 – 100, mean 68.1, median 51.
- Medical history (n = 4134 cases): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Asthma (406), Drug hypersensitivity (390), Hypersensitivity (311), Food allergy (275), Seasonal allergy (240), Diabetes mellitus (192), Hypothyroidism (180), Psoriasis (132), Type 2 diabetes mellitus (114), Immunodeficiency (110), Colitis ulcerative (103), and Rheumatoid arthritis (102). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n = 370 cases): Medical conditions reported more than twice were coded to the PTs COVID-19 (205), Suspected COVID-19 (139), SARS-CoV-2 test positive (11), Exposure to SARS-CoV-2 (7), COVID-19 pneumonia, Occupational exposure to SARS-CoV-2 (5 each), Coronavirus infection and Post-acute COVID-19 syndrome (3 each). Of note, more than 1 medical history was reported in some cases.
- Co-suspects: 151 cases. Frequently (>5 occurrences) reported relevant co-suspects were adalimumab (14) and paracetamol (6)
- Number of relevant events: 7152
- Relevant event seriousness: serious (4669) and non-serious (2483).
- Most frequently reported relevant PTs (≥2%): Hypersensitivity (3177), Myocarditis (502), Pericarditis (364), Dermatitis (207), and Psoriasis (172).
- Time to event onset (n = 4703),[67] range: <24 hours to 151 days, median 1 day.

[67] This number does not include 10 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- <24 hours: 1857 events (5 of which had a fatal outcome);
- 1 day: 740 events (7 of which had a fatal outcome);
- 2-7 days: 1192 events (18 of which had a fatal outcome);
- 8-14 days: 445 events (9 of which had a fatal outcome);
- 15-30 days: 313 events (9 of which had a fatal outcome);
- 31-181 days: 156 events (1 of which had a fatal outcome).

- Duration of relevant events (n = 765 out of 1822 occurrences with outcome of resolved/resolved with sequelae), range: 5 minutes to 99 days, median 1 day.

  - <24 hours: 182 events;
  - 1 day: 218 events;
  - 2-7 days: 224 events;
  - 8-14 days: 64 events;
  - 15-30 days: 41 events;
  - 31-181 days: 36 events.

- Relevant event outcome:[34] fatal (82), resolved/resolving (3069), resolved with sequelae (116), not resolved at the time of reporting (1524), and unknown (2386).

  - In 77 cases (reporting 82 relevant events with a fatal outcome), the reported cause of death (≥4 occurrences) were coded to the PTs Myocarditis (15), Dyspnoea (7), Interstitial lung disease (6), Acute respiratory failure, Diabetes mellitus, Encephalitis (5 each), Condition aggravated, Diabetic ketoacidosis, Haemophagocytic lymphohistiocytosis, Hypersensitivity, and Toxic epidermal necrolysis (4 each). Of note, in 3 cases limited information regarding the cause of death was provided (PT Death). Most (61 of 77 cases) of the fatal cases involved elderly subjects. When the medical history was provided (53 cases), significant medical conditions included cardiac failure, chronic obstructive pulmonary disease, COVID-19, dermatitis atopic, general physical health deterioration, hypersensitivity idiopathic pulmonary fibrosis, interstitial lung disease, type 1 and 2 diabetes mellitus, and various malignancies.

- The lot/batch number which reported ≥2% of cases reporting immune mediated/autoimmune AESIs is: #EM0477 (192 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT: Adults (13) and Elderly (2).

- PM: Paediatric (92), Adults (4437), Elderly (1594) and Unknown (779).

  - Among the frequently (≥2%) reported immune mediated/autoimmune AESIs, a higher reporting proportion of events coded to the PTs Myocarditis and Pericarditis were observed in paediatric population when compared to adult or elderly population

(Myocarditis [53.3.% in paediatrics vs 8.6% in adults vs 3.1% in elderly] and Pericarditis [14.1% in paediatrics vs 4.9% in adults vs 6.5% in elderly]).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 2392 (34.6% of the CT and PM cases reporting immune mediated/autoimmune AESIs).

- The reporting proportion of immune mediated/autoimmune AESIs with a fatal outcome (1.6%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.8% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Autoimmune thyroiditis, Encephalitis, Myasthenia gravis, Myelitis, Myocarditis, Pericarditis, Polymyalgia rheumatica,[68] Thrombocytopenic purpura,[69] Thrombotic thrombocytopenic purpura,[69] Type 1 diabetes mellitus, and Urticarial vasculitis[68] (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

- Myocarditis and Pericarditis is an ongoing signal[70] (see Section 16.2.2).
  The O/E analysis for myocarditis, is >1 in some age-stratified analyses in the 14-and 21-day risk windows. A warning about myocarditis has been added to product information. It should be noted that O/E may be influenced by factors including an increased awareness and diagnosis by HCPs.

- The O/E analysis for Myasthenia gravis is >1 in the 14-day risk window. Of note, on case review over half of the observed cases occurred in patients with underlying myasthenia gravis (for further analysis see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*),

- The O/E analysis for Transverse myelitis is above 1, however, the observed cases include both transverse myelitis and myelitis while the expected case count is based on a background rate for transverse myelitis only, which may be appropriate for signal detection. The O/E ratio would be lower if only transverse myelitis reports were included. Future O/E of transverse myelitis will include a narrower inclusion criteria for the observed cases.

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[68] Included under Vasculitis in Appendix 6C.

[69] Included under Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia in Appendix 6C.

[70] Myocarditis and pericarditis was closed as Important Identified Risk after the PSUR DLP.

- Cases myasthenia gravis, polyneuropathy, and transverse myelitis will continue to be reviewed and monitored.

No new safety signals have emerged based on a review of the remaining events and on O/E analysis. Safety surveillance will continue.

16.3.3.1.9. Musculoskeletal AESIs

- Search Criteria: PTs Arthralgia; Arthritis; Chronic fatigue syndrome; Polyarthritis; Post viral fatigue syndrome; Rheumatoid arthritis.

Clinical Trial Data

- Number of cases: 2 (0.28% of 702 cases, the total CT dataset; 1 case involved BNT162b2; and other case involved blinded therapy).
- Country of incidence: [redacted] (2).
- Subjects' gender: female (2).
- Subjects' age: 58 years in both cases.
- Number of subjects' reporting medical history: 2 cases.
- Relevant subjects' medical histories reported coded to the PTs Arthritis, Hip fracture, Joint injury, Obesity, Osteoarthritis (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PT (2): Arthritis (2), not related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of relevant cases: 36,146 (11.05% of 327,125 cases, the total PM dataset).
- MC cases (21,105), NMC cases (15,041).
- Country of incidence(≥100 occurrences): Italy (8097),UK (6472), Mexico (4782),US (4273), Netherlands (3496), Spain (1063), Austria (1053), France (948), Japan (583), Czech Republic (579), Germany (525), Australia (478), Belgium (452), Portugal (423), Sweden (304), Norway (303), Ireland (253), Denmark (240), Finland (171), Greece (159), Poland (151), Canada (139), Romania (114), Estonia (110), Lithuania (107), Hungary (102); the remaining 769 cases were distributed among 41 countries.
- Subjects' gender: female (27,973), male (7456), and No data (717).

- Subjects' age in years (n = 33,839)[71], range: 12 – 101, mean 46.9, median 47.

- Number of subjects' reporting medical history: 15463 cases.

- Relevant subjects' medical histories most frequently (≥20 occurrences) reported coded to the PTs Hypothyroidism (517), Rheumatoid arthritis (492), Arthritis (445), Osteoarthritis (304), Obesity (176), Spinal osteoarthritis (32), Joint injury (28), Alcohol use (26), Autoimmune hypothyroidism (20). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 medical history: (n = 3253 cases). Medical conditions reported were coded to the PTs COVID-19 (1780), Suspected COVID-19 (1274), SARS-CoV-2 test positive (101), COVID-19 pneumonia (30), SARS-CoV-2 antibody test positive (25), Exposure to SARS-CoV-2 (13), Asymptomatic COVID-19 (9), SARS-CoV-2 test (8), SARS-CoV-2 antibody test (6), Occupational exposure to SARS-CoV-2, Post-acute COVID-19 syndrome (3 each), COVID-19 prophylaxis (1). Of note, more than 1 relevant medical history was reported in some cases.

- Co-suspects: 207 cases. Reported relevant co-suspects were atorvastatin calcium (3), leflunomide (2), amitriptyline, furosemide, olanzapine, pitavastatin (1 each).

- Number of relevant events: 36,454

- Relevant event seriousness[62]: serious (6685), non-serious (29,776)

- Most frequently reported relevant PTs (≥50 occurrences): Arthralgia (35410), Arthritis (568), Rheumatoid arthritis (251), Chronic fatigue syndrome (65), Post viral fatigue syndrome (61), Rhabdomyolysis (55), Polyarthritis (44).

- Time to relevant event onset (n = 30,107),[72] range: <24 hours to 117 days, median 1 day.

  - <24 hours: 12,283 events (3 of which had a fatal outcome);
  - 1 day: 13028 events (5 of which had a fatal outcome);
  - 2-7 days: 3629 events (4 of which had a fatal outcome);
  - 8-14 days: 620 events (4 of which had a fatal outcome);
  - 15-30 days: 385 events.
  - 31-180 days: 162 events.

- Duration of relevant events was reported in 6135 out of 15,249 occurrences with outcome of resolved/resolved with sequelae; it ranged from 5 minutes to 109 days.

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[71] Of note there were 8 cases with contradictory demographic information (physical characteristics not matching with the reported age value).

[72] This number does not include 6550 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- <24 hours: 459 events;
- 1 day: 1792 events;
- 2-7 days: 3645 events;
- 8-14 days: 102 events;
- 15-30 days: 89 events;
- 31-180 days: 48 events.

- Relevant event outcome (36,708):[34] fatal (19), resolved or resolving (21,958), resolved with sequelae (293), not resolved at the time of reporting (7020), and unknown (7418).

  - In 19 cases, the reported cause of death (≥2 occurrences) was coded to the PTs Arthralgia (16), Rhabdomyolysis (2). Most (17 of 19 cases) of the fatal cases involved elderly subjects. When the medical history was provided (13 cases), significant medical conditions included Rheumatoid arthritis, Osteoarthritis (3 each), Arthralgia, Hypothyroidism, Alcohol use (2 each), Arthritis (1).

- The lot/batch number which reported > 5% of cases involving musculoskeletal related ADRs is EL1484 (2283 cases) and EJ6797 (2196 cases). No quality issues were identified during investigations of the impacted lot.

Analysis by age group

- CT: Adult (2).

- PM: Paediatric (65), Adult (29,744), Elderly (4240), Unknown (2096).

  - No significant difference observed in the reporting proportion of frequently reported musculoskeletal AEs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 4930 (13.6% of the cases reporting musculoskeletal AESIs)

- A higher reporting proportion of musculoskeletal AESIs was reported in patients without significant comorbidities (86.4%) when compared to patients with significant comorbidities.

- The reporting proportion of musculoskeletal AESIs with resolved (42.9%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (29.2% of events with resolved).

O/E Analysis

O/E analysis was performed for Rheumatoid arthritis, Polyarthritis, Chronic fatigue syndrome, and Post viral fatigue syndrome (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.10. 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.

  – Upon review, 3 PM cases were determined to be non-contributory and are not included in the discussion since these 3 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route).

Clinical Trial Data

- Number of cases: 8 (1.14% 702 cases, the total CT dataset; 4 cases involved BNT162b2, 1 case involved placebo and 3 cases involved blinded therapy).
- Country of incidence: US (7), Argentina (1).
- Subjects' gender: female (1), male (7).
- Subjects' age in years (n = 8), range: 34 – 73, mean 51.1, median 49.
- Number of subjects' reporting medical history: 7 cases.
- Relevant subjects' medical histories reported coded to the PT Seizure (1).
- COVID-19 medical history: 1 case (COVID-19).
- Co-suspect: None.
- Reported relevant PTs: Seizure (3), Encephalopathy, Guillain-Barre syndrome, Hypergammaglobulinaemia benign monoclonal, Neuropathy peripheral, Optic neuritis (1 each). However, none of the SAE were assessed as related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of relevant cases: 3471 (1.1% of 327,125 cases, the total PM dataset).
- MC cases (2174), NMC cases (1297).

- Country of incidence (≥50 occurrences): UK (862), US (631), Japan (281), France (226), Italy (224), Mexico (187), Germany (172), Netherlands (118), Spain (113), Australia, Poland (52 each); the remaining 88 cases were distributed among 27 countries.

- Subjects' gender: female (2290), male (1064), and unknown (117).

- Subjects' age in years (n = 3155),[73] range: 12 – 107, mean 51.6, median 50.

- Number of subjects' reporting medical history: 2234 cases.

- Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Epilepsy (381), Seizure (133), Multiple sclerosis (114), Headache (36), Dementia Alzheimer's type (29), Trigeminal neuralgia (27), Generalised tonic-clonic seizure, Partial seizures, Polyneuropathy (20 each), Parkinson's disease (16), Ischaemic stroke (15), Petit mal epilepsy (13) and Relapsing-remitting multiple sclerosis (10). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 Medical history (n = 223 cases). Medical conditions reported were coded to the PTs COVID-19 (124), Suspected COVID-19 (80), COVID-19 pneumonia (6), SARS-CoV-2 test positive, Occupational exposure to SARS-CoV-2 (4 each), Asymptomatic COVID-19, Exposure to SARS-CoV-2, Post-acute COVID-19 syndrome, SARS-CoV-2 antibody test positive, SARS-CoV-2 test (1 each). Of note, more than 1 relevant medical history was reported in some cases.

- Co-suspects: 55 cases. Reported relevant co-suspect drug were carbamazepine, etanercept, tramadol, tacrolimus (1 each).

- Number of relevant events: 3809.

- Relevant event seriousness: serious (3446), non-serious (363).

- Most frequently reported relevant PTs (≥50 occurrences): Seizure (1165), Epilepsy (420), Neuropathy peripheral (398), Guillain-Barre syndrome (226), Generalised tonic-clonic seizure (175), Fibromyalgia (137), Trigeminal neuralgia (125), Febrile convulsion (107), Multiple sclerosis (99), Status epilepticus (86), Ataxia, Optic neuritis (66 each), Multiple sclerosis relapse (65), Myelitis transverse (55), Petit mal epilepsy (54).

- Time to relevant event onset (n = 2780)[74], range: <24 hours to 111 days, median 1 day.

  – <24 hours: 1016 events (5 of which had a fatal outcome);
  – 1 day: 588 events (8 of which had a fatal outcome);

[73] Of note there was 1 case with contradictory demographic information (physical characteristics not matching with the reported age value).

[74] This number does not include 1053 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

  - 2-7 days: 663 events (16 of which had a fatal outcome);
  - 8-14 days: 262 events (15 of which had a fatal outcome);
  - 15-30 days: 180 events (9 of which had a fatal outcome);
  - 31-180 days: 71 events (8 of which had a fatal outcome).

- Duration of relevant events (n = 501 out of 1289 occurrences with outcome of resolved/ resolved with sequelae), range: from 1 minute to 99 days.

  - <24 hours: 151 events;
  - 1 day: 204 events;
  - 2-7 days: 97 events;
  - 8-14 days: 20 events;
  - 15-30 days: 17 events;
  - 31-180 days: 12 events.

- Relevant event outcome: fatal (82), resolved or resolving (1793), resolved with sequelae (102), not resolved at the time of reporting (765), and unknown (1082). In 82 cases, the reported cause of death (≥5 occurrences) was coded to the PTs Seizure (31), Epilepsy (18), Guillain-Barre syndrome (6), Generalised tonic-clonic seizure, Status epilepticus (5 each). Most (57 of 82 cases) of the fatal cases involved elderly subjects. When the medical history was provided (26 cases), significant medical conditions included epilepsy (9), Dementia Alzheimer's type, Parkinson's disease (4 each), Seizure, Headache (2 each).

Analysis by age group

- CT: Adult (6) and Elderly (2).

- PM: Adolescent (49), Adult (2247), Elderly (895), unknown (280).

  - No significant difference observed in the reporting proportion of frequently reported neurological AEs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 1078 (31.5% of the cases reporting neurological AESIs). A higher reporting proportion of neurological AESIs was reported in patients without significant comorbidities (87.1%) when compared to patients with significant comorbidities.

- The reporting proportion of neurological AESIs with fatal outcome (3.5%) is higher in individuals with co morbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute disseminated encephalomyelitis (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 (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

- Seizure was a signal evaluated and determined not to be a risk. Optic neuritis and Polyneuropathy/Neuropathy peripheral were reviewed as safety topics and determined not to be validated signals.

- ADEM and Myelitis transverse are not validated signals.
  The O/E analysis for cases reporting ADEM narrow definition is slightly above 1. The number of cases reported are 21 nevertheless, 4 cases were meeting the BC definition of level 5, ie, not and ADEM case. If we would consider only ADEM cases meeting the BC level 1 to 4 (17 cases) the O/E analysis would be lower (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

No new safety signals have emerged based on a review of these cases or of the Observed versus Expected analysis. Safety surveillance will continue.

16.3.3.1.11. 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; Multiple organ dysfunction syndrome; 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; Systemic inflammatory response syndrome.

  – Upon review, 30 PM cases were determined to be non-contributory and are not included in the discussion since these 30 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route).

Clinical Trial Data

- Number of cases: 3 (0.43% of 702 cases, the total CT dataset; 1 case involved BNT162b2/placebo and 2 cases involved blinded therapy).

- Country of incidence: US (2), Brazil (1).

- Subjects' gender: male (3).

- Subjects' age in years (n = 3), range: 48 - 73 years, mean 62, median 65.

- Number of subjects' reporting medical history: 3 cases. Relevant subjects' medical histories reported coded to the PT Neoplasm malignant (1 each).

- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (3): Herpes zoster oticus, Multiple organ dysfunction syndrome, Pyrexia (1 each). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of cases: 70,105 (21.4% of 327,125 cases, the total PM dataset).
- MC cases (43,119), NMC cases (26,986).
- Country of incidence (≥100 occurrences): Italy (15,166), UK (10,209), US (9397), Mexico (5253), Spain (5081), Netherlands (4108), France (2853), Germany (2115), Austria (1982), Japan (1970), Portugal (1012), Czech Republic (997), Belgium (993), Sweden (932), Norway (883), Australia (728), Denmark (678), Ireland (662), Greece (456), Finland (448), Estonia (406), Poland (401), Romania (354), Hungary (352), Lithuania (324), Israel (264), Canada (244), Croatia (195), Switzerland (175), Slovakia (156), Serbia (140), Latvia (123), Hong Kong (120), Luxembourg(113); the remaining 815 cases were distributed among 44 countries.
- Subjects' gender: female (53,099), male (15,284), and unknown (1722).
- Subjects' age in years (n = 64,584), range: 12 – 120, mean 46.9, median 46.
- Medical history (n = 27,409). Relevant subjects' medical histories most frequently (≥50 occurrences) reported coded to the PTs Herpes zoster (450), Immunodeficiency (293), Breast cancer (277), Neoplasm malignant (110), Prostate cancer (90), Oral herpes (79), Herpes simplex (58), Thyroid cancer (49), Lung neoplasm malignant (45). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 7480 cases). Medical conditions (≥50 occurrences) reported were coded to the PTs COVID-19 (4517), Suspected COVID-19 (2243), SARS-CoV-2 test positive (236), COVID-19 pneumonia (114), Coronavirus infection (80), Exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (52 each), Asymptomatic COVID-19 (51).
- Co-suspects: 339 cases. Reported relevant co-suspects were apixaban (8), etanercept (7), adalimumab (6), methotrexate sodium (5), aflibercept, infliximab, rituximab (1 each).
- Number of relevant events: 71,230.
- Relevant event seriousness: serious (13,136), non-serious (58,112).

- Most frequently reported relevant PTs (≥ 25 occurrences): Pyrexia (64,212), Herpes zoster (3215), Inflammation (2040), Oral herpes (780), Ophthalmic herpes zoster (130), Herpes simplex (124), Herpes virus infection (105), Multiple organ dysfunction syndrome (79), Product supply issue (76), Genital herpes (69), Herpes zoster reactivation (46), Herpes ophthalmic (43), Herpes zoster oticus (41), Nasal herpes, Systemic inflammatory response syndrome, Varicella (32 each), and Herpes simplex reactivation (26).

- Time to relevant event onset (n = 60,334),[75] range: <24 hours to 151 days, median 1 day.

  - <24 hours: 23,640 events (41 of which had a fatal outcome);
  - 1 day: 27211 events (82 of which had a fatal outcome);
  - 2-7 days: 6380 events (99 of which had a fatal outcome);
  - 8-14 days: 1460 events (25 of which had a fatal outcome);
  - 15-30 days: 1178 events (25 of which had a fatal outcome);
  - 31-180 days: 465 events (11 of which had a fatal outcome).

- Duration of relevant events (n = 16,677 out of 36,255 occurrences with outcome of resolved/ resolved with sequelae), range: from 1 second to 116 days.

  - <24 hours: 1527 events;
  - 1 day: 5716 events;
  - 2-7 days: 8666 events;
  - 8-14 days: 425 events;
  - 15-30 days: 213 events;
  - 31-180 days: 130 events.

- Relevant event outcome:[34] fatal (351), resolved or resolving (48,722), resolved with sequelae (610), not resolved at the time of reporting (8995), and unknown/no data (12,925).

  - In 351 cases, the reported cause of death (≥50 occurrences) was coded to the PTs Multiple organ dysfunction syndrome (57). Most (310 of 351 cases) of the fatal cases involved elderly subjects.

- The lot/batch number which reported > 5% of cases involving other AESI related ADRs is EJ6797, EK9788, and EJ6136. No quality issues were identified during investigations of the impacted lot.

[75] This number does not include 11,240 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

Analysis by age group

- CT: Adult (1) and Elderly (2).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (245), Adult (56,190), Elderly (8941), and Unknown (4729).
  - No significant difference observed in the reporting proportion of frequently reported other AESIs (≥2%) between adult and elderly population.

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 9022 (12.9% of the cases reporting other AESI AESIs). A higher reporting proportion of other AESIs was reported in patients without significant comorbidities (87.1%) when compared to patients with significant comorbidities.
- The reporting proportion of other AESIs with fatal outcome (2.2%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.2% of events with fatal outcome).

O/E Analysis

O/E analysis was performed on Herpes zoster, Herpes ophthalmic, Herpes zoster oticus, Multiple organ dysfunction syndrome, Systemic inflammatory response syndrome (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

- Herpes zoster, including Ophthalmic herpes zoster, was a signal evaluated and determined not to be a risk.
- O/E analysis for Multisystem inflammatory syndrome is >1 in some age-stratified analyses in the 14- and 21-day risk windows. This may be influenced by factors including its association with COVID-19 and an increased awareness of this condition by HCPs.
- No other safety signals have emerged based on a review of these cases.

16.3.3.1.12. Pregnancy related AESIs

- Search Criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia.

For relevant cases, please refer to the Section 16.3.5.3 *Use in Pregnant/Lactating Women.*

16.3.3.1.13. Renal AESIs

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

Clinical Trial Data

- Number of cases: 3 (0.43% of 702 cases, the total CT dataset; 2 cases involved BNT162b2 and 1 case involved blinded therapy).
- Country of incidence: [redacted] (3).
- Subjects' gender: female (1), male (2).
- Subjects' age in years (n = 3), range: 32 – 81, mean 60.7, median 69.
- Medical history (n = 3 cases). Relevant subjects' medical histories reported coded to the PTs Renal artery stenosis, and Type 2 diabetes mellitus (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (3): Acute kidney injury (3). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

Post-Authorization Data

- Number of cases: 387 (0.12% of 327,125 cases, the total PM dataset).
- MC cases (309), NMC cases (78).
- Country of incidence: France (66), UK (57), Germany (44), US (43), Italy (25), Spain (21), Netherlands (14), Sweden (12), Belgium, Denmark, Japan (11 each); the remaining 72 cases were distributed among 20 countries.
- Subjects' gender: female (203), male (178), and Unknown (6).
- Subjects' age in years (n = 367), range: 18 – 103, mean 76.5, median 81.
- Medical history (n = 316 cases). Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Chronic kidney disease (53), Type 2 diabetes mellitus (50), Diabetes mellitus (28), Obesity (24), Renal failure (22),Acute kidney injury (12). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 19 cases). Medical conditions reported were coded to the PTs COVID-19 (11), Suspected COVID-19 (3), Asymptomatic COVID-19, COVID-19 pneumonia, COVID-19 immunisation, COVID-19 prophylaxis, Exposure to SARS-CoV-2(1 each).

- Co-suspects: 27 cases. Reported relevant co-suspects were methotrexate sodium, tacrolimus, valaciclovir hydrochloride, zoledronic acid monohydrate.

- Number of relevant events: 391.

- Relevant event seriousness: serious (389), non-serious (2).

- Most frequently reported relevant PTs: Acute kidney injury (224), Renal failure (167).

- Time to relevant event onset (n = 229)[76], range: <24 hours to 71 days, median 5 days.

  – <24 hours: 22 events (6 of which had a fatal outcome);
  – 1 day: 24 events (5 of which had a fatal outcome);
  – 2-7 days: 94 events (31 of which had a fatal outcome)
  – 8-14 days: 45 events (11 of which had a fatal outcome);
  – 15-30 days: 32 events (13 of which had a fatal outcome);
  – 31-180 days: 12 events (2 of which had a fatal outcome).

- Duration of relevant events (n = 17 out of 44 occurrences with outcome of resolved/resolved with sequelae), range: 1 - 47 days.

  – 1 day: 1 event;
  – 2-7 days: 7 events;
  – 8-14 days: 6 events;
  – 15-30 days: 2 events;
  – 31-180 days: 1 event.

- Relevant event outcome: fatal (106), resolved or resolving (88), resolved with sequelae (4), not resolved at the time of reporting (60), and unknown (133). In 106 cases, the reported cause of death was coded to the PTs Acute kidney injury (52), Renal failure (54). Most (95 of 106 cases) of the fatal cases involved elderly subjects. When the medical history was provided (73 cases), significant medical conditions included Chronic kidney disease (22), Type 2 diabetes mellitus (13), Diabetes mellitus (15), Obesity (8), Renal failure (12), Acute kidney injury (3).

- The lot/batch number which reported >3% of cases involving renal related ADRs is EM0477 and EJ6788. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

- CT: Adult (1) and Elderly (2).

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[76] This number does not include 162 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- PM: Adult (64), Elderly (307) and Unknown (16).
  - 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 [24.7% in adults vs 37.5% in elderly].

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 259 (66.9% of the cases reporting renal AESIs).
- The reporting proportion of renal AESIs with fatal outcome (30.5%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (19% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute kidney injury and Renal failure (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No new safety signals have emerged based on a review of these cases. Safety surveillance will continue.

16.3.3.1.14. 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; Pulmonary haemorrhage; Respiratory disorder.

Clinical Trial Data

- Number of cases: 28 (4% of 702 cases, the total CT dataset; 15 cases involved BNT162b2, 12 cases involved blinded therapy and 1 case involved placebo).
- Country of incidence: US (20), Argentina (5), Brazil (2), Japan (1).
- Subjects' gender: female (12), male (16).
- Subjects' age in years (n = 28), range: 22 – 84, mean 62.4, median 68.
- Medical history (n = 22 cases). Relevant subjects' medical histories reported coded to the PTs Asthma, Chronic obstructive pulmonary disease (3 each), Asthma exercise induced,

Interstitial lung disease, Lung neoplasm malignant, Nicotine dependence, Seasonal allergy, Tobacco user (1 each).

- COVID-19 medical history (n = 1 case). The subjects' medical history was significant for COVID-19.

- Co-suspects: None.

- Reported relevant PTs (30): Pneumonia (15), Acute respiratory failure (8), Respiratory failure (3), Cardio-respiratory arrest (2), Lower respiratory tract infection, Respiratory syncytial virus bronchiolitis (1 each). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of cases: 2263 (0.7% of 327,125 cases, the total PM dataset).

- MC cases (1534), NMC cases (729).

- Country of incidence: US (359), UK (286), France (236), Japan (218), Italy (149), Germany (121), Spain (119), Belgium (104), Netherlands (87), Mexico (61), Norway (55), Australia (50); the remaining 418 cases were distributed among 45 countries.

- Subjects' gender: female (1258), male (959), and unknown (46).

- Subjects' age in years (n = 2066), range: 12 – 102, mean 69.1, median 74.

- Medical history (n = 1613 cases). Relevant subjects' medical histories most frequently (≥10 occurrences) reported coded to the PTs Chronic obstructive pulmonary disease (175), Asthma (169), Pneumonia (78), Lower respiratory tract infection (38), Pulmonary embolism (32), Seasonal allergy (27), Bronchitis (24), Lung disorder (18), Chronic respiratory failure, Respiratory failure (17 each), Lung neoplasm malignant (16), Bronchitis chronic (14), Respiratory tract infection (12), Pleural effusion, Pneumonia aspiration (11 each), Pulmonary fibrosis (10). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 Medical history (n = 189 cases). The subjects' medical history was significant for COVID-19 or suspected COVID-19. The most frequently reported medical conditions (≥5 occurrences) were coded to the PTs COVID-19 (99), Suspected COVID-19 (52), COVID-19 pneumonia (13), Exposure to SARS-CoV-2 (7). Of note, more than 1 relevant medical history was reported in some cases.

- Co-suspects: 56 cases. Reported relevant co-suspects were adalimumab, atorvastatin (2 each), amiodarone hydrochloride, cyclophosphamide, etanercept, methotrexate sodium, phenytoin sodium, rituximab (1 each).

- Number of relevant events: 2468.

- Relevant event seriousness:[62] serious (2216), non-serious (253).

- Most frequently reported relevant PTs (≥ 50 occurrences): Pneumonia (831), Respiratory disorder (329), Respiratory failure (280), Cardio-respiratory arrest (227), Hypoxia (210), Lower respiratory tract infection (184), Bronchitis (151), Acute respiratory failure (96) and Acute respiratory distress syndrome (60).

- Time to relevant event onset (n = 1673),[77] range: <24 hours to 124 days, median 0 day.

  - <24 hours: 327 events (56 of which had a fatal outcome);
  - 1 day: 290 events (102 of which had a fatal outcome);
  - 2-7 days: 580 events (199 of which had a fatal outcome);
  - 8-14 days: 214 events (71 of which had a fatal outcome);
  - 15-30 days: 178 events (63 of which had a fatal outcome);
  - 31-180 days: 84 events (19 of which had a fatal outcome).

- Duration of relevant events (n = 139 out of 371 occurrences with outcome of resolved/resolved with sequelae), range: from 20 minutes to 61 days.

  - <24 hours: 17 events;
  - 1 day: 22 events;
  - 2-7 days: 49 events;
  - 8-14 days: 30 events;
  - 15-30 days: 15 events;
  - 31-180 days: 6 events.

- Relevant event outcome[34]: fatal (667), resolved or resolving (704), resolved with sequelae (22), not resolved at the time of reporting (341), and unknown (736).

  - In 667 cases, the reported cause of death (≥10 occurrences) was coded to the PTs Pneumonia (185), Cardio-respiratory arrest (180), Respiratory failure (124), Acute respiratory failure (43), Hypoxia (33), Acute respiratory distress syndrome (27), Cardiopulmonary failure (24), Respiratory disorder (14), Lower respiratory tract infection (11). Most (536 of 667 cases) of the fatal cases involved elderly subjects. When the medical history was provided (496 cases), significant medical conditions included Chronic obstructive pulmonary disease (71), Asthma (169), Pneumonia (28), Lower respiratory tract infection (5), Pulmonary embolism (15), Lung neoplasm malignant (13), Bronchitis, Lung disorder, Respiratory tract infection Respiratory failure, Pleural effusion, Pulmonary fibrosis (7 each), Seasonal allergy (5), Pneumonia aspiration (4).

[77] This number does not include 801 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- The lot/batch number which reported >2% of cases involving respiratory related ADRs is EM0477, EJ6796, EK9788 and EJ6795. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

- CT: Adult (13) and Elderly (15).
- PM: Paediatric (5), Adult (746), Elderly (1335) and Unknown (177).
  - 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 Respiratory disorder and Lower respiratory tract infection was observed in adult population when compared to elderly population (Respiratory disorder [15.3% vs 5.6%], Lower respiratory tract infection [18.2% vs 4.8%].

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 1108 (48.4% of the cases reporting respiratory AESIs).
- A higher reporting proportion of respiratory AESIs was reported in patients without significant comorbidities (51.6 %) when compared to patients with significant comorbidities.
- The reporting proportion of respiratory events with fatal outcome (35.8%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (16.1%).

O/E Analysis

O/E analysis was performed for Acute respiratory distress syndrome (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

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

16.3.3.1.15. Thromboembolic AESIs

- Search Criteria: HLGT (All path) Embolism and thrombosis, excluding PTs reviewed as Stroke AESIs.

Clinical Trial Data

- Number of cases: 23 (3.3% of 702 cases, the total CT dataset; 15 cases involved BNT162b2, 5 cases involved blinded therapy, and 3 cases involved placebo).

- Country of incidence: US (14), Brazil (4), Argentina (3), South Africa and Turkey (1 each).
- Subjects' gender: female (9) and male (14).
- Subjects' age in years (n = 23 cases), range: 16 – 74, mean 52.2, median 55.
- Medical history (n = 22 cases): the frequently (≥3 cases) reported relevant medical conditions included Hypertension (7), Deep vein thrombosis (5), Nephrolithiasis, Pulmonary embolism (4 each), and Hypercholesterolaemia (3). Of note, more than 1 medical history was reported in some cases.
- COVID-19 medical history (n = 2 cases): COVID-19 (2).
- Co-suspects: 3. The co-suspects reported were drospirenone/ethinylestradiol, ethinylestradiol/levonorgestrel, and naproxen (1 each)
- Reported relevant PTs (27): Pulmonary embolism (13), Deep vein thrombosis (8), Embolism, Portal vein thrombosis, Portosplenomesteric venous thrombosis, Renal vein thrombosis, Thrombosis, and Venous thrombosis limb (1 each). Of the above SAEs, Portal vein thrombosis was assessed as related to BNT162b2 (time to onset of event was recorded as 60 days and the event outcome was reported as resolved). None of other SAEs were related to blinded therapy or placebo.

Post-Authorization Data

Number of cases: 4726. Upon review, 1 case was determined to be non-contributory and is not included in the discussion since this case involved a foetus who was indirectly exposed to BNT162b2 (transplacental route).

- Number of relevant cases: 4725 (1.4% of 327,125 cases, the total PM dataset).
- MC cases (3117), NMC cases (1608).
- Country of incidence: UK (755), US (700), France (623), Germany (445), Italy (323), Spain (270), Sweden (228), Netherlands (226), Norway (127), Denmark (106); the remaining 922 cases were distributed among 50 countries.
- Subjects' gender: female (2653), male (1956) and unknown (116).
- Subjects' age in years (n = 4370), range: 13 – 102, mean 58, median 70.
- Medical history (n = 3175 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (918), Type 2 diabetes mellitus (193), Deep vein thrombosis (177), Pulmonary embolism (167), Diabetes mellitus (164), Obesity (159), Hypothyroidism (152), Hypercholesterolaemia (127), Atrial fibrillation, Chronic obstructive pulmonary disease (121 each), Dyslipidaemia (116),

Osteoarthritis (92), Tobacco user (90), Chronic kidney disease (89), Rheumatoid arthritis (86), Thrombosis (83), Cerebrovascular accident (79), Breast cancer (78), Varicose vein (71), and Ex-tobacco user (63). Of note, more than 1 medical history was reported in some cases.

- COVID-19 Medical history (n = 229 cases). Medical conditions reported more than twice were coded to the PTs COVID-19 (148), Suspected COVID-19 (58), COVID-19 pneumonia (12), SARS-CoV-2 test positive (9), Asymptomatic COVID-19 (4), and Exposure to SARS-CoV-2 (3). Of note, more than 1 medical history was reported in some cases.

- Co-suspects: 119 cases. Frequently (≥3 occurrences) reported relevant co-suspects were COVID-19 AstraZeneca vaccine (8), ethinylestradiol/levonorgestrel (5), cisplatin, methotrexate, and prednisone (3 each).

- Number of relevant events: 5517.

- Relevant event seriousness[62]: serious (5297), non-serious (221).

- Most frequently reported relevant PTs (≥2%): Pulmonary embolism (1758), Deep vein thrombosis (1197), Thrombosis (1030), Thrombophlebitis superficial (207), Thrombophlebitis (152), Pulmonary thrombosis (114), Coagulopathy (113), Venous thrombosis limb (108), and Embolism (107).

- Time to event onset (n = 4196),[78] range: <24 hours to 140 days, median 8 days.

  - <24 hours: 215 events (13 of which had a fatal outcome);
  - 1 day: 373 events (26 of which had a fatal outcome);
  - 2-7 days: 1446 events (80 of which had a fatal outcome);
  - 8-14 days: 954 events (39 of which had a fatal outcome);
  - 15-30 days: 867 events (48 of which had a fatal outcome);
  - 31-181 days: 341 events (14 of which had a fatal outcome).

- Duration of relevant events (n = 230 out of 718 occurrences with outcome of resolved/resolved with sequelae), range: 8 minutes to 94 days, median 7 days.

  - <24 hours: 4 events;
  - 1 day: 28 events;
  - 2-7 days: 90 events;
  - 8-14 days: 53 events;
  - 15-30 days: 37 events;
  - 31-181 days: 18 events.

[78] This number does not include 6 events for which partial administration and/or event onset dates were reported.

- Relevant event outcome[34]: fatal (325), resolved/resolving (2344), resolved with sequelae (158), not resolved at the time of reporting (1447), and unknown (1266).
  - In 275 cases (reporting 325 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Pulmonary embolism (166), Thrombosis (33), Cardiac arrest (24), Dyspnoea (21), Deep vein thrombosis (18), Pyrexia, Thrombocytopenia (12 each), Coagulopathy and Myocardial infarction (11 each), and Sudden death (10). Of note, in 10 cases limited information regarding the cause of death was provided (PT Death) or not reported the cause of death. Most (204 of 275 cases) of these fatal cases involved elderly subjects. When the medical history was provided (213 cases), significant medical conditions included aortic thrombosis, cardiac failure, cerebral artery embolism, chronic obstructive pulmonary disease, coronary artery stenosis, deep vein thrombosis, fall, general physical health deterioration, hospitalisation, major surgeries, Parkinson's disease, pulmonary embolism, and various malignancies.

- The lot/batch number which reported ≥2% of cases reporting thromboembolic events is: #ER9470 (100 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT: Paediatric (1), Adults (16), and Elderly (6).

- PM: Paediatric (10), Adults (1747), Elderly (2647) and Unknown (321).
  - There was no significant difference observed in the reporting proportion of thromboembolic events between age groups.

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 1743 (36.7% of the CT and PM cases reporting thromboembolic events).

- The reporting proportion of thromboembolic events with fatal outcome (7.7%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (3.7%).

O/E Analysis

O/E analysis was performed for Deep vein thrombosis, Disseminated intravascular coagulation, and Pulmonary embolism (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Thromboembolic events, has emerged as a concern for some COVID-19 vaccines; it has been evaluated by the MAH as a signal and closed as no risk (Section 15 and Section 16.2.1.2).

No additional safety signals have emerged based on a review of these cases and of the O/E analysis performed. Surveillance will continue.

16.3.3.1.16. Stroke

- Search Criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents; Cerebrovascular venous and sinus thrombosis (Primary Path).
  - Upon review, 2 PM cases were determined to be non-contributory and are not included in the discussion since these 2 cases involved babies who were indirectly exposed to BNT162b2 (trans-mammary route).

Clinical Trial Data

- Number of cases: 20 (2.85% of 702 cases, the total CT dataset; 13 cases involved BNT162b2, 5 cases involved blinded therapy and 2 cases involved placebo).
- Country of incidence: US (14), Argentina, China, Germany (2 each).
- Subjects' gender: female (10), male (10).
- Subjects' age in years (n = 20), range: 44 – 82, mean 64.2, median 65.5.
- Medical history (n = 18 cases). Relevant subjects' medical histories reported coded to the PTs Coronary artery disease, Hypercholesterolaemia, Hyperlipidaemia (4 each), Obesity (3), Atrial fibrillation, Sleep apnoea syndrome, and Tobacco user (2 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (20): Cerebrovascular accident (14), Cerebral infarction, Ischaemic stroke (2 each), Haemorrhagic stroke, Subarachnoid haemorrhage (1 each). Of the above SAEs, cerebrovascular event was assessed as related to BNT162b2 (duration of event was 1 day and the event outcome was reported as resolved). All the other SAEs were assessed as not related to BNT162b2/blinded therapy/placebo.

Post-Authorization Data

- Number of cases: 2930 (0.9% of 327,125 cases, the total PM dataset).
- MC cases (1010), NMC cases (1920).
- Country of incidence: UK (443), France (393), US (359), Japan (271), Germany (220), Netherlands (216), Italy (177), Sweden (112), Spain (104), Norway (81), Denmark (67); the remaining 489 cases were distributed among 40 countries.
- Subjects' gender: female (1664), male (1200), and unknown (66).

- Subjects' age in years (n = 2754), range: 16 – 102, mean 72.3, median 76.

- Medical history (n = 2053 cases). Relevant subjects' medical histories most frequently (≥50 occurrences) reported coded to the PTs Atrial fibrillation (278), Diabetes mellitus (150), Type 2 diabetes mellitus (149), Dyslipidaemia (141), Hypercholesterolaemia (119), Obesity (79), Transient ischaemic attack (68), Tobacco user (65), Myocardial ischaemia (64), Cerebral infarction (62), Cardiac failure (57), Ischaemic stroke (52), Myocardial infarction (51). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 medical history (n = 108 cases). The subjects' medical history was significant for COVID-19 or suspected COVID-19. Medical conditions reported more than twice were coded to the PTs COVID-19 (77), Suspected COVID-19 (24). Of note, more than 1 relevant medical history was reported in some cases.

- Number of subjects' reporting co-suspects: 82 cases. Reported relevant co-suspect was methotrexate sodium (2).

- Number of relevant events: 3365.

- Relevant event seriousness: serious (3349), non-serious (16).

- Most frequently reported relevant PTs (≥20 occurrences): Cerebrovascular accident (1199), Ischaemic stroke (424), Cerebral infarction (403), Cerebral haemorrhage (312), Cerebral venous sinus thrombosis (106), Subarachnoid haemorrhage (101), Cerebral thrombosis (95), Haemorrhagic stroke (69), Cerebral ischaemia (68), Ischaemic cerebral infarction (56), Embolic stroke (39), Cerebral venous thrombosis (34), Cerebral haematoma (30), Haemorrhage intracranial (29), Lacunar infarction(23), Cerebral artery embolism (20).

- Time to relevant event onset (n = 2679)[79], range: <24 hours to 127 days, median 4 days.

  - <24 hours: 270 events (37 of which had a fatal outcome);
  - 1 day: 420 events (74 of which had a fatal outcome);
  - 2-7 days: 1030 events (174 of which had a fatal outcome);
  - 8-14 days: 471 events (68 of which had a fatal outcome);
  - 15-30 days: 346 events (59 of which had a fatal outcome);
  - 31-181 days: 142 events (22 of which had a fatal outcome).

- Duration of relevant events (n = 129 out of 560 occurrences with outcome of resolved/resolved with sequelae), range: 30 minutes to 74 days.

  - <24 hours: 11 events;
  - 1 day: 24 events;

[79] This number does not include 693 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- 2-7 days: 51 events;
- 8-14 days: 16 events;
- 15-30 days: 19 events;
- 31-180 days: 8 events.

- Relevant event outcome: fatal (545), resolved or resolving (986), resolved with sequelae (245), not resolved at the time of reporting (753), and unknown (843).

  - Of the 545 fatal events, the most commonly reported cause of death (≥10 occurrences) were coded to the PTs Cerebrovascular accident (152), Cerebral haemorrhage (136), Ischaemic stroke (49), Cerebral infarction (45), Haemorrhagic stroke (33), Subarachnoid haemorrhage (27) and Cerebral thrombosis (12). Most (409 of 545 cases) of the fatal cases involved elderly subjects. When the medical history was provided (316 cases), significant medical conditions included atrial fibrillation (88), Type 2 diabetes mellitus (30), Diabetes mellitus (29), Cardiac failure, Cardiac failure (23 each), Dyslipidaemia (21), Myocardial ischaemia (20), Transient ischaemic attack (18), Hypercholesterolaemia (17), Cerebral infarction (15), Obesity (12), Myocardial infarction, Tobacco user (10 each).

Analysis by age group

- CT: Adult (10) and Elderly (10)

- PM: Paediatric (6), Adult (729), Elderly (2052), Unknown (143).

  - No significant difference observed in the reporting proportion of stroke AEs (≥2%) between adult and elderly population. However, a higher reporting proportion of events coded to the Ischaemic stroke and Cerebral infarction was observed in elderly population when compared to adult population and paediatric (Ischaemic stroke [4.4% vs 8.8% vs 0%; Cerebral infarction [3.3% in adults vs 8.3% in elderly vs 5% in paediatric].

Analysis by presence of comorbidities[22,57]

- Number of subjects reporting comorbidities: 1148 (38.9% of the cases reporting stroke AESIs). A higher reporting proportion of stroke AESIs was reported in patients without significant comorbidities (61.9 %) when compared to patients with significant comorbidities.

- The reporting proportion of stroke AESIs with fatal outcome (18.9%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (13% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Ischemic strokes and Hemorrhagic strokes (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

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

16.3.3.1.17. 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.

Post-Authorization Data

- Number of cases: 360 (0.1% of 327,125 cases, the total PM dataset).
- MC cases (267), NMC cases (93).
- Country of incidence: UK (91), France (55), Italy (40), US (31), Germany (23), Spain (20), Netherlands (17), Japan (15), Portugal, Sweden (10 each), Norway (5); the remaining 43 cases were distributed among 21 countries.
- Subjects' gender: female (239), male (117), and unknown (4).
- Subjects' age in years (n = 326 cases), range: 13 – 99, mean 58.9, median 68.
- Medical history (n = 230 cases). The most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (69), Type 2 diabetes mellitus (14), Dyslipidaemia (12), Diabetes mellitus, Ex-tobacco user, Obesity (9 each), Drug hypersensitivity, Hypersensitivity, Rheumatoid arthritis, Vasculitis (8 each), Behcet's syndrome (7), Hypercholesterolaemia (6), Aortic aneurysm and Myocardial ischaemia (5 each). Of note, more than 1 medical history was reported in some cases.
- COVID-19 Medical history (n = 22 cases). The medical conditions were coded to the PTs COVID-19 (15), Suspected COVID-19 (5), and Exposure to SARS-CoV-2 (2).
- Co-suspects: 10. Relevant co-suspects are acenocoumarol, acetylsalicylic acid, and enoxaparin (1 each).
- Number of events: 380.
- Relevant event seriousness: serious (269) and non-serious (111).
- Most frequently reported relevant PTs (≥2%): Vasculitis (124), Peripheral ischaemia (56), Cutaneous vasculitis (43), Giant cell arteritis (38), Vasculitic rash (25), Henoch-Schonlein purpura (23), and Hypersensitivity vasculitis (17).

- Time to event onset (n = 269),[80] range: <24 hours to 75 days, median 3 days.
  - <24 hours: 28 events;
  - 1 day: 38 events (2 of which had a fatal outcome);
  - 2-7 days: 122 events (3 of which had a fatal outcome);
  - 8-14 days: 43 events (1 of which had a fatal outcome);
  - 15-30 days: 28 events (2 of which had a fatal outcome);
  - 31-181 days: 10 events (1 of which had a fatal outcome).
- Duration of relevant events (n = 28 out of 69 occurrences with outcome of resolved/resolved with sequelae); range: 10 minutes to 44 days, with a median of 7 days.
  - <24 hours: 2 events;
  - 1 day: 3 events;
  - 2-7 days: 10 events;
  - 8-14 days: 6 events;
  - 15-30 days: 6 events;
  - 31-181 days: 1 event.
- Relevant event outcome: fatal (11), resolved/resolving (166), resolved with sequelae (5), not resolved at the time of reporting (101), and unknown (97).
  - In 10 cases (reporting 11 relevant events with a fatal outcome), the reported cause of death (≥2 occurrences) were coded to the PTs Peripheral ischaemia (6), Coagulopathy, Pulmonary vasculitis, and Renal vasculitis (2 each). Most (8 of 10 cases) of these fatal cases involved subjects who were ≥75 years of age. When the medical history was provided (8 cases), medical conditions included arterial disorder, cardiac ventricular thrombosis, chronic kidney disease, chronic obstructive pulmonary disease, and peripheral arterial occlusive disease.
- Lot/Batch Number: The lot/batch number which reported ≥3% of cases reporting vasculitic events is: #EM0477 (14 cases). No quality related issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- PM: Paediatric (3), Adults (146), Elderly (180) and Unknown (31).
  - Among the frequently (≥2%) reported relevant PTs, the reporting proportion of PT Giant cell arteritis was significantly higher in elderly population when compared to adult population (16.7% in elderly vs 4.8% in adult). No paediatric cases reported

[80] This number does not include 1 event for which partial administration or event onset date was reported.

PT Giant cell arteritis. This is not surprising because giant cell arteritis is the most common vasculitis of the elderly.

Analysis by presence of comorbidities[22]

- Number of subjects with comorbidities: 147 (40.8% of the PM cases reporting vasculitic events).

- The reporting proportion of vasculitic AESIs with a fatal outcome (4.5%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (1.5% for fatal outcome).

O/E Analysis

O/E analysis was performed for Behcet's syndrome, Cutaneous vasculitis, Giant cell arteritis, Peripheral ischaemia, Vasculitic rash, and Vasculitis (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

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.

16.3.3.1.18. Sudden Death

- Search Criteria: PT Sudden Death.

Please refer to Section 16.3.4.1.

16.3.3.1.19. 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: 3 (0.4% of 702 cases, the total CT dataset; 3 were blinded therapy).
- Country of incidence: US (2), South Africa (1).
- Subjects' gender: female (2), and male (1).
- Subjects' age in years (n = 3), range: 55 – 75, mean 64, median 62.
- Medical history = HIV infection (3).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported PTs (4): COVID-19 pneumonia, Pneumonia, Road traffic accident, and Type 2 diabetes mellitus (1 each). None of the events were related to BNT162b2 or blinded therapy.

Post-Authorization Data

- Number of cases: 294 (0.09% of 327,125 cases, the total PM dataset).

Patients with pre-existing HIV Infection: 114 (0.03% of 327,125 cases, the total PM dataset).

- MC cases (49), NMC cases (65).
- Country of incidence[81]: US (33), UK (29), France (19), Italy (11), Switzerland (3), Belgium, Germany, Netherlands, Norway, Portugal, Spain (2 each). The remaining 7 cases were distributed among 7 countries.
- Subjects' gender: female (28), male (84) and unknown (2).
- Subjects' age in years (n = 107), range: 20 – 89, mean 50.6, median 52.
- COVID-19 Medical history (n = 11): COVID-19, Suspected COVID-19 (5 each), and Exposure to SARS-CoV-2 (1).
- Co-suspects: Acyclovir, etravirine, emtricitabine, tenofovir alafenamide (1 each).
- Of the 114 cases reporting a pre-existing HIV condition, 9 subjects reported cardiac disorders. The events in these cases were coded to PTs Arrhythmia (3), Tachycardia (2), Acute myocardial infarction, Cardiac arrest, Cardio-respiratory arrest, Extrasystoles, Hypertensive heart disease, Myocardial infarction, Palpitations, Ventricular extrasystoles,

[81] The cases were not reported from any low- and middle-income countries.

Ventricular fibrillation (1 each). Of the 14 events 12 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (6), and unknown (4).

- Of the 114 cases, 44 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (21), Dizziness (7), Generalised tonic-clonic seizure, Lethargy, Somnolence (3 each), Ageusia, Anosmia, Dysgeusia, Loss of consciousness, Sciatica, Taste disorder (2 each), Cerebrovascular accident, Disturbance in attention, Dysaesthesia, Dysgraphia, Dyslexia, Dysstasia, Facial paralysis, Guillain-Barre syndrome, Hypersomnia, Hypoaesthesia, Hypokinesia, Hypotonia, Migraine, Paraesthesia, Paresis, Presyncope, Sinus headache, Speech disorder, Status epilepticus, Syncope, Tremor, Vocal cord paralysis (1 each). Twenty-six (26) were assessed as serious and 46 were non-serious[82]. Outcome of the events was reported as resolved/resolving (30), not resolved (25), and unknown (17).[83]

- Of the 114 cases, 8 subjects reported infectious events. The events in these cases were coded to PTs COVID-19, Herpes zoster, Suspected COVID-19 (2 each), Asymptomatic COVID-19, Conjunctivitis, Influenza (1 each). Of the 9 events 7 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as resolved/resolving (4), not resolved (2), and unknown (3).

- 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 114 cases, 92 cases involved adults, 15 cases involved elderly and in 7 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: 85 (0.02% of 327,125 cases, the total PM dataset).

- MC cases (62), NMC cases (23).

- Country of incidence[84]: France (30), UK (18), US (12), Spain (5), Ireland, Italy (4 each), Germany, and Japan (3 each). The remaining 6 cases were distributed among 6 countries.

- Subjects' gender: female (57), male (28).

- Subjects' age in years (n = 85), range: 18 – 97, mean 61.6, median 66.

[82] The event dizziness was assessed as both serious and non-serious.

[83] The event dizziness reported more than one outcome.

[84] The cases were not reported from any low- and middle-income countries

- COVID-19 Medical history (n = 7): COVID-19 (4), and Suspected COVID-19 (3).

- Co-suspects: None.

- Of the 85 cases reporting a pre-existing tuberculosis, 15 subjects reported cardiac disorders. The events in these cases were coded to PTs Tachycardia (5), Atrial fibrillation, Palpitations (3 each), Acute myocardial infarction, Arrhythmia, Cardiac failure, Cardiac failure chronic, Cardiac flutter, Cardio-respiratory arrest, Coronary artery disease, Left ventricular hypertrophy, Myocardial ischaemia, Myocarditis, Pericardial effusion, Sinus bradycardia, and Ventricular tachycardia (1 each). Of the 24 events, 22 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (8), not resolved (9), and unknown (3).

- Of the 85 cases, 32 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (13), Dizziness (4), Paraesthesia (3), Facial paralysis, Guillain-Barre syndrome, Hemiplegia, Somnolence, Syncope (2 each), Ageusia, Amnesia, Aphasia, Circadian rhythm sleep disorder, Coma, Dysarthria, Hemianopia homonymous, Hypoaesthesia, Incoherent, Ischaemic stroke, Lethargy, Monoparesis, Motor dysfunction, Paresis, Petit mal epilepsy, Sensory loss, Tension headache, Transient ischaemic attack, Tremor, Unresponsive to stimuli (1 each). Of the 50 events, 33 were assessed as serious and 17 events were non-serious. Outcome of the events was reported as resolved/resolving (20), not resolved (15), resolved with sequelae (3), and unknown (12).

- Of the 85 cases, 9 subjects reported infectious events. The events in these cases were coded to PTs COVID-19, Pneumonia (3 each), Influenza, Nasopharyngitis, Pyelonephritis, Staphylococcal bacteraemia, Tonsillitis, Urinary tract infection, and Urosepsis (1 each). Of the 13 events, 11 were assessed as serious and 2 events were non-serious. Outcome of the events was reported as fatal (5), resolved (6), and unknown (2).

- 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 85 cases, 42 cases involved adults, and 43 cases involved elderly. The reporting proportion of cardiac events was higher in elderly (41.9%) compared to the adult population (14.3%). No significant difference was observed in the reporting proportion of infections (16.3% in elderly vs 14.3% in adults), and nervous system disorders (79.1% in elderly vs 38.1% in adults) between the elderly and adult population.

Patients with pre-existing malnutrition: 91 (0.03% of 327,125 cases, the total PM dataset).

Patients with pre-existing malnutrition: There were 91 cases that reported a medical history of malnutrition. However, 72 cases were determined to be non-contributory and are not included in the discussion as limited information was available regarding weight and/or height of subjects, and precise aetiology of the underlying malnutrition.

- Number of cases: 19 (0.01% of 327,125 cases, the total PM dataset).
- MC cases (17), NMC cases (2).
- Country of incidence[85]: France (9), Norway (4), Switzerland (2), Czech Republic, Sweden, UK, US (1 each).
- Subjects' gender: female (17), male (2).
- Subjects' age in years (n = 19), range: 23 – 103, mean 79.2, median 85.
- COVID-19 Medical history (n = 3): COVID 19 (2), and Suspected COVID-19 (1).
- Co-suspects: None.
- In 19 these cases, the most frequently reported events (>1 occurrence) were Death, Decreased appetite, Drug ineffective, Fall (3 each), Acute respiratory failure, Dyspnoea, Fatigue, General physical health deterioration, Pyrexia, Thrombocytopenia, Urinary incontinence (2 each).
- Of the 19 cases reporting pre-existing malnutrition, 5 subjects reported PTs Decreased appetite (3), General physical health deterioration (2), Condition aggravated, and Weight decreased (1 each). Four (4) events were assessed as serious and 3 events were non-serious. Outcome of the events was reported as fatal (2), resolving (1), and unknown (4).
- Of the 19 cases, 17 were reported in elderly and 2 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.

Conclusion

No safety signals have emerged based on the review of these cases. Safety surveillance will continue.

16.3.3.2. 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

[85] The cases were not reported from any low- and middle-income countries

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.

16.3.3.3. Local Adverse Reactions

- Search Criteria: PTs Erythema; Injection site erythema; Injection site pain; Injection site swelling; Swelling.

- Of the 21,816 cases, 10 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

  – In 1 case the event of interest was due to reactivation of rheumatoid arthritis,

  – In 9 cases the event of interest was attributed to another co-suspect drug and not Covid-19 mRNA vaccine.

  Therefore, 21,806 cases are included in the analysis below.

Clinical Trial Data

- There were no serious clinical trial cases of local reactions reported during the reporting interval.

Post-Authorization Data

- Number of cases: 21,806 (6.7% of 327,125 cases, the total PM dataset).

- MC cases (14,816), NMC cases (6990).

- Country of incidence (≥2%): Italy (9021), UK (3657), US (3369), Mexico (1208), Japan (985), France (673).

- Subjects' gender: female (17,150), male (4174) and unknown (482).
- Subjects' age in years (n = 20,417), range: 0.04 - 109, mean 48, median 47.
- Medical history (n = 7572).[86] The most frequently (≥2%) reported medical conditions included Hypertension (998), Asthma (779), Suppressed lactation (765), Drug hypersensitivity (753), Hypersensitivity (685), Food allergy (523), Seasonal allergy (411).
- COVID-19 Medical history: COVID-19 (494), Suspected COVID-19 (405), SARS-CoV-2 test positive (92), SARS-CoV-2 test negative (44), COVID-19 pneumonia (15), COVID-19 immunisation (14), Exposure to SARS-CoV-2 (8), SARS-CoV-2 antibody test positive (7), SARS-CoV-2 test (3), Asymptomatic COVID-19, Occupational exposure to SARS-CoV-2, Post-acute COVID-19 syndrome, SARS-CoV-2 antibody test (2 each), SARS-CoV-2 antibody test negative (1).
- Co-suspects reported in ≥ 2 cases: paracetamol (11), apixaban (6), diphenhydramine hydrochloride (5), COVID-19 AstraZeneca vaccine, etanercept, ibuprofen (4 each), bisoprolol, cortisone, methylprednisolone, prednisone, rosuvastatin (3 each), acrivastine, adalimumab, amoxicillin, beclometasone, cetirizine, digoxin, hyaluronic acid, iodine, leflunomide, mirtazapine, montelukast, vitamin B complex, vitamin D NOS (2 each).
- Number of events: 105,498 (of which 23,518 were PTs of interest).
- Relevant event seriousness[62]: serious (3048), non-serious (20,475).
- Most frequently reported relevant PTs (≥2%): Injection site pain (10,105), Erythema (7884), Swelling (3737), Injection site erythema (1170), Injection site swelling (622).
- Most frequently co-reported PTs (> 5%): Headache (5546), Pyrexia (4187), Fatigue (3720), Myalgia (3627), Arthralgia (3067), Chills (3000), Pruritus (2802), Nausea (2373), Pain (2366), Asthenia (2303), Malaise (2229), Pain in extremity (1991), Lymphadenopathy (1791), Rash (1422), Vaccination site pain (1317), and Dizziness (1208).
- Time to event onset (n = 19,140),[87] range: < 24 hours – 131 days, median < 24 hours.
  - <24 hours: 11,106 events;
  - 1 day: 5186 events;
  - 2-7 days: 2090 events;
  - 8-14 days: 506 events;

[86] Some cases reported more than 1 medical history event.

[87] This number does not include 4456 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- > 14 days: 252 events.

- Duration of event[88]:
  - <24 hours: 1226 events;
  - 1 day: 2422 events;
  - 2-7 days: 4526 events;
  - 8-14 days: 361 events;
  - > 14 days: 542 events.

- Relevant event outcome[34]: fatal (7), resolved/resolving (15,470), resolved with sequelae (138), not resolved (3015), unknown (4984).
  - Time to onset of fatal events were < 24 hours (1 event), 1 day (2 events), 5 days (1 event), 8 days (1 event), and unknown (2 events). There were 7 cases reporting fatal events of interest (Erythema [6 cases] and Swelling [1 case]) in elderly 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.

- Lot/Batch Number: Lot/Batch Number (#) information by Country was available in 17,525 cases.

- Product quality analysis was provided for the following lot/batch numbers (EE8492, EE8493, EJ3002, EJ6134, EJ6136, EJ6788, EJ6795, EJ6797, EK1768, EK4176, EK4243, EK9788, EL0739, EL1406, EL1484, EL8982, EM0477, EM4965, EP6775, EP9605, ER8737, EW6126, EW0150, and EX3617) with no related quality issues identified during investigations of the impacted lot/batch numbers.

Analysis by age group

- PM: Paediatric (56), Adults (17,245), Elderly (3166) and Unknown (1339).

Event of Interest	Paediatric (n/%)	Adult (n/%)	Elderly (n/%)	Unknown (n/%)
Erythema	21 (35.6)	5729 (31.0)	1569 (44.5)	565 (39.0)
Injection site erythema	1 (1.7)	864 (4.7)	251 (7.1)	54 (3.7)
Injection site pain	14 (23.7)	8776 (47.5)	974 (27.6)	341 (23.6)
Injection site swelling	2 (3.4)	442 (2.4)	137 (3.9)	41 (2.8)
Swelling	21 (35.9)	2677 (14.5)	593 (16.8)	446 (30.8)
Total[a]	**59**	**18,488**	**3524**	**1447**

a. Some cases reported more than 1 event.

[88] This number does not include 14,544 events for which duration of event, event onset dates, or event cessation dates were not reported or events with a not meaningful duration of event value as per reported information.

- 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[22]

- PM
  - Number of subjects with comorbidities: 2920 (0.9% of 327,125 cases, the total PM dataset). Subjects with comorbidities were reported in 13.4% 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

- Number of post-authorization vaccine doses[89] administered at the time of the event onset: Dose 1 in 7617 cases, Dose 2 in 4859 cases and the dose number was not specified in 9689 cases.

PT	Dose 1[a]	Dose 2[a]	Dose Unspecified[a]
Erythema	3844	1867	2310
Injection site erythema	333	280	574
Injection site pain	2439	1574	6211
Injection site swelling	178	189	265
Swelling	1396	1366	1084

a. Vaccine dose count by PT differs than vaccine dose count by case given that some cases reported more than 1 PT.

- The majority of post-authorization events reported across doses were similar with the exception of erythema being reported more frequently after the 1st dose and Injection site erythema and Injection site pain being more frequently reported in the unspecified dose group. The majority of events (87%) were non-serious.

Conclusion

Local adverse reactions were reported in 21,806 cases representing 6.7% of the cases in the reporting period. The majority of events (87%) were non-serious events with 66.1% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 7 fatal cases describing local adverse reactions; all were in elderly patients. 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 patients. When

[89] Number of vaccine doses is reported by case number.

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.

16.3.3.4. Systemic Adverse Reactions

- Search Criteria: PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia.
- Of the 157,947 cases, 87 cases were determined to be non-contributory and are not included in the discussion for the following reasons
  - Foetal, neonate, or infant exposures via pregnancy/breast feeding were reported in 37 cases (cases reporting exposure in utero or exposure during lactation are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*).
  - Use in subjects less than 12 years of age was reported in 50 cases (cases reporting unauthorized use [ie, PT Product administered to patient of inappropriate age] are reviewed in Section 16.3.4.6 *Off-Label Use*).

Clinical Trial Data

- Number of cases: 3 (0.4% of 702 cases, the total CT dataset; BNT162b2 [2], and blinded therapy [1]).
- Country of incidence: [redacted] (3).
- Subjects' gender: female (2), and male (1).
- Subjects' age (n = 3), 44, 56, and 73 years, respectively.
- Medical history (n = 2): Cervical radiculopathy, hypertension, migraine, and osteoarthritis (1 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 1): codeine/paracetamol, oxycodone (1 each).
- Number of events: 4 (of which 3 were PTs of interest).
- Relevant PTs: Fatigue, Myalgia, and Pyrexia (1 each). Of these SAEs, no SAEs were assessed as related to BNT162b2 or blinded therapy by the Sponsor.
- Time to event onset (n = 3): 2, 58 and 203 days, respectively.
- Duration of event (n = 1): 48 days.

- Relevant event outcome: resolved/resolving (3).

Post-Authorization Data

- Number of cases: 157,857 (48.3% of 327,125 cases in the total PM dataset).
- MC cases (87,004), NMC cases (70,853).
- Country of incidence (≥2%): UK (31,636), Italy (27,998), US (23,668), Mexico (11,793), Netherlands (11,564), Spain (7638), France (6056), Germany (5091), Austria (3967), and Japan (3163).
- Subjects' gender: female (120,768), male (32,995) and unknown (4094).
- Subjects' age in years (n = 144,347), range: 12 – 120, mean 47.2; median 46.
- Medical history (n = 59,963): the most frequently (≥2%) reported medical conditions included disease risk factor (9218), hypertension (7327), suppressed lactation (5457), asthma (5176), hypersensitivity (3941), drug hypersensitivity (3837), hypothyroidism (2302), seasonal allergy (2075), diabetes mellitus (2071), food allergy (2056), depression (1972), migraine (1747), anxiety (1561), gastrooesophageal reflux disease (1212), and type 2 diabetes mellitus (1208).
- COVID-19 Medical history (n = 13,451): reported medical conditions included COVID-19 (7783), suspected COVID-19 (5507), COVID-19 pneumonia (146), coronavirus infection (124), asymptomatic COVID-19 (73), post-acute COVID-19 syndrome (12), coronavirus test positive (6), congenital COVID-19, and COVID-19 treatment (1 each).
- Co-suspects (n = 849): the most frequently (≥2%) reported co-suspect medications included paracetamol (63), COVID-19 vaccine (56 [non-MAH or unspecified]), tofacitinib (41), ibuprofen (34), adalimumab (27), apixaban (26), and levothyroxine (14).
- Number of events: 782,639 (of which 328,517 were PTs of interest).
- Relevant event seriousness:[62] serious (56,426), non-serious (272,148).
- Relevant PTs: Headache (83,668), Pyrexia (64,190), Fatigue (54,664), Myalgia (49,373), Chills (41,220), and Arthralgia (35,402).
- Time to event onset (n = 274,746),[90] range < 24 hours to 151 days, median 1 day.
  - < 24 hours: 121,702 events (64 of which had a fatal outcome);

[90] This number does not include events for which event onset dates or event cessation dates were not reported or events with a not meaningful time to event cessation value as per reported information.

- 1 day: 118,623 events (144 of which had a fatal outcome);
- 2-7 days: 26,571 events (136 of which had a fatal outcome);
- 8-14 days: 3924 events (37 of which had a fatal outcome);
- 15-30 days: 2907 events (14 of which had a fatal outcome);
- 31-181 days: 1019 events (7 of which had a fatal outcome).

- Duration of event (n = 71,710),[91] range: <24 hours to 109 days, median 2 days.

  - <24 hours: 5092 events;
  - 1 day: 25,916 events;
  - 2-7 days: 37,589 events;
  - 8-14 days: 1927 events;
  - 15-30 days: 903 events;
  - 31-181 days: 283 events.

- Relevant event outcome[34]: fatal (483), not resolved (52,475), resolved/resolving (214,179), resolved with sequelae (2494), and unknown (60,508).

  - In 395 cases, the relevant event was reported as fatal: Pyrexia (263), Fatigue (102), Headache (36), Chills, Myalgia (33 each), and Arthralgia (16).[92] In 383 of these 395 cases, the relevant fatal event occurred in the context of other fatal events; the most frequently reported other fatal events (≥10 occurrences included Dyspnoea (76), Malaise (59), Asthenia (47), General physical health deterioration (46), Death (45), Oxygen saturation decreased (36), Cardiac arrest, Vomiting (32 each), COVID-19, Nausea, Pneumonia (29 each), Cough (27), Decreased appetite (24), Somnolence (21), Cardiac failure (19), Diarrhoea (17), Sudden death (16), Loss of consciousness, Pain, Respiratory failure (13 each), Cardio-respiratory arrest, Coma, Condition aggravated, Drug ineffective, Respiratory distress (12 each), Confusional state, Hypotension, Pneumonia aspiration, Pulmonary embolism (11 each), Dizziness, and Pain in extremity (10 each). Most (360 of 395 cases) of the fatal cases involved elderly subjects. When the medical history was provided (334 cases), significant medical conditions (≥10 cases) included Hypertension (103), Atrial fibrillation (62), Cardiac failure (50), Dementia (47), Diabetes mellitus (32), Dementia Alzheimer's type (30), Chronic obstructive pulmonary disease (28), Type 2 diabetes mellitus (27), Living in residential institution (24), and Parkinson's disease (20), Cerebrovascular accident, Coronary artery disease (19 each), Chronic kidney disease, COVID-19 (18 each), Osteoporosis (16), Hypothyroidism, Myocardial ischaemia, Renal failure (14 each), Myocardial infarction, Osteoarthritis, Pneumonia, Vascular dementia (13 each), Hospitalisation, Rheumatoid arthritis (12 each), Obesity (11), Depression, Dyslipidaemia, and Dysphagia (10 each).

[91] This number does not include events for which event onset dates or event cessation dates were reported or events with a not meaningful time to event cessation value as per reported information.

[92] A case may report more than 1 relevant fatal event.

Analysis by age group

- CT: Adults (2 PTs [Fatigue, Myalgia]), Elderly (1 PT [Pyrexia]).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM
  - An analysis of relevant PM events by age group, event seriousness and event outcome are provided in Table 25. Per the RSI, the most frequent systemic adverse reactions in participants 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 paediatric population had the highest proportion of the PTs Fatigue, Headache and Pyrexia; the adult population had the highest proportion of the PT Myalgia; the elderly population had the highest proportion of the PT Arthralgia; and the PT Chills was evenly distributed across populations. In general, relevant events were more likely to be assessed as serious and/or associated with a worse outcome (ie, fatal or not resolved) with increasing age. Of note, none of the relevant events were fatal in the paediatric population.

Table 25. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric (n = 993) [a,b,c]	Adults (n = 273,382) [b,d]	Elderly (n = 34,910) [a,b,e]	Unknown (n = 19,289) [b,f]
Arthralgia				
Total Events	65 (6.5%)	29595 (10.8%)	3963 (11.4%)	1779 (9.2%)
Serious Events	13 (1.3%)	4523 (1.7%)	1146 (3.3%)	332 (1.7%)
Event Outcome: Fatal	0 (0%)	3 (<0.1%)	13 (<0.1%)	0 (0%)
Not Resolved	9 (0.9%)	5132 (1.9%)	1084 (3.1%)	417 (2.2%)
Resolved/Resolving [g]	42 (4.2%)	19414 (7.1%)	1947 (5.5%)	520 (2.7%)
Unknown	14 (1.4%)	5226 (1.9%)	980 (2.8%)	851 (4.4%)
Chills				
Total Events	122 (12.3%)	34287 (12.5%)	4351 (12.5%)	2460 (12.8%)
Serious Events	15 (1.5%)	4909 (1.8%)	981 (2.8%)	313 (1.6%)
Event Outcome: Fatal	0 (0%)	4 (<0.1%)	29 (0.1%)	0 (0%)
Not Resolved	11 (1.1%)	4001 (1.5%)	541 (1.5%)	291 (1.5%)
Resolved/Resolving [g]	72 (7.2%)	24800 (9%)	2719 (7.7%)	853 (4.4%)
Unknown	39 (3.9%)	5572 (2%)	1074 (3.1%)	1322 (6.8%)
Fatigue				
Total Events	222 (22.4%)	43064 (15.8%)	7617 (21.8%)	3761 (19.5%)
Serious Events	23 (2.3%)	8617 (3.2%)	2141 (6.1%)	721 (3.7%)
Event Outcome: Fatal	0 (0%)	8 (<0.1%)	91 (0.3%)	3 (<0.1%)
Not Resolved	38 (3.8%)	9324 (3.4%)	1659 (4.7%)	711 (3.7%)

Table 25. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric (n = 993) [a,b,c]	Adults (n = 273,382) [b,d]	Elderly (n = 34,910) [a,b,e]	Unknown (n = 19,289) [b,f]
Resolved/Resolving [g]	122 (12.2%)	27306 (9.9%)	3904 (11.1%)	1192 (6.2%)
Unknown	64 (6.4%)	6692 (2.4%)	2022 (5.8%)	1887 (9.7%)
Headache				
Total Events	267 (26.9%)	70290 (25.7%)	7923 (22.7%)	5188 (26.9%)
Serious Events	49 (4.9%)	11771 (4.3%)	2092 (6%)	806 (4.2%)
Event Outcome: Fatal	0 (0%)	7 (<0.1%)	28 (0.1%)	1 (<0.1%)
Not Resolved	53 (5.3%)	11325 (4.1%)	1455 (4.1%)	961 (5%)
Resolved/Resolving [g]	143 (14.3%)	47679 (17.4%)	4656 (13.3%)	1815 (9.4%)
Unknown	71 (7.1%)	11614 (4.2%)	1833 (5.2%)	2431 (12.5%)
Myalgia				
Total Events	75 (7.6%)	42894 (15.7%)	4075 (11.7%)	2329 (12.1%)
Serious Events	15 (1.5%)	5759 (2.1%)	1010 (2.9%)	319 (1.7%)
Event Outcome: Fatal	0 (0%)	5 (<0.1%)	28 (0.1%)	0 (0%)
Not Resolved	7 (0.7%)	6623 (2.4%)	952 (2.7%)	487 (2.5%)
Resolved/Resolving [g]	52 (5.2%)	30054 (10.9%)	2326 (6.6%)	907 (4.7%)
Unknown	16 (1.6%)	6339 (2.3%)	782 (2.2%)	941 (4.9%)
Pyrexia				
Total Events	242 (24.4%)	53214 (19.5%)	6966 (20%)	3768 (19.5%)
Serious Events	48 (4.8%)	8312 (3%)	2041 (5.8%)	470 (2.4%)
Event Outcome: Fatal	0 (0%)	18 (<0.1%)	242 (0.7%)	3 (<0.1%)
Not Resolved	32 (3.2%)	6043 (2.2%)	795 (2.3%)	524 (2.7%)
Resolved/Resolving [g]	120 (12%)	40167 (14.6%)	4521 (12.9%)	1342 (6.9%)
Unknown	92 (9.2%)	7296 (2.7%)	1435 (4.1%)	1915 (9.9%)

a. Pediatric age range: 12 to 17 years. Elderly age range: ≥ 65 years.
b. Multiple episodes of the same PT event were reported with different seriousness and clinical outcomes within some cases hence the sum of the events for seriousness and outcome differ.
c. n (event outcome) = 997
d. n (event outcome) = 274,652
e. n (event outcome) = 35,116
f. n (event outcome) = 19,374
g. Includes resolved with sequelae.

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 21,863 (6.7% of 327,827 cases in the total dataset and 13.8% of 157,860 [3 CT and 157,857 PM] cases reporting systemic adverse reactions).

- CT:
  - None of the CT cases reported selected comorbidities.

- PM:
  - An analysis of relevant PM events by presence of selected comorbidities, event seriousness and event outcome are provided in Table 26. 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 serious and/or associated with a worse outcome (ie, fatal or not resolved). Of note, subjects that reported comorbidities were more likely to be of advanced age, polypharmacy users, report more AEs on average (eg, 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.

Table 26. Analysis of Systemic Adverse Reactions by Presence of Selected Comorbidities, Event Seriousness and Event Outcome

	Comorbidities Not Reported (n = 286,969) [a,b]	Comorbidities Reported (n = 41,605) [a,c]
Arthralgia		
Total Events	30887 (10.8%)	4522 (10.9%)
Serious Events	4524 (1.6%)	1490 (3.6%)
Event Outcome: Fatal	7 (<0.1%)	9 (<0.1%)
Not Resolved	5396 (1.9%)	1246 (3%)
Resolved/Resolving [d]	19482 (6.8%)	2441 (5.8%)
Unknown	6176 (2.1%)	895 (2.1%)
Chills		
Total Events	36110 (12.6%)	5112 (12.3%)
Serious Events	4819 (1.7%)	1399 (3.4%)
Event Outcome: Fatal	12 (<0.1%)	21 (0.1%)
Not Resolved	4065 (1.4%)	779 (1.9%)
Resolved/Resolving [d]	25094 (8.7%)	3350 (8%)
Unknown	7031 (2.4%)	976 (2.3%)
Fatigue		
Total Events	45822 (16%)	8853 (21.3%)
Serious Events	8452 (2.9%)	3050 (7.3%)
Event Outcome: Fatal	30 (<0.1%)	72 (0.2%)
Not Resolved	9385 (3.3%)	2347 (5.6%)
Resolved/Resolving [d]	27908 (9.7%)	4616 (11%)
Unknown	8759 (3%)	1906 (4.5%)
Headache		
Total Events	73179 (25.5%)	10504 (25.2%)
Serious Events	11305 (3.9%)	3413 (8.2%)
Event Outcome: Fatal	24 (<0.1%)	12 (<0.1%)
Not Resolved	11446 (4%)	2348 (5.6%)
Resolved/Resolving [d]	47837 (16.6%)	6456 (15.4%)
Unknown	14171 (4.9%)	1778 (4.2%)
Myalgia		
Total Events	44559 (15.5%)	4818 (11.6%)
Serious Events	5615 (2%)	1488 (3.6%)
Event Outcome: Fatal	15 (<0.1%)	18 (<0.1%)
Not Resolved	6930 (2.4%)	1139 (2.7%)
Resolved/Resolving [d]	30363 (10.5%)	2976 (7.1%)

Table 26. Analysis of Systemic Adverse Reactions by Presence of Selected Comorbidities, Event Seriousness and Event Outcome

	Comorbidities Not Reported (n = 286,969) [a,b]	Comorbidities Reported (n = 41,605) [a,c]
Unknown	7370 (2.6%)	708 (1.7%)
Pyrexia		
Total Events	56412 (19.7%)	7796 (18.7%)
Serious Events	8290 (2.9%)	2581 (6.2%)
Event Outcome: Fatal	81 (<0.1%)	182 (0.4%)
Not Resolved	6213 (2.2%)	1181 (2.8%)
Resolved/Resolving [d]	40932 (14.2%)	5218 (12.4%)
Unknown	9475 (3.3%)	1263 (3%)

a. Multiple episodes of the same PT event were reported with different seriousness and clinical outcomes within some cases hence the sum of the events for seriousness and outcome differ.
b. n (event outcome) = 288,202
c. n (event outcome) = 41,937
d. Includes resolved with sequelae.

Analysis by dose

Number of vaccine doses administered: 1 dose in 49,212 cases, 2 doses in 48,264 cases; and in 60,386 cases the dose was either not specified or reported as other.

- CT:
  - Vaccination dose number: 2 doses (2) and 3 doses (1).
  - A meaningful comparison by dose is not possible due to the low number of CT cases.
- PM:
  - An analysis of relevant PM events by dose, event seriousness and event outcome are provided in Table 27. In general, the total proportion of relevant events, event seriousness, and event outcome were evenly distributed by dose and no significant differences were noted.

Table 27. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose (n = 93,213) [a,b]	2 Doses (n = 109,769) [a,c]	Dose Not Specified/Other (n = 125,597) [a,d]
Arthralgia			
Total Events	10214 (11%)	11440 (10.4%)	13755 (11%)
Serious Events	2354 (2.5%)	2333 (2.1%)	1327 (1.1%)
Event Outcome: Fatal	11 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Not Resolved	1956 (2.1%)	2173 (2%)	2513 (2%)
Resolved/Resolving [e]	5022 (5.4%)	6983 (6.3%)	9918 (7.9%)
Unknown	3318 (3.5%)	2356 (2.1%)	1397 (1.1%)
Chills			
Total Events	11123 (11.9%)	15287 (13.9%)	14812 (11.8%)

Table 27. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose (n = 93,213) [a,b]	2 Doses (n = 109,769) [a,c]	Dose Not Specified/Other (n = 125,597) [a,d]
Serious Events	2246 (2.4%)	2397 (2.2%)	1575 (1.3%)
Event Outcome: Fatal	18 (<0.1%)	7 (<0.1%)	8 (<0.1%)
Not Resolved	1224 (1.3%)	1762 (1.6%)	1858 (1.5%)
Resolved/Resolving [e]	6405 (6.8%)	10836 (9.8%)	11203 (8.9%)
Unknown	3509 (3.7%)	2710 (2.5%)	1788 (1.4%)
Fatigue			
Total Events	17307 (18.6%)	16999 (15.5%)	20370 (16.2%)
Serious Events	4854 (5.2%)	3695 (3.4%)	2953 (2.4%)
Event Outcome: Fatal	55 (0.1%)	28 (<0.1%)	19 (<0.1%)
Not Resolved	3526 (3.8%)	3670 (3.3%)	4536 (3.6%)
Resolved/Resolving [e]	9113 (9.7%)	10163 (9.2%)	13249 (10.5%)
Unknown	4743 (5.1%)	3244 (2.9%)	2678 (2.1%)
Headache			
Total Events	26337 (28.3%)	26081 (23.8%)	31266 (24.9%)
Serious Events	5997 (6.4%)	5080 (4.6%)	3641 (2.9%)
Event Outcome: Fatal	16 (<0.1%)	13 (<0.1%)	7 (<0.1%)
Not Resolved	3969 (4.2%)	4291 (3.9%)	5534 (4.4%)
Resolved/Resolving [e]	14854 (15.8%)	17074 (15.5%)	22365 (17.7%)
Unknown	7614 (8.1%)	4798 (4.4%)	3538 (2.8%)
Myalgia			
Total Events	12320 (13.2%)	16399 (14.9%)	20659 (16.4%)
Serious Events	2490 (2.7%)	2856 (2.6%)	1757 (1.4%)
Event Outcome: Fatal	20 (<0.1%)	6 (<0.1%)	7 (<0.1%)
Not Resolved	1751 (1.9%)	2544 (2.3%)	3774 (3%)
Resolved/Resolving [e]	6979 (7.4%)	11103 (10.1%)	15258 (12.1%)
Unknown	3626 (3.9%)	2774 (2.5%)	1678 (1.3%)
Pyrexia			
Total Events	15912 (17.1%)	23563 (21.5%)	24735 (19.7%)
Serious Events	3679 (3.9%)	4604 (4.2%)	2588 (2.1%)
Event Outcome: Fatal	121 (0.1%)	87 (0.1%)	55 (<0.1%)
Not Resolved	1686 (1.8%)	2560 (2.3%)	3148 (2.5%)
Resolved/Resolving [e]	9826 (10.5%)	17203 (15.6%)	19122 (15.1%)
Unknown	4357 (4.6%)	3785 (3.4%)	2597 (2.1%)

a. Multiple episodes of the same PT event were reported with different seriousness and clinical outcomes within some cases hence the sum of the events for seriousness and outcome differ.
b. n (event outcome) = 93,719
c. n (event outcome) = 110,171
d. n (event outcome) = 126,254
e. Includes resolved with sequelae.

Conclusion

Systemic adverse reactions were reported in 157,860 (3 CT and 157,857 PM) cases representing 48.2% of the cases in the total dataset for the reporting period. The majority of events (82.8%) were non-serious events with 65.6% of the events resolved, resolved with sequelae or resolving at the time of reporting. When reported, the majority onset of events

occurred within 48 hours with a median duration of 2 days. 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.

16.3.3.5. Severe Reactogenicity

- Search Criteria: PT Extensive swelling of vaccinated limb.

Clinical Trial Data

During the current reporting interval, there were no serious CT cases indicative of extensive swelling of vaccinated limb.

Post-Authorization Data

- Number of cases: 427 (0.13% of 327,125 cases, the total PM dataset).
- MC cases (90), NMC cases (337).
- Country of incidence (≥2%): Netherlands (295), Belgium (45), Croatia (26), France (15), UK (12), Australia (9); the remaining 25 cases were distributed among 13 countries.
- Subjects' gender: female (383), male (42), unknown (2).
- Subjects' age in years (n = 409), range: 18.0 - 95.0, mean 46, median 46.
- Medical history (n = 310): the relevant reported medical conditions included Drug hypersensitivity (7), Hypersensitivity (5).
- COVID-19 Medical history: In 82 cases, the subjects' medical history was significant for COVID-19 or suspected COVID-19. Medical conditions reported more than twice were coded to the PTs COVID-19 (48), and Suspected COVID-19 (34).
- Co-suspects: allergens, animal fur & epithelium and herbal pollen.
- Number of events: 3608 (of which 427 were PTs of interest).
- Relevant event seriousness: serious (85), non-serious (342).
- Most frequently reported relevant PTs: 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 = 384)[93], range: <24 hours to 91 days, median 0 day.
  - <24 hours: 155 cases;
  - 1 day: 158 cases;
  - 2-7 days: 56 cases;
  - 8-14 days: 12 cases (1 case had a fatal outcome);
  - 15 -91 days: 3 cases.
- Duration of relevant events was reported in 57 out of 115 occurrences with outcome of resolved; it ranged from 1 hour to 15 days.
  - <24 hours: 3 cases;
  - 1 day: 6 cases;
  - 2-7 days: 42 cases;
  - 8-15 days: 6 cases.
- Relevant event outcome: fatal (1), resolved/resolving (274), resolved with sequelae (1), not resolved (133), unknown (18).
- The lot/batch number which reported >10 % of cases involving severe reactogenicity-related ADRs is EJ6795, and EJ6134. No quality issues were identified during investigations of the impacted lot.

Analysis by age group

- PM: Adult (377), Elderly (43), Unknown (7).
  - A higher reporting proportion of events coded to the PTs Extensive swelling of vaccinated limb was observed in elderly versus adult population (Extensive swelling of vaccinated limb [17.2% in adults vs 21.7% in elderly]

Analysis by presence of comorbidities[22]

- Number of subjects reporting comorbidities: 41 (9.6% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (90.4%) when compared to patients with significant comorbidities.

[93] This number does not include 43 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- The reporting proportion of event severe reactogenicity with fatal outcome (none) and resolving (38.6%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (26.8% of events with resolving).

Conclusion

There was a total of 427 cases, in the safety database reporting the Preferred Term Extensive swelling of vaccinated limb with the use of BNT162b2, and were mostly reported from the Netherlands (295, 69.1%) and Belgium (45, 10.5%). Majority of cases involved females (383, 89.7%) and were reported in patients aged 31-64 years (377, 88.2%). Eighty-five (19.9; 19.3%) of the cases were assessed as serious due to meeting medically significant criteria (there were no hospitalizations due to reported events). There was 1 case reporting a fatal outcome. There was limited information provided in the case for a meaningful assessment.

Three hundred and thirteen (313) cases reported time to onset of the event as the same day or the day following vaccination

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.

16.3.3.6. Age-Related Adverse Reactions

For the overall demographic information for all CT and PM cases refer to Section 6.3.1 *General Overview - All cases*.

Clinical Trial Data

- Number of cases: 702
- Time to event onset (n = 704), range <24 hours to 181 days, median 74 days.
  - <24 hours: 15 events;
  - 1 day: 8 events;
  - 2-7 days: 36 events;
  - 8-14 days: 41 events;
  - 15-30 days: 91 events;
  - 31-181 days: 513 events.

Relevant event outcome[34]: fatal (59), resolved/resolving (684), resolved with sequelae (51), not resolved (79), unknown (11).

Post-Authorization Data

- Number of cases: 327,125
- Time to event onset (n = 898,933), range <24 hours to 151 days, median 1 day.

- <24 hours: 410,018 events;
- 1 day: 291,576 events;
- 2-7 days: 135,212 events;
- 8-14 days: 31,086 events;
- 15-30 days: 20,494 events;
- 31-151 days: 10,547 events.

- Relevant event outcome[34]: fatal (11,112), resolved/resolving (630,717), resolved with sequelae (10,706), not resolved (201,052), unknown (323,571).

Analysis by age group

- CT: Paediatric (27), Adults (412), Elderly (255) and Unknown (2).

The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 28, Table 29, and Table 30. The Cardiac disorders and Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOCs was included in the top 5 SOCs for the adult and elderly age group, however, was not seen in the paediatric age group.

There were 84 cases reporting 94 events in the Cardiac disorders SOC for the adult and elderly age group. Sixty-six (66) cases reported relevant medical history (eg, hypertension, coronary artery disease, myocardial infarction, cardiac disorder) 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 Acute myocardial infarction, Atrial fibrillation (15 each), Myocardial infarction (11), Coronary artery disease (7) and Cardiac failure congestive (5). It is not unexpected for events of cardiac disorders to be reported more frequently in adult and elderly patients compared to paediatric patients.

There were 86 cases reporting 92 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Thirty (30) cases reported pre-existing medical history of cancer (eg, breast cancer, uterine leiomyoma, prostate cancer, colon cancer, leukaemia). The most frequently reported events (>3 occurrences) in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group were Breast cancer (11), Uterine leiomyoma (5), Invasive ductal breast carcinoma and Prostate cancer (4 each). When reported, latency ranged from <24 hours to 203 days with a median of 87 days.

There were 13 cases reporting 15 events in the Psychiatric disorders SOC for the paediatric age group. Twelve (12) cases reported relevant medical history (eg, anxiety, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder) that may have contributed to the relevant events. The 15 events reported were Depression, Suicidal ideation (5 each), Major depression (2), Anxiety, Bipolar I disorder, Conversion disorder (1 each).

Table 28. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups

SOC	Adult	Pediatric	Elderly	Unknown
Infections and infestations	80	5	46	0
Injury, poisoning and procedural complications	55	2	21	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	48	0	44	1
Cardiac disorders	43	0	51	0
General disorders and administration site conditions	35	1	22	0

Table 29. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

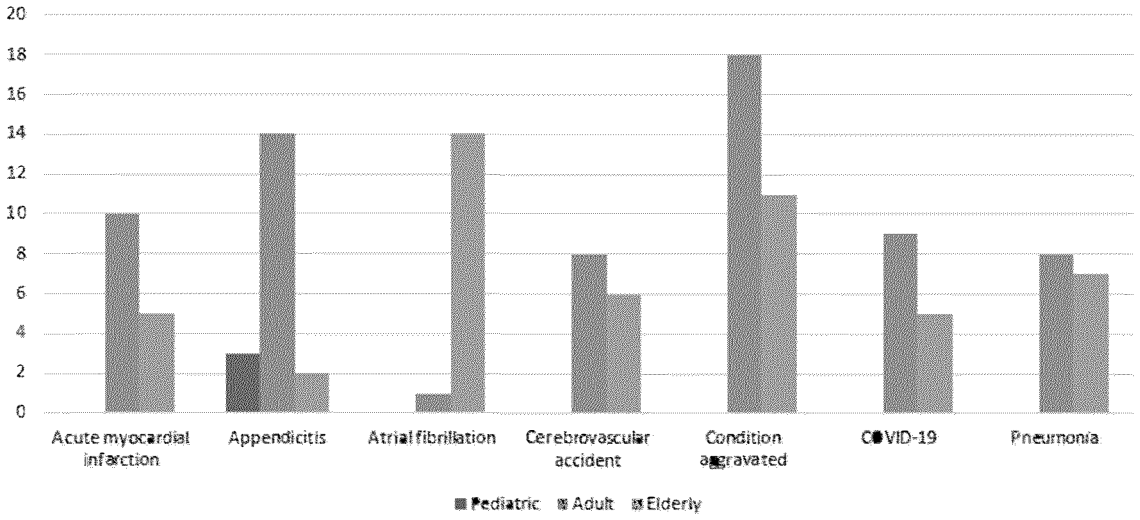
SOC	Pediatric	Adult	Elderly	Unknown
Psychiatric disorders	15	31	5	0
Infections and infestations	5	80	46	0
Gastrointestinal disorders	3	32	23	0
Injury, poisoning and procedural complications	2	55	21	1
General disorders and administration site conditions	1	35	22	0

Table 30. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups

SOC	Elderly	Adult	Pediatric	Unknown
Cardiac disorders	51	43	0	0
Infections and infestations	46	80	5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44	48	0	1
Nervous system disorders	27	31	1	0
Gastrointestinal disorders	23	32	3	0

The distribution of the most frequently reported overall PTs (≥ 2%) by age group in the CT cases is shown in Figure 15. Events of cardiac disorders to be reported more frequently in adult and elderly patients compared to paediatric patients is expected.

Figure 15. Events Reported in ≥2% of All Clinical Trial Cases by Age Group



- PM: Paediatric (1605), Adults (220,883), Elderly (61,781) and Unknown (42,429).

  The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 31, Table 32, and Table 33. The top 5 SOCs were generally comparable for all age groups except Injury, poisoning and procedural complications in the paediatric age group and Skin and subcutaneous tissue disorders in the adult and elderly age group.

  The most commonly reported PTs (>30) in Injury, poisoning and procedural complications for the paediatric age group were Off label use (126), Poor quality product administered, Product administered to patient inappropriate age (94 each), Product use issue (70), and Overdose (43) reported in 347 cases. Of note, some cases more reported more than 1 PT. Off label use, Product administered to patient inappropriate age and Product use issue cases are reviewed in Section 16.3.4.6 *Off-Label Use*. Poor quality product administered and Overdose are reviewed in Section 9.2 *Medication Errors* and Section 16.3.4.2 *Overdose*, respectively. Of the 347 cases, there were no clinical events co-reported in 258 cases. The most commonly co-reported PTs (>10 occurrences) in the remaining 84 cases were Pyrexia (19), Pain in extremity (16), and Headache (13). These events are considered listed or consistent with listed AEs in current RSI.

  In the Skin and subcutaneous tissue disorders SOC for the adult and elderly age group, event seriousness was assessed as serious (16,160) and non-serious (44,265). Event outcome was reported as resolved/resolving (31,583), not resolved (11,855), resolved with sequel (485), unknown (16,827) and fatal (80). The fatal cases are reviewed in Section 16.3.4.1 *Death*. The most commonly reported PTs (>800) in Skin and subcutaneous tissue disorders for the adult and elderly age group were Pruritis (10,456), Rash (9553), Sensitive skin (7402), Erythema (7367), Urticaria (5043), Hyperhidrosis (4634), Rash pruritic (1690), Rash erythematous (1462), Cold sweat (1095), Rash macular (878). Most of these events are listed or consistent with listed events as per the current RSI.

Table 31. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups

SOC	Adult	Pediatric	Elderly	Unknown
General disorders and administration site conditions	318,957	1,392	57,019	27,868
Nervous system disorders	139,716	802	28,521	12,838
Musculoskeletal and connective tissue disorders	116,126	391	19,480	10,044
Gastrointestinal disorders	71,904	390	16,232	6,206
Skin and subcutaneous tissue disorders	47,986	235	12,424	4,493

Table 32. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

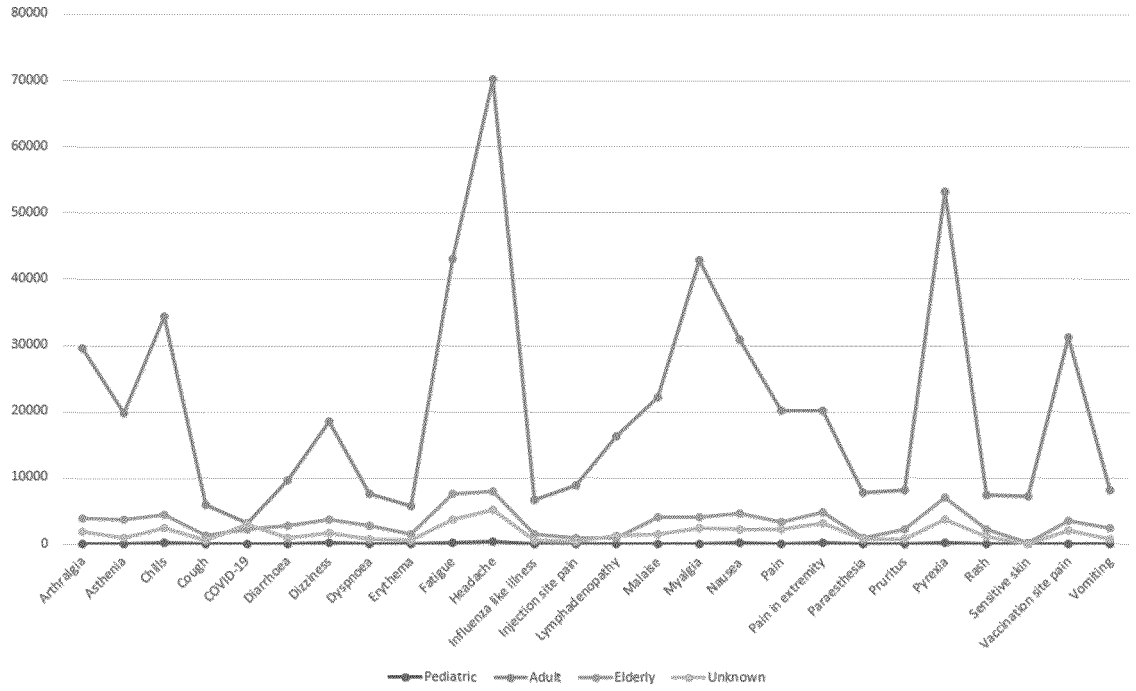
SOC	Pediatric	Adult	Elderly	Unknown
General disorders and administration site conditions	1,392	318,957	57,019	27,868
Nervous system disorders	802	139,716	28,521	12,838
Injury, poisoning and procedural complications	655	12,697	6,112	17,694
Musculoskeletal and connective tissue disorders	391	116,126	19,480	10,044
Gastrointestinal disorders	390	71,904	16,232	6,206

Table 33. Post-Authorization Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups

SOC	Elderly	Adult	Pediatric	Unknown
General disorders and administration site conditions	57,019	318,957	1,392	27,868
Nervous system disorders	28,521	139,716	802	12,838
Musculoskeletal and connective tissue disorders	19,480	116,126	391	10,044
Gastrointestinal disorders	16,232	71,904	390	6,206
Skin and subcutaneous tissue disorders	12,424	47,986	235	4,493

The distribution of the most frequently reported overall PTs (≥ 2%) by age group is shown in Figure 16. Most of these events are listed or consistent with listed events as per the current RSI.

Figure 16. Events Reported in ≥2% of All Post-Authorization Cases by Age Group



Conclusion

Overall, the highest number of events was reported in the adult group, compared to the elderly group; this is partially reflected in the overall European exposure data (see Table 3 assuming the European data well represent the worldwide picture). 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.

16.3.3.7. 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: 16 (2.3% of 702 cases in the total CT dataset; blinded therapy [8], BNT162b2 [7], placebo [1]).
- Country of incidence: US (12), Argentina (4).
- Subjects' gender: female (9), male (7).

- Subjects' age in years (n = 16), range: 13 – 85, mean 57.2, median 57.5.
- Medical history (n = 15): the subjects' relevant medical conditions reported more than once were coded to the PTs Depression (6), Hypertension (5), Anxiety, Myocardial infarction (4 each), Atrial fibrillation (3), Angina pectoris, and Ventricular extrasystoles (2 each). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (16): Syncope (6), Dyspnoea (5), Anxiety (2), Blood pressure increased, Dizziness, Palpitations (1 each). None of the events were assessed as related to BNT162b2/blinded therapy by the investigators.

Post-Authorization Data

Number of cases: 57,808 cases. Upon review, 2 cases were determined to be non-contributory and are not included in the discussion as these individuals (baby) were indirectly exposed to BNT162b2 (trans-mammary route).

- Number of relevant cases: 57,806 (18% of 327,125 cases, the total PM dataset).
- MC cases (33,739), NMC cases (24,067).
- Country of incidence (≥2%): UK (13,367), US (10,632), Mexico (6610), Italy (5457), France (2830), Japan (2553), Germany (1997), Spain (1679), Netherlands (1423).
- Subjects' gender: female (44,721), male (11,639) and unknown (1446).
- Subjects' age in years (n = 52,861),[94] range: 5[95] - 107, mean 48.6, median 47.
- Medical history (n = 28,316): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (4182), Asthma (3006), Depression (935), Anxiety (908), Atrial fibrillation (668), and Chronic obstructive pulmonary disease (544). Of note, more than 1 relevant medical history was reported in some cases.
- COVID-19 Medical history (n = 3642): COVID-19 (1999), Suspected COVID-19 (1643).
- Co-suspects: 468 cases. Frequently (≥ 5 occurrences) reported co-suspects were COVID-19 vaccine NRVV AD (29), apixaban (18), adalimumab, paracetamol (15 each),

[94] Excluded 15 cases with contradictory demographic information (physical characteristics not matching with the reported age value) from reported minimum age calculation.

[95] This case reported off label use of BNT162b2 vaccine (PT Product administered to patient of inappropriate age) of

diphenhydramine (14), lenvatinib (12), acetylsalicylic acid, ibuprofen (10 each), epinephrine, treprostinil (8 each), pregabalin (7), atorvastatin, levothyroxine, and macrogol (5 each).

- Number of events: 328,287 (of which 73,819 were relevant PTs for this topic).
- Relevant event seriousness[62]: serious (27,975), non-serious (45,871).
- Most frequently reported relevant PTs (≥2%): Dizziness (23,935), Dyspnoea (11,041), Paraesthesia (9532), Tachycardia (6238), Hyperhidrosis (5023), Palpitations (4405), Syncope (3213), Blood pressure increased (3176), Paraesthesia oral (2659), Loss of consciousness (2086), and Anxiety (1683).
- Time to event onset (n = 58,529)[96], range < 24 hours to 122 days, median < 24 hours.
  - < 24 hours: 34,591 events (94 of which had a fatal outcome);
  - 1 day: 12,544 events (94 of which had a fatal outcome);
  - 2-7 days: 8416 events (153 of which had a fatal outcome);
  - 8-14 days: 1586 events (40 of which had a fatal outcome);
  - 15-30 days: 1024 events (22 of which had a fatal outcome);
  - 31-181 days: 368 events (3 of which had a fatal outcome).
- Duration of event (n = 11,617 of 73,819 relevant events with outcome of resolved/resolved with sequelae)[97]:
  - <24 hours: 2856 events;
  - 1 day: 4643 events;
  - 2-7 days: 3414 events;
  - 8-14 days: 388 events;
  - 15-30 days: 217 events;
  - 31-181 days: 95 events.
- Relevant event outcome[34]: fatal (529), resolved/resolving (41,237), resolved with sequelae (951), not resolved (11,577), unknown (20,032).
  - The reported cause of death (≥30 occurrences) coded to the PTs Dyspnoea (261), Loss of consciousness (77), Pyrexia (60), Cardiac arrest (53), Death and Malaise (41 each), Oxygen saturation decreased (39), Tachycardia (32), and Asthenia (30). When the medical history was provided (n = 372), significant medical conditions included (≥ 30 occurrences) Hypertension (145), Atrial fibrillation (63), Cardiac failure (44),

[96] This number does not include 137 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[97] This number does not include 4 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

Chronic obstructive pulmonary disease, Dementia, Diabetes mellitus (43 each), and Type 2 diabetes mellitus (41).

- Lot/Batch Number: The lot/batch number which reported ≥3% of cases reporting vaccination stress/anxiety related ADRs is: #EL1484 (1788 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT Data: Paediatric (1), Adults (9) and Elderly (6).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (289), Adults (42,718), Elderly (9990) and Unknown (4809).
  - 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 PTs, Loss of consciousness and Syncope was observed in the paediatric population when compared to the adult or elderly population (Loss of consciousness [12.8% in paediatrics vs 3.0% in adults vs 6.5% in elderly], Syncope [16.3.% in paediatrics vs 5.1% in adults vs 6.7% in elderly]. This is consistent with expectations based on age-related event reports from other vaccines.[98]

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 11,256 (19.5% of the cases reporting stress/anxiety ADRs).
  - The reporting proportion of cases with fatal outcome is higher in individuals with comorbid conditions (0.9%) when compared to the reporting proportion observed in individuals without comorbidities (0.2%). In these cases, underlying comorbidities or events not related to stress/anxiety, are likely to be contributory to individual's death.

Conclusion

No new significant safety information was identified based on a review of these cases.

16.3.4. Evaluation of Special Situations

New data identified during the reporting interval for use of BNT162b2 by special patient situations is described below.

[98] Sutherland A, Izurieta H, Ball R, et al. Syncope after vaccination--United States, January 2005-July 2007. Centers for Disease Control and Prevention (CDC). MMWR 2008; 57(17):457-60.

16.3.4.1. 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 filed 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: 46[99] (6.6% of 702 cases, the total CT dataset; 41 cases involved blinded therapy [22]/BNT162b2 [19]). In the remaining 5 cases[100] subjects received placebo).
- Country of incidence: US (32), Argentina (5), Brazil (3) and South Africa (1).
- Subjects' gender: female (15) and male (26).
- Subjects' age in years (n = 41), range: 29 – 87, mean 62.4, median 64.
- Medical history (n = 35). The most frequently (≥6 occurrences) reported medical conditions included Hypertension (16), Gastrooesophageal reflux disease (12), Hyperlipidaemia (10), Hypercholesterolaemia (9), Seasonal allergy, Type 2 diabetes mellitus (7 each), and Depression (6). There was no COVID-19 medical history reported.
- Causes of death most frequently reported (≥3 occurrences): Disease progression (9), Cardiac arrest (6), Acute respiratory failure, COVID-19, Pneumonia (4 each), Completed suicide, COVID-19 pneumonia, and Myocardial infarction (3 each).
- Autopsy results were provided in 3 cases. Arteriosclerosis, Death, Embolism, Gastrointestinal haemorrhage, Hypertensive heart disease, and Overdose were singularly reported.
- Events with a fatal outcome (n = 53): The most frequently reported PTs (≥3 occurrences): Acute respiratory failure, Cardiac arrest (4 each), Completed suicide, COVID-19, COVID-19 pneumonia, Myocardial infarction (3 each). None of these events are considered related to blinded therapy/BNT162b2.

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[99] During the current reporting interval, there were 3 additional cases reporting subjects' death that were excluded from further analysis in this subsection as death was mentioned as an incidental information only with none of the reported events presenting a fatal outcome.

[100] The cases involved placebo are not included in the analysis.

- Co-suspects were reported in 2 cases and they were naproxen and warfarin (1 each).
- Time to event onset (n = 17),101 range: 4 – 128 days, median 58.5 days.
  - 2-7 days: 1 event;
  - 15-30 days: 4 events;
  - 31-181 days: 12 events.
- Lot Number (#) information by country was available in 5 cases. The list of Lot #s reported is presented hereinafter:
  - Lot # P220395-0020L in 3 cases from Brazil (2) and US (1);
  - Lot #s 0068L and P220395-0051L in 1 case each from US.

Post-Authorization Data

- Number of cases: 5042[102] (1.5% of 327,125 cases, the total PM dataset).
- MC cases (3961), NMC cases (1081).
- Country of incidence (≥2%): Germany (721), France (632), UK (443), Japan (377), Netherlands (322), US (321), Italy (240), Sweden (220), Spain (178), Norway (171), Australia (168), Hungary (144), Belgium (119), Romania (110), Austria (103), and Poland (102).
- Subjects' gender: female (2455), male (2316), unknown (271).
- Subjects' age in years (n = 4614), range: 2 - 105, mean 80.3, median 83.
- COVID-19 Medical history (n = 250): COVID-19 (202), COVID-19 pneumonia (20), Suspected COVID-19 (17), Asymptomatic COVID-19 (11), SARS-CoV-2 test positive (7), Coronavirus infection (5), Coronavirus test positive and SARS-CoV-2 sepsis (1 each). Of note, more than 1 medical history was reported in some cases.
- Other relevant Medical history (n = 3765).[103] The most frequently reported (>100 occurrences) medical conditions included cardiac and vascular disorders (eg, Hypertension [1416], Atrial fibrillation [582], Cardiac failure [393], Myocardial

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[101] This number does not include 7 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[102] During the current reporting interval, there were 70 additional cases reporting subjects' death that were excluded from further analysis in this subsection as: death was mentioned as an incidental information only with none of the reported events presenting a fatal outcome (26) and cases which reported foetal death/still birth/spontaneous abortion/involved transplacental or trans-mammary exposure are reviewed under *Use in Pregnancy and While Breast Feeding* (44).

[103] This list excluded the medical history terms indicative of COVID-19.

ischaemia [219], Cerebrovascular accident [212], Myocardial infarction [163], Dyslipidaemia [136], Coronary artery disease [131], Hypercholesterolaemia [113] and Cardiac disorder [110]). Other most frequently reported (>100 occurrences) medical conditions included Dementia (442), Diabetes mellitus (371), Type 2 diabetes mellitus (348), Chronic obstructive pulmonary disease (314), Chronic kidney disease (268), Dementia Alzheimer's type (222), Obesity (174), Renal failure (156), Depression (151), Hypothyroidism (147), Cognitive disorder (142), Osteoporosis (140), Osteoarthritis (129), Parkinson's disease (122), Pain (120), and Benign prostatic hyperplasia (104). Of note, more than 1 medical history was reported in some cases.

- Causes of death most frequently reported (>100 occurrences): Death (1236), COVID-19 (461), Cardiac arrest (321), Sudden death (309), Dyspnoea (263), Pyrexia (227), Cardiac failure, Myocardial infarction (190 each), Pneumonia (180), General physical health deterioration (171), Drug ineffective (170), Pulmonary embolism (166), Cardio-respiratory arrest (163), Cerebrovascular accident (151), Malaise (138), Cerebral haemorrhage (133), Vomiting (123), Respiratory failure (119), and COVID-19 pneumonia (111).

- Autopsy results were provided in 189 cases and the most commonly reported (>5 occurrences) were: Pulmonary embolism (24), Pulmonary oedema (19), Arteriosclerosis (18), Myocardial infarction (16), Arteriosclerosis coronary artery (14), Cardiac hypertrophy (13), Acute myocardial infarction (12), Pneumonia (11), Cardiomegaly Nephrosclerosis (9 each), Cerebral haemorrhage, Coronary artery stenosis, Deep vein thrombosis (8 each), Aortic arteriosclerosis, Brain oedema, Cardiac failure, Death, Myocardial ischaemia (7 each), Circulatory collapse, and Renal cyst (6 each).

- Co-suspects (n = 130): The most frequent reported (>2 occurrences) were apixaban (12), acenocoumarol (11), acetylsalicylate lysine (8), rivaroxaban (7), COVID-19 vaccine NRVV AD (5), acetylsalicylic acid, atorvastatin, clopidogrel, fentanyl, furosemide, paracetamol (4 each), amoxicillin/clavulinic acid, fluindione, morphine and oxycodone (3 each).

- Events with a fatal outcome (n = 11,051): The most frequently reported (≥2%) events coded to the PTs: Death (1268), COVID-19 (485), Sudden death (332), Cardiac arrest (325), Dyspnoea (291), Pyrexia (263), Drug ineffective (229), Cardiac failure (194), Myocardial infarction (192), Pneumonia (185), General physical health deterioration (181), Cardio-respiratory arrest (180), Pulmonary embolism (170), Malaise (166), Cerebrovascular accident (152), Vomiting (140), Cerebral haemorrhage (136), Respiratory failure (124), Vaccination failure (122), COVID-19 pneumonia (120), Asthenia (114), Oxygen saturation decreased (105), and Fatigue (101).

- Time to fatal event onset (n = 8127),[104] range: <24 hours to 133 days, median 1 day.
  - Same day: 1059 events;
  - 1 day: 1575 events;
  - 2-7 days: 3061 events;
  - 8-14 days: 1126 events;
  - 15-30 days: 908 events;
  - 31-181 days: 400 events.

- Lot/Batch Number (#) information by Country was available in 3132 cases with no related quality issues identified during investigations of the impacted lot/batch numbers. The list of Lot/Batch #s most frequently reported (>2% of cases) is presented hereinafter:
  - Lot/batch # EM0477 in 263 cases from France (80), Germany (64), Netherlands (37), Belgium (26), Norway (23), Spain (11), Denmark (8), Malta (6), Ireland (5), Switzerland (2), Estonia (1).
  - Lot/batch # EJ6795 in 160 cases from France (67), Norway (49), Sweden (22), Netherlands (9), Finland (5), Germany (4), Greece, and Poland (2 each).
  - Lot/batch # EJ6796 in 138 cases from Germany (48), Spain (18), Sweden (17), Norway (13), Austria (12), France (9), Iceland (7), Switzerland (5), Belgium, Slovenia (2 each), Croatia, Denmark, Finland, Hungary, and Malta (1 each).
  - Lot/batch # EJ6788 in 133 cases from France (116), Netherlands (8), Germany (7), Malta and Switzerland (1 each).

Analysis by age group

- CT: Adults (22), and Elderly (19).
  - A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.

- PM: Paediatric (4), Adults (542), Elderly (4138) and Unknown (358).
  - There is a significant difference observed in the reporting proportion of most 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 (82.1% vs 10.7%, respectively). There is no meaningful comparison between elderly vs paediatric population is possible due to the low number of paediatric fatal cases reported (0.1% vs 82.1%, respectively).

[104] This number does not include 6 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- Most of the cases reporting a fatal outcome (68.6%) 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.[105,106,107]

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 2760 (0.8% of 327,827 cases, the total dataset).
- Upon review, there were no significant differences observed in the patterns of fatal events reported between the group with comorbidities and the one without comorbidities.

Analysis by dose

- Number of vaccine doses administered at the time of the subjects' death:
  - First dose (2264)
  - Second dose (1437). Of the 1437 cases, 781 cases (54.3%) reported a latency of same day to 3 days after vaccination. There were 3374 fatal events. The most frequently reported (>50 occurrences) fatal events were coded to PTs Death (355), COVID-19 (155), Vaccination failure (121), Cardiac arrest (105), Sudden death (88), Dyspnoea, Pyrexia (87 each), Drug ineffective (66), Myocardial infarction (61), Cardiac failure (55), Pneumonia (52), and Cardio-respiratory arrest (51).
  - Third dose (1). There was 1 case that reported a 57-year-old male subject who had a fatal outcome after receiving a third dose of BNT162b2 in an outpatient setting with "no effect or specific complaint immediately after". One (1) day after he "spoke a little inconsistently" and was not feeling well. He was found deceased in his home 2 days later. Medical history included bi-pulmonary and hepatic transplant with COPD and non-alcoholic liver cirrhosis and concomitant medications were not reported. It was unknown if an autopsy was completed, however, the physician reported that there was no cardiovascular antecedent, no hypertension, normal coronary angiography and ultrasound, no kidney damage. The subject was hospitalized a few days before for suspected acute rejection and was given a corticosteroid bolus (as reported).
  - In the remaining cases (1340), it was not specified if the subjects received the first or the second vaccine dose at the time of the subject's death.

[105] Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA. ECDC, February 2021.

[106] https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19/evidence-table-phase-1b-1c.html.

[107] WHO Roadmap for Prioritizing Population Groups for Vaccines against COVID-19; ACIP COVID-19 Vaccines Working Group, Phased Allocation of COVID-19 Vaccines (Dec 01, 2020); JCVI updated interim advice on priority groups for COVID-19 vaccination (Sept 25, 2020).

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and death.

Conclusion

No new risks were identified following review of fatal cases, particularly in the comorbid elderly population.

16.3.4.1.1. Death Review by Age Group

This is a high-level overview of the 5088 cases are in the interval reporting period (see Section 16.3.4.1 for further details. According to the core PSUR19 guidance,[43] summary tabulation of fatal reports by Age groups and SOCs is provided in Appendix 6D.1.

Interval Reporting Period

- CT (46 cases): Adults (23), and Elderly (23).

The top MedDRA SOCs with the most frequently reported (>5 occurrences) events with a fatal outcome cumulative by age group is presented in the table below.

Table 34. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval

SOC	Total number of events	25-49 years	50-59 years	60-69 years	70+ years
Infections	15	3	5	4	3
Cardiac	12	0	2	4	6
General disorders	6	0	2	3	1
Respiratory	6	2	1	3	0

Of note, multiple AEs may be reported in a single case.

- PM (5042 cases): Paediatric (17 years and under) (4), Adults (18-64 years) (533), Elderly (65 years and older) (4145) and Unknown (360).

The top 5 MedDRA SOCs with the most frequently reported (>1000 occurrences) events with a fatal outcome cumulative by age group in the post authorization data are presented in the table below.

Table 35. Post-Authorization Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval

SOC	Total number of events	≤ 17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years	Unk
General disorders	3277	1	2	106	110	247	2532	279
Cardiac	1589	1	8	63	83	145	1254	35
Respiratory	1333	1	2	36	57	114	1091	32
Nervous system	1262	0	1	32	56	98	1036	39
Infections	1115	0	1	7	21	79	853	154

Of note, multiple AEs may be reported in a single case.

Cumulative Reporting Period

This is a high-level overview of the 5109 relevant cumulative cases with a fatal outcome. According to the core PSUR19 guidance,[43] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 6D.2.

Clinical Trial Data

- Number of cases: 70 (10.0% of 702 cases, the total CT dataset; 64 cases involved blinded therapy [40]/BNT162b2 [24]). In the remaining 6 cases[108] subjects received placebo).
- Causes of death most frequently reported (>2 occurrences): Disease progression (18), Cardiac arrest (8), Pneumonia (6), COVID-19, Myocardial infarction (5 each), Acute respiratory failure, Cardio-respiratory arrest (4 each), Arteriosclerosis, Completed suicide, and COVID-19 pneumonia (3 each).
- Autopsy results were provided in 4 cases. Accidental death, Arteriosclerosis, Death, Embolism, Gastrointestinal haemorrhage, Hypertensive heart disease and Overdose were singularly reported.
- Events with a fatal outcome (n = 65): The most frequently reported PTs (>2 occurrences): Cardiac arrest (6), Myocardial infarction (5), Acute respiratory failure, Cardio-respiratory arrest, COVID-19, Pneumonia (4 each), Arteriosclerosis, Completed suicide, COVID-19 pneumonia (3 each). None of these events are considered related to blinded therapy/BNT162b2.

[108] The cases involved placebo are not included in the analysis.

Post-Authorization Data

- Number of cases: 5027[109] (1.5% of 327,603 cases, the total cumulative PM dataset)
- MC cases (3947), NMC cases (1080).
- Causes of death most frequently reported (>100 occurrences): COVID-19 (459), Cardiac arrest (322), Sudden death (308), Dyspnoea (262), Pyrexia (227), Cardiac failure, Myocardial infarction (190 each), Pneumonia (178), General physical health deterioration (171), Drug ineffective (169), Pulmonary embolism (166), Cardio-respiratory arrest (163), Cerebrovascular accident (151), Malaise (138), Cerebral haemorrhage (133), Vomiting (123), Respiratory failure (118), COVID-19 pneumonia (111).
- Autopsy results were provided in 189 cases and the most commonly reported (>5 occurrences) were: Pulmonary embolism (24), Pulmonary oedema (19), Arteriosclerosis (18), Myocardial infarction (16), Arteriosclerosis coronary artery (14), Cardiac hypertrophy (13), Acute myocardial infarction (12), Pneumonia (11), Cardiomegaly, Nephrosclerosis (9 each), Cerebral haemorrhage, Coronary artery stenosis, Deep vein thrombosis (8 each), Aortic arteriosclerosis, Brain oedema, Cardiac failure, Myocardial ischaemia (7 each), Circulatory collapse, and Renal cyst (6 each).
- Events with a fatal outcome (n = 11,027): The most frequently reported (>2% events) events coded to the PTs: COVID-19 (483), Sudden death (331), Cardiac arrest (326), Dyspnoea (290), Pyrexia (263), Drug ineffective (228)[110,111] Cardiac failure (194), Myocardial infarction (192), Pneumonia (183), General physical health deterioration (181), Cardio-respiratory arrest (180), Pulmonary embolism (170), Malaise (166), Cerebrovascular accident (152), Vomiting (140), Cerebral haemorrhage (136), Respiratory failure (123), COVID-19 pneumonia (120), Asthenia (114), Oxygen saturation decreased (104), and Fatigue (101).

Analysis by age group:

- CT: Adults (39), and Elderly (31).

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[109] During the current reporting interval, there were 70 additional cases reporting subjects' death that were excluded from further analysis in this subsection as: death was mentioned as an incidental information only with none of the reported events presenting a fatal outcome (26) and cases which reported foetal death/still birth/spontaneous abortion/involved transplacental or trans-mammary exposure are reviewed under *Use in Pregnancy and While Breast Feeding* (44).

[110] Of the 229 cases reporting the PT Drug ineffective, 17 cases cannot be considered true lack of efficacy cases because the subjects developed SARS-CoV-2 infection during the early days from the 1st dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine

[111] Two (2) of these 229 cases, reporting the PT Drug ineffective, were assessed as true Vaccination failure cases after the PSUR DLP

The top 5 MedDRA SOCs with the most frequently reported (>5 occurrences) events with a fatal outcome cumulative by age group is presented in the table below.

Table 36. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	Total number of events	25-49 years	50-59 years	60-69 years	70+ years
Cardiac	19	1	7	4	7
Infections	19	3	5	5	6
General disorders	8	1	2	4	1
Respiratory	8	2	2	4	0
Vascular disorders	6	1	1	3	1

Of note, multiple AEs may be reported in a single case.

- A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.

- PM: Paediatric (17 years and under) (4), Adults (18-64 years) (528), Elderly (65 years and older) (4128) and Unknown (367).

The top 5 MedDRA SOCs with the most frequently reported (>1000 occurrences) events with a fatal outcome cumulative by age group in the post authorization data are presented in the table below.

Table 37. Post-Authorization Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	Total number of events	≤ 17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years	Unk
General disorders	3277	1	2	106	110	247	2532	279
Cardiac	1590	1	8	64	83	145	1254	35
Respiratory	1333	1	2	36	57	114	1091	32
Nervous system	1262	0	1	32	56	98	1036	39
Infections	1115	0	1	7	21	79	853	154

Of note, multiple AEs may be reported in a single case.

- There is a significant difference observed in the reporting proportion of most 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 65 years of age (82% vs 11.2%, respectively). There is no meaningful comparison between elderly vs paediatric population is possible due to the low number of paediatric fatal cases reported (0.1% vs 82%, respectively).

- Most of the cases reporting a fatal outcome (68.7%) 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.[105,106,107]

O/E Analysis

O/E analysis was performed for events with a fatal outcome (see Appendix 6C *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

No safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

16.3.4.2. Overdose

- Search Criteria: HLT Overdoses NEC OR PT Accidental overdose.
- Of the 1523 cases, 23 cases were determined to be non-contributory and are not included in the discussion for the following reasons:
  - dosage regimes inconsistent with BNT162b2 vaccine dosing (eg, grams) were reported in 19 cases;
  - the reported PTs of overdose referred to opiates, paracetamol, methamphetamine and venlafaxine and not to BNT162b2 in 4 cases.

Clinical Trial Data

- Number of cases: 2 (0.3% of 702 cases, the total CT dataset; one case involved blinded therapy and one case involved BNT162b2).
- Country of incidence: [redacted] (both cases).
- Subjects' gender: female (1) and male (1).
- Subjects' age (n = 2): 17 years, and 39 years.
- Medical history (n = 2): the reported medical conditions included: Anxiety (2), Attention deficit hyperactivity disorder, Depression, Hot flush, Insomnia, Invasive ductal breast carcinoma, Metastases to lymph nodes and Migraine (1 each).
- Co-suspects: alprazolam, cyclobenzaprine, escitalopram and sertraline (1 each).
- Number of events: 3 (of which 2 were events of interest).

- Relevant PTs: Overdose [2, both assessed as unrelated to BNT162b2 (1) and blinded therapy (1)].
- Relevant event outcome: resolved (1), resolved with sequelae (1).
- Co-reported PT: Suicide attempt (1), assessed as unrelated to blinded therapy.

Post-Authorization Data

- Number of cases: 1498 (0.5% of 327,125 cases, the total PM dataset).
- MC cases (1300), NMC cases (198).
- Country of incidence (≥2%): US (1089), Portugal (115), Italy (73), UK (64) and France (31).
- Subjects' gender: female (442), male (223) and unknown (833).
- Subjects' age in years (n = 607), range: 12 – 100, mean 49.1, median 49.
- Medical history (n = 167): the most frequently (≥2%) reported medical conditions included: Hypertension (104), COVID-19 (60), Asthma (36), Migraine (26), Drug hypersensitivity (25), Food allergy (23) and Seasonal allergy (20).
- Co-suspects: COVID-19 Moderna (mRNA-1273) vaccine, COVID-19 vaccine AstraZeneca vaccine (2 each), amoxicillin, clarithromycin, diazepam, ergocalciferol, hepatitis B vaccine, metronidazole, sodium chloride, topiramate, varicella zoster vaccine rgE (CHO) (1 each).
- Number of events: 3647 (of which 1500 were events of interest).
- Relevant event seriousness: serious (42), non-serious (1458).
- Relevant PTs: Overdose (1368), Accidental overdose (126), Intentional overdose[112] (5) and Prescribed overdose[113] (1).
- Relevant event outcome: resolved/resolving (55), not resolved (7), unknown (1438).

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[112] In 3 cases, the subjects (1 male and 1 female, both of unknown age and a 52-year-old male subject) received 4 doses of vaccine (2 doses in one facility and 2 doses in another facility) deliberately (2 of these 3 subjects believed that "the more the better"). In the fourth case, a female subject (age unknown) requested to repeat the dose, since the shot for the first dose of vaccine was administered high in the arm. In the last case, the reporting physician assistant inquired about a possible third dose to a 19-year-old male subject (it was unclear if the additional dose was administered).

[113] A 52-year-old male subject received the second dose of BNT162b2 at 0.6 ml intramuscularly. The event was reported as Prescribed overdose, but no further details are available.

- Most frequently co-reported PTs (≥2%): Product preparation issue (572), Product preparation error (172), Headache (100), Pyrexia (77), Pain in extremity (60), Arthralgia (57), Vaccination site pain (55), Myalgia (53), Pain (49) and Fatigue (45).

- Clusters of cases:

  - a physician reported 15 subjects (age and gender unknown) who received the vaccine from vials reconstituted with 1.3 mL instead of 1.8 mL of saline;

  - a healthcare professional reported 304 subjects (age and sex unknown) who received the vaccine from vials diluted with 1.3 ml instead of 1.8 ml of saline;

  - a pharmacist reported that 9 staff members accidentally received 0.5 ml of vaccine instead of 0.3 ml for their second dose;

  - a physician stated that 64 subjects received 0.5 ml of vaccine instead of 0.3 ml;

  - a nurse reported that 77 subjects inadvertently received a full undiluted vial (all vials from batch PAA165969);

  - a nurse administered both doses of vaccine in a single shot (one syringe) to 17 inmates (unknown gender and age).

Analysis by age group

- CT: Paediatric (1) and Adults (1).

  - A meaningful comparison between the different age groups is not possible due to the low number of CT cases.

- PM: Paediatric (48), Adults (415), Elderly (158) and Unknown (877).

  - Upon review, events indicative of overdose occurred more in adult subjects, but no significant differences in the reporting proportion of the most frequently co-reported AEs was noted between the different age groups. In addition, more adults than paediatric subjects were vaccinated during the reporting period.

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 74 (4.9% of the total cases reporting overdose and 0.02% of 327,827 cases, the total dataset).

- 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.

Conclusion

The most commonly reported reasons (≥ 2%) for overdose were:

- dilution with a volume of sodium chloride different from the recommended 1.8 ml (532; 35.5% of the total cases reporting overdose);
- administration of incorrect dose of diluted vaccine, different from the recommended 0.3 ml (361; 24.1% of the total cases reporting overdose);
- administration of undiluted vaccine (268; 17.9% of the total cases reporting overdose);
- administration of a double dose of vaccine (118; 7.9% of the total cases reporting overdose);
- third dose of vaccine was administered (35[114]; 2.3% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 181 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 commonly 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.

16.3.4.3. 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

[114] In 9 of these 35 cases Off label use was co-reported (Section 16.3.4.6).

underdose; Performance enhancing product use; Prescription drug used without a prescription; Treatment noncompliance.

- Of the 104 cases, 40 cases were determined to be non-contributory and are not included in the discussion for the following reasons:
  - They involved the abuse of illicit substances including nitrous oxide, valium, lithium, etc.

Clinical Trial Data

There were no serious clinical trial cases of abuse or misuse of the vaccine reported during the reporting period.

Post-Authorization Data

- Number of cases: 65 (0.01% of 327,125 cases, the total PM dataset).
- MC cases (16), NMC cases (49).
- Country of incidence (≥2%): US (38), UK (13), Italy, Mexico, Spain (2 each).
- Subjects' gender: female (38), male (20) and unknown (7).
- Subjects' age in years (n = 38), range: 24 - 90, mean 59.2, median 62.
- Medical history (n = 24): the most frequently (≥2%) reported medical conditions included Supressed lactation (4), Depression, Drug hypersensitivity (3 each), Asthma, Epilepsy, Fatigue, Hypersensitivity, Hypertension, Hypoaesthesia, Paraesthesia (2 each).
- COVID-19 Medical history (n = 2): COVID-19, Suspected COVID-19 (1 each).
- Co-suspects: COVID-19 Moderna (mRNA 1273) vaccine, ipilimumab, levothyroxine, medroxyprogesterone, methotrexate, nivolumab, ocrelizumab, zonisamide (1 each).
- Number of events: 276 (of which 66 were events of interest).
- Relevant event seriousness: serious (12), non-serious (54).
- Most frequently reported relevant PTs (≥2%): Intentional dose omission (19), Intentional product misuse (17), Withdrawal syndrome (9), Intentional product use issue, Toxicity to various agents (6 each), Disturbance in social behaviour (3).
- Time to event onset (n = 8), range: 0 - 2 days, median 0 days.
  - >24 hours: 5 cases;
  - 1 day: 1 case;
  - 2-7 days: 2 cases.

- Relevant event outcome: fatal (1), resolved/resolving (5), not resolved (5), unknown (55).

Analysis by age group

- PM: Adults (20), Elderly (18) and Unknown (27).
  - There was no meaningful difference between different age groups.

Analysis by dose

- PM: Number of vaccine doses administered at the time of the event onset: 1 dose in 29 cases, 2 doses in 23 cases; in 18 cases the dose was either not specified or reported as other.
  - There are no differences between the AEs that occurred after the 1st and 2nd dose.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and abuse, dependence or misuse.

Conclusion

Overall, there were 65 cases representing 0.01% of the overall post-marketing dataset, that reported events indicative of misuse. The majority of the cases involved subjects who intentionally did not receive their second BNT162b2 dose or the second dose was received after the recommended time frame per the RSI. In general, the most frequently reported events observed in the cases reporting abuse or misuse was consistent with those observed in the overall population. No safety signals have emerged that would be considered specific to this population.

16.3.4.4. Occupational Exposure

- Search criteria: PTs Exposure to contaminated device; Occupational exposure to product; Occupational exposure to radiation; Occupational exposure to toxic agent.

Clinical Trial Data

- There were no serious clinical trial cases indicative of occupational exposure during the reporting period.

Post-Authorization Data

- Number of cases: 32 (0.01% of 327,125 cases, the total PM dataset).
- MC cases (27), NMC cases (5).

- Country of incidence: US (17), France (4), UK (3), Italy, Japan (2 each), Belgium, Germany, Greece Netherlands (1 each).
- Subjects' gender: female (20), male (7) and unknown (5).
- Subjects' age in years (n = 8), range: 26 - 47, mean 36.9, median 38.5.
- Medical history (n = 1): Allergy to animal, Food allergy, Seasonal allergy (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of events: 67 (of which 32 were events of interest).
- Relevant event seriousness: all non-serious (32).
- Reported relevant PT: Occupational exposure to product (32).
- Co-reported AEs (≥2 occurrences): Eye irritation (4), Exposure via eye contact (3), Exposure via skin contact, Injury associated with a devise (2 each).
- Time to event onset (n = 7): < 24 hours.
- Relevant event outcome: resolved (2), not resolved (1), unknown (29).

Analysis by age group

- PM: Adults (8), Unknown (24).
  - 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.

Conclusion

Overall, there were 32 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.

16.3.4.5. Lack of Therapeutic Efficacy

Company conventions for coding cases indicative of lack of efficacy:

- The coding conventions for lack of efficacy in the context of administration of the COVID-19 vaccine was revised on 12 February 2021, as shown below: PT "Vaccination failure" is coded when ALL of the following criteria are met:
    - The subject has received the appropriate series of two doses based on the labeling.
    - At least 7 days have elapsed since the second dose of vaccine has been administered.
    - The subject experiences SARS-CoV-2 infection (confirmed laboratory tests).
- PT "Drug ineffective" is coded when either of the following applies:
    - The infection is not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied, eg, "the vaccine did not work", "I got COVID-19".
    - It is unknown:
        - Whether the subject has received the appropriate series of two doses in correct timing based on the labeling instructions;
        - How many days have passed since the first dose (including unspecified number of days like "a few days", "some days", etc);
        - If 7 days have passed since the second dose of the vaccine administration
    - The subject experiences a vaccine preventable illness 14 days after receiving the first dose up to and through 6 days after receipt of the second dose.
- Note: after the immune system has had sufficient time (14 days) to respond to the vaccine, this is considered a potential lack of efficacy even if the vaccination course is not complete.

This is the summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date:

1st dose (day 1-13)	**From day 14 post 1st dose to day 6 post 2nd dose**	**Day 7 post 2nd dose**
Code only the events describing the SARS-CoV-2 infection	Code "Drug ineffective"	Code "Vaccination failure"
Scenario Not considered LOE	Scenario considered LOE as "Drug ineffective"	Scenario considered LOE as "Vaccination failure"

- Search Criteria: PTs Drug ineffective; Vaccination failure.

- Of the 6836 cases, 468 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

  - Four hundred forty-five (456 cases), upon review, cannot be considered true lack of efficacy cases because the subjects developed SARS-CoV-2 infection during the early days from the 1st dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine.

  - Nine (9) cases were invalidated in the safety database after the PSUR DLP;

  - One (1) case was identified as no report of lack of efficacy because the patient did not develop the COVID-19 infection;

  - In 2 cases the LOE PT did not refer to BNT162b2 vaccine.

Clinical Trial Data

There were no lack of efficacy cases in the clinical trial dataset.

Post-Authorization Data

- Number of cases: 6376 (1.9% of 327,125 cases, the total PM dataset).
- MC cases (4024), NMC cases (2344).
- Number of lack of efficacy events[115]: 6376 (Drug ineffective [4767] and Vaccination failure [1609]).
- Country of incidence (≥2%): the US (2091), the UK (728), France (645), Italy (600), Germany (387), Austria (204), Portugal (149), Croatia (144), Belgium (141) and Spain (127).
- Subjects' gender: female (3404), male (1904) and unknown (1060).
- Subjects' age in years (n = 3958), range: 15 – 104, mean 61.8, median 61.0.
- Relevant event seriousness: all serious[116].

[115] Relevant LOE PTs recorded in the 6376 cases were Drug ineffective (4767) and Vaccination failure (2346). Upon review after DLP, some cases were re-assessed: in 45 cases the PT Drug ineffective was reassessed to Vaccination failure; in 44 cases the PT Vaccination failure was reassessed to Drug ineffective.

[116] Includes 26 cases where LOE was captured as non serious and upgraded to serious after the PSUR DLP.

Confirmed and not confirmed vaccination failure cases (1611 cases in total)

Vaccination failure was reported in 1611 cases, indicative of appropriately (correct interval between dose 1 and dose 2) and fully vaccinated (2 doses) patients, who developed a COVID-19 infection, at least 7 days after the 2nd vaccine dose. Of these:

- One thousand four hundred and ninety-two (1492) were confirmed vaccination failure: the infection was confirmed by laboratory test (ie, COVID-19 PCR positive test or antigen test).

- One hundred nineteen (119) were not confirmed vaccination failure: the infection was clinically diagnosed but not laboratory confirmed (ie, COVID-19 PCR positive test or antigen test was not performed on results were unknown).

Confirmed vaccination failure (1492 cases)

Vaccination failure was reported in 1492 cases[117] where the COVID-19 infection was confirmed by laboratory test (ie, COVID-19 PCR positive test or antigen test).

- Age groups: Adolescent (1), Adults (662), Elderly (724) and Unknown (105).

Time to event onset was known for 1431 cases; in the remaining 61 cases, it was implied that vaccination failure was reported on or after day 7 post second dose but detailed information was not provided.

- day 7 to ≤30 days: 477 subjects;
- ≥ 31 days to ≤ 60 days: 548 subjects;
- ≥ 61 days to ≤ 90 days: 340 subjects;
- ≥ 91 days to ≤ 120 days: 66 subjects.

Reported vaccine preventable infections[118]: COVID-19 (1090), Asymptomatic COVID-19 (299), SARS-CoV-2 test positive (86), COVID-19 pneumonia (72), Suspected COVID-19 (3)[119].

Vaccination failure outcome: fatal (116), resolved/resolving (494), resolved with sequelae (8), not resolved (271), unknown (603).

[117] Includes 45 cases reporting the PT Drug ineffective reassessed to Vaccination failure (confirmed by a COVID-19 test) after the PSUR DLP.

[118] Some cases reported more than 1 PT referring to a COVID-19 infection.

[119]In the 3 cases reporting Suspected COVID-19 the infection was then confirm by a positive COVID-19 test.

Not confirmed vaccination failure (119 cases)

Vaccination failure was reported in 119 cases where subjects received 2 doses of the vaccine at the appropriate interval and developed a COVID-19 infection, clinically diagnosed but not laboratory confirmed (ie, COVID-19 PCR positive test or antigen test), at least 7 days after the 2nd dose.

- Age groups: Adults (51), Elderly (56) and Unknown (12).

Time to event onset was known for 107 cases; in the remaining 12 cases, it was implied that vaccination failure was reported on or after day 7 post second dose but detailed information was not provided.

- day 7 to ≤30 days: 33 subjects;
- ≥ 31 days to ≤ 60 days: 42 subjects;
- ≥ 61 days to ≤ 90 days: 24 subjects;
- ≥ 91 days to ≤ 120 days: 8 subjects.

Reported vaccine preventable infections[120]: COVID-19 (96), Asymptomatic COVID-19 (10), COVID-19 pneumonia (3), and Suspected COVID-19 (3).

Vaccination failure outcome: fatal (5), resolved/resolving (45), not resolved (29), unknown (40).

Not a vaccination failure cases

There were 4757 cases[121] reporting Drug ineffective, indicative of occurrence of the disease:

- in patients who have not received the full dose schedule;
- during the incubation period;
- in patients for which it was possible to determine whether they received the appropriate series of 2 doses at the appropriate interval.
- in patients for which it was not possible to determine how many days have passed since the last dose administration.

- Lack of efficacy term was reported:
  - after the 1st dose in 2450 cases

[120] Some cases reported more than 1 PT referring to a COVID-19 infection.

[121] Includes 44 cases reporting the PT vaccination failure, reassessed to Drug ineffective (the cases did not meet the criteria for vaccination failure) after the PSUR DLP.

- after the 2nd dose in 1199 cases
- in 1108 cases it was unknown after which dose the lack of efficacy occurred

- Time to event onset reported after the 1st dose was known for 851 cases:

  - day 14 to ≤ 30 days: 727 subjects
  - ≥ 31 days to ≤ 60 days: 99 subjects;
  - ≥ 61 days to ≤ 90 days: 19 subjects;
  - ≥ 91 days to ≤ 112 days: 6 subjects.

- Time to event onset reported after the 2nd dose was known for 571 cases

  - before day 7: 263 subjects;
  - day 7 to ≤ 30 days: 122 subjects;
  - ≥ 31 days to ≤ 60 days: 103 subjects;
  - ≥ 61 days to ≤ 90 days: 61 subjects;
  - ≥ 91 days to ≤ 124 days: 22 subjects.

COVID-19 variant (287 cases)

- *Alpha (UK) variant (219 cases)*

  - In 219 of the 6376 cases, COVID-19 infection with British variant was reported. Country of incidence: France (105), Italy (63), Austria (32), Germany, Spain (5 each), Switzerland (2); the remaining 7 cases originated from 7 different countries.
  - Lack of efficacy events: Vaccination failure (124) and Drug ineffective (95).
  - The outcome of COVID-19 infection related events reported in these 219 cases were: fatal (34), resolved or resolving (61), not resolved (51), and unknown (72).

- *Beta/Gamma (South African or South African/Brazilian) variant (55 cases)*

  - In 55 of the 6376 cases, COVID-19 infection with South African variant (33) or South African or Brazilian variant (22) was reported. Country of incidence: France (54), Finland (1).
  - Lack of efficacy events: Vaccination failure (36) and Drug ineffective (18).
  - The outcome of COVID-19 infection related events reported in these 55 cases were: fatal (5), resolved or resolving (17), not resolved (8), and unknown (25).

- *Gamma (Brazilian) variant (7 cases)*

  - In 7 of the 6376 cases, COVID-19 infection with Brazilian variant was reported. Country of incidence: Italy (5) and France (2).
  - Lack of efficacy events: Vaccination failure (4) and Drug ineffective (3).
  - The outcome of COVID-19 infection related events reported in these 7 cases were: fatal (1), resolved (2), resolved with sequelae (1) and unknown (2).

- *Delta (Indian) variant (5 cases)*

  - In 5 of the 6376 cases, COVID-19 infection with Brazilian variant was reported. Country of incidence: Germany (2), Belgium, India and the US (1 each).
  - Lack of efficacy events: Vaccination failure (1) and Drug ineffective (4).
  - The outcome of COVID-19 infection related events reported in these 5 cases were: fatal (1), resolved (1), not resolved (1), and unknown (2).

- In 1 additional case it was reported that the patient had a "new variant" (not further specified).

Literature

Review of the literature did not identify any significant new information with regards the use of BNT162b2 and lack of therapeutic efficacy.

Conclusion

According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 4757 cases where lack of efficacy was reported after the first dose or the second dose, 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. No new safety signals have emerged based on a review of these cases.

16.3.4.6. 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.

- Of the 4719 cases, 47 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

  - Twenty-four (24) cases reporting the PTs Contraindicated product administered (13) and Product administered to patient of inappropriate age (11) were found to be indicative of a potential medication error. These cases are referenced in Section 9.2 *Medication Errors*.

  - Eleven (11) cases reported the events Intentional product use issue (9), Intentional device use issue and Intentional underdose (1 each). Six (6) of these cases were not reported with use of the BNT162b2 vaccine. These cases did not report any additional

events potentially indicative of off label use. The remaining 5 cases are referenced in Section 16.3.4.3 *Abuse, Misuse and Drug Dependency.*

– Twelve (12) cases reported the PT Drug effective for unapproved indication with no additional events indicative of a potential medication error. These cases are referenced in Section 16.3.4.7 *Unexpected Therapeutic Effect.*

Clinical Trial Data

- Not applicable.

Post-Authorization Data

- Number of cases: 4672 (1.4% of 327,125 cases, the total PM dataset).
- MC cases (1832), NMC cases (2840).
- Country of incidence (≥2%): US (1812), UK (1781), Norway (153), Canada (148), Hungary (131), and Germany (94).
- Subjects' gender: female (3319), male (924) and unknown (429).
- Subjects' age in years (n = 3196), range: 0.08 - 99 years, mean 47.7, median 44.0.
- Medical history (n = 2314 cases): the most frequently (≥2%) reported medical conditions included Suppressed lactation (395), Breast feeding (241), Immunodeficiency (236), Suspected COVID-19 (214), Hypertension (202), Asthma (180), COVID-19 (136), Hypothyroidism (114), Drug hypersensitivity (109), Diabetes mellitus (89), Rheumatoid arthritis (84), Hypersensitivity (82), Depression (76), Migraine (68), Clinical trial participant (64), Pregnancy (61), Steroid therapy (60), Anxiety (59), Food allergy (56), Gastrooesophageal reflux disease (53), Seasonal allergy (51), and Pain (49).
- COVID-19 Medical history (n = 363 cases): the most frequently (≥2%) reported medical conditions included Suspected COVID-19 (214), COVID-19 (136), and SARS-CoV-2 test positive (16).
- Co-suspects (n = 204 cases): the most frequently (≥2%) reported co-suspect medications included COVID-19 AstraZeneca vaccine (72), COVID-19 Moderna (mRNA 1273) vaccine (33), Tofacitinib citrate (8), COVID-19 vaccine NRVV AD 26 JNJ 78436735 (6), Paracetamol (5), Adalimumab and Tetanus vaccine (4 each).
- Number of events: 21,162 (of which 6444 were events of interest).
- Relevant event seriousness: serious (240), non-serious (6204).
- Most frequently reported relevant PTs (≥2%): Off label use (4311), Product use issue (2029). Of note, 880 of these cases did not report additional events. Most of the cases described off-label use in

- breastfeeding/pregnancy
  - 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 fetus.
- an unapproved population (ie. Immunocompromised, active disease, concurrently on immunosuppressive medications)
  - Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.
- alternative dosing or scheduling regimens (ie. either only 1 dose or a 3rd dose given longer/shorter amount of days between doses than recommended)
  - Off label is currently considered when the 2nd dose of the vaccine is administered outside the 19-42 day range from the 1st dose. This range may have differed initially following launch of the vaccine.
- administration of COVID-19 vaccines from different manufacturers
  - There is currently no data available on the interchangeability of the BNT162b2 vaccine and other COVID-19 vaccines to complete the series.
- co-administration with other vaccines (ie influenza)
  - No interaction studies have been performed

The PT Product administered to patient of inappropriate age was reported in 87 cases. These 87 cases only represent those which were possibly indicative of off label use. Of note, the use of the BNT162b2 vaccine in adolescents aged 12 to 15 years old was approved in the EU on 31 May 2021 and received emergency use authorization in the US on 10 May 2021. When reported (N = 84), patient ages ranged from 1 month to 16 years. These cases are also referenced in Section 16.3.5.2 *Use in Paediatric Patients*.

Of note, a physician spontaneously reported the administration of 131 vaccine doses to HCP volunteers after the vials had been stored at room temperature for 19 hours (PTs Product temperature excursion issue, Off label use, Poor quality product administered [131 each]). Batch/lot numbers were not reported. The patients' anti-body tests were normal/same levels as patients administered vaccine that was properly stored. As per the reporter, there was a report of one person experiencing an adverse event, but details were not reported.

Literature

Review of the literature did not identify any significant new information with regards to the off-label use of BNT162b2.

Conclusion

Review of these cases did not identify new safety information related to off-label use.

16.3.4.7. Unexpected Therapeutic Effect

- Search Criteria: PTs Device effect increased; Drug effect faster than expected; Drug effective for unapproved indication; Therapeutic product effective for unapproved

indication; Therapeutic response changed; Therapeutic response increased; Therapeutic response prolonged; Therapeutic response unexpected; Therapeutic product effect increased; Therapeutic product effect prolonged.

Clinical Trial Data

- There were no serious clinical trial cases with the above PTs reported during the reporting period.

Post-Authorization Data

- Number of cases: 472 (0.1% of 327,125 cases, the total PM dataset).
- MC cases (78), NMC cases (394).
- Country of incidence (≥2%): US (256), UK (78), Germany (42), Canada, Israel (16 each), France (10).
- Subjects' gender: female (253), male (152) and unknown (67).
- Subjects' age in years (n = 298), range: 16 - 101, mean 62.4, median 64.
- Medical history (n = 391): the most frequently (≥2%) reported medical conditions included Hypertension (27), Asthma (24), Pain (20), Arthritis (18), Arthralgia, Psoriasis (17 each), Rheumatoid arthritis (16), Chronic obstructive pulmonary disease, Diabetes mellitus (14 each), Dementia, Drug hypersensitivity (13 each), Dyspnoea, Hypersensitivity, Multiple sclerosis (12 each), Herpes Zoster (11), Anosmia, Anxiety, Fibromyalgia, Hypothyroidism, Parkinson's disease (10 each).
- COVID-19 Medical history (n = 35): COVID-19 (23), Suspected COVID-19 (11), COVID-19 pneumonia, SARS-CoV-2 test positive (1 each).
- Co-suspects: antilymphocyte immunoglobulin, ginseng, hydrocortisone, metoprolol, ocrelizumab, tofacitinib, varicella zoster vaccine (1 each).
- Number of events: 1208 (of which 473 were events of interest).
- Relevant event seriousness: serious (16), non-serious (457).
- Most frequently reported relevant PTs (≥2%): Therapeutic response unexpected (456), Drug effective for unapproved indication (12).
- In the majority of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, breathing, dementia, skin conditions, inflammation, taste, smell, cognitive skills, blood sugar, asthma.

- Time to event onset (n = 129), range: 0 - 54 days.
  - <1 day: 33 events;
  - 1 day: 46 events;
  - 2-7 days: 31 events;
  - 8-14 days: 7 events;
  - 15-30 days: 9 events;
  - 31-181 days: 3 events.
- Relevant event outcome: resolved/resolving (50), resolved with sequelae (2), not resolved (35), unknown (386).

Analysis by age group

- PM: Paediatric (1), Adults (151), Elderly (149) and Unknown (171).
  - 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.

Conclusion

In the majority of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, breathing, dementia, skin conditions, inflammation, taste, smell, cognitive skills, blood sugar, asthma. In the majority of the cases, the subject's experienced the unexpected therapeutic effect following their 1st dose. No significant new information was identified with regards the use of BNT162b2 and unexpected therapeutic effect.

16.3.5. Update on Special Patient Populations

New data identified during the reporting interval for use of BNT162b2 by special patient populations is described below.

16.3.5.1. Use in Elderly Patients

Clinical Trial Data

- Number of cases: 255 (36.0% of 704 cases, the total CT dataset; 121 were blinded therapy, 110 BNT162b2, 23 placebo and 1 BNT162b1).
- Country of incidence (≥2%): US (205), Argentina (31), Germany (10), Brazil (6)
- Subjects' gender: female (98), male (157).
- Subjects' age in years (n = 255), range: 65 – 87, mean 72.5, median 72.

- Medical history (n = 241): the most frequently HLGT (≥20 occurrences) reported medical conditions included Vascular hypertensive disorders (153), Lipid metabolism disorders (122), Joint disorders (69), Gastrointestinal motility and defaecation conditions (64), Glucose metabolism disorders (incl DM) (54), Depressed mood disorders and disturbances (45), Coronary artery disorders (44), Thyroid gland disorders (41), Prostatic disorders (excl infections and inflammation) (38), Cardiac arrhythmias (37), Peripheral neuropathies (32), Appetite and general nutritional disorders (30), Respiratory disorders NEC (29), Bone and joint therapeutic procedures (27), Sleep disorders and disturbances (25), Bronchial disorders (excl neoplasms), Vascular therapeutic procedures (24 each), Age related factors, Gastrointestinal therapeutic procedures, Purine and pyrimidine metabolism disorders (23 each), Bone disorders (excl congenital and fractures) and Infections – pathogen unspecified (22 each), Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders) (21).

- COVID-19 Medical history (n = 2): COVID-19 immunization, COVID-19 pneumonia (1 each).

- Co-suspects: 6 cases reported co-suspect drugs none of which were reported more than once.

- Number of events: 312

- Most frequently reported relevant PTs (≥2%): Atrial fibrillation (14), Condition aggravated (11), Osteoarthritis (8), Pneumonia (7).

- The 312 SAEs were assessed as not related to blinded therapy, BNT162b1, BNT162b2 or placebo.

- Relevant event outcome[34]: fatal (27), resolved/resolving (240), resolved with sequelae (17), not resolved (25), unknown (3).

Post-Authorization Data

- Number of cases: 61,833 (18.9% of 327,125 cases, the total PM dataset).

- MC cases (30,242), NMC cases (31,591).

- Country of incidence (≥2%): US (15,652), UK (12,254), France (9163), Italy (4711), Germany (2412), Netherlands (2395), Spain (2114), Japan (1549), Sweden (1272).

- Subjects' gender: female (39,099), male (21,692) and unknown (1042).

- Subjects' age in years (n = 60,849), range: 65 – 95, mean 77.3, median 76.

- Medical history (n = 36,012): the most frequently (≥2000 occurrences) reported HLGT medical conditions included Vascular hypertensive disorders (11,153), Glucose metabolism disorders (incl diabetes mellitus) (5214), Allergic conditions (4461), Viral

infectious disorders (3901), Cardiac arrhythmias (3754), Bronchial disorders (excl neoplasms (3384), Joint disorders (3291), Thyroid gland disorders (2640), Mental impairment disorders (2542), Central nervous system vascular disorders (2422), Coronary artery disorders (2415), Lipid metabolism disorders (2210).

- COVID-19 Medical history (n = 36,012): the most frequently (≥25 occurrences) reported medical conditions included COVID-19 (2091), Suspected COVID-19 (912), SARS-CoV-2 test positive (92), COVID-19 pneumonia (81), Exposure to SARS-CoV-2 (60), Asymptomatic COVID-19 (30), Coronavirus infection (29), COVID-19 immunisation (28).

- Co-suspects (n = 1116) the most frequently (≥15 occurrences) reported co-suspect drugs included apixaban (99), acetylsalicylic acid (52), paracetamol (44), ibuprofen (30), tofacitinib (25), adalimumab (24), rivaroxaban (23), amoxicillin (20), methotrexate (19), warfarin (18), acenocoumarol (15).

- Number of events: 196,246 the most frequently (≥2%) reported PTs: Headache (7928), Fatigue (7620), Pyrexia (6967), Pain in extremity (4856), Nausea (4611), Chills (4353), Myalgia (4079), Malaise (4070), Arthralgia (3966), Asthenia (3700) Dizziness (3615), Vaccination site pain (3566), Pain (3360), Dyspnoea (2700), Diarrhoea (2699), Vomiting (2435), Pruritus (2283), COVID-19 (2151), Rash (2148), Hypertension (1619), Erythema (1570), Influenza like illness (1451), Herpes zoster (1408), Cough (1244).

- Relevant event seriousness: serious (82,506), non-serious (113,798).

- Relevant event outcome: fatal (9431), resolved/resolving (87,657), resolved with sequelae (2192), not resolved (36,929), unknown (60,878).

Analysis by presence of comorbidities[22,57]

Number of elderly subjects with comorbidities: 35,715 (11.0% of 327,827 cases, the total dataset).

During the current reporting period, there were 2501 (48.9% of 5115 cases, total fatal dataset) fatal outcomes in the elderly populations with comorbidities compared to 263 (5.1%) in the non-elderly population with comorbidities.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 in elderly patients.

Conclusion

The interval data reviewed did not identify any new safety information regarding the use of BNT162b2 in elderly patients.

16.3.5.2. Use in Paediatric Patients

- Search Criteria: Paediatric cases are identified as cases where the Age Range derived field value for the patient is "Less than or equal to 17 years". Paediatric cases involving exposure to the vaccine through trans-mammary or transplacentally route are excluded.

- Of the 1643 cases, 39 cases were determined to be non-contributory and are not included in the discussion since the data reported (eg, clinical details, height, weight, etc) were not consistent with paediatric subjects.

16.3.5.2.1. Paediatric Subjects <12 Years of Age[122]

Clinical Trial Data

There were no serious clinical trial cases involving paediatric subjects aged less than 12 years during the reporting period.

Post-Authorization Data

- Number of cases: 132 (0.04% of 327,125 cases, the total PM dataset).

- MC cases (67), NMC cases (65).

- Country of incidence (≥2%): UK (60) and US (53).

- Subjects' gender: female (80), male (34) and unknown (18).

- Subjects' age in years (n = 119), range: 0.02-11, mean 4.7, median 4.0.

- Medical history (n = 43): the most frequently (≥2) reported medical conditions included Asthma (7), Suspected COVID-19 (5), Hypersensitivity (4), Attention deficit hyperactivity disorder, Food allergy, Gastrooesophageal reflux disease, Pneumonia, Rash, Rheumatoid arthritis and Viral infection (2 each).

- COVID-19 Medical history (n = 7): the reported medical conditions included Suspected COVID-19 (5), COVID-19 and SARS-CoV-2 test positive (1 each).

- Co-suspects: None.

- Number of events: 343. The most frequently reported PTs (≥2%): Product administered to patient of inappropriate age (43), Off label use (37), Product use issue (26), Pyrexia (13), Fatigue, Headache (11 each), Pain in extremity (10), Nausea (8), Malaise and Myalgia (7 each).

[122] The administration of BNT162b2 in this subpopulation is not approved.

- Event seriousness: serious (34), non-serious (309).
- Time to event onset (n = 189)[123], range: <24 hours to 15 days, median <24 hours.
  - <24 hours: 109 events;
  - 1 day: 56 events;
  - 2-7 days: 18 events;
  - 8-14 days: 5 events;
  - 15 days: 1 event.
- Duration of event (n = 33)[124], range: from 1 hour to 3 days, median 1 day.
  - 1 hour: 1 event;
  - 1 day: 17 events;
  - 2 days: 10 events;
  - 3 days: 5 events.
- Event outcome[34]: fatal (2), resolved/resolving (110), not resolved (53), unknown (192).

16.3.5.2.2. Paediatric Subjects ≥12 Years and ≤ 15 Years of Age[125]

Clinical Trial Data

- Number of cases: 14, all originated from Protocol C4591001 [2.0% of 702 cases, the total CT dataset; these cases involved blinded therapy (11), BNT162b2 (2) and placebo (1)].
- Country of incidence: US (all relevant 13 cases involving BNT162b2 and blinded therapy).
- Subjects' gender: female (7), male (6).
- Subjects' age in years (n = 13), range: 12 – 15, mean 13.7, median 14.
- Medical history (n = 13): the most frequently (≥2) reported medical conditions included Anxiety (9), Attention deficit hyperactivity disorder (8), Depression (7), Asthma, Migraine, Rhinitis allergic (3 each), Corrective lens user and Post-traumatic stress disorder (2 each).

[123] This number does not include 154 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[124] This number does not include 24 events with outcome resolved for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[125] The administration of BNT162b2 in this subpopulation was approved by EMA on 31 May 2021.

- COVID-19 Medical history: no data in the relevant 13 cases.
- Co-suspects: none.
- PTs reported in the relevant cases (16): Depression[126] (4), Suicidal ideation[126] (3), Appendicitis (2), Abdominal pain, Anal abscess, Anxiety[126], Constipation, Conversion disorder[126], Femur fracture and Focal peritonitis (1 each). All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset: n = 16, range: 1 - 77 days, median 38.5 days.
  - 1 day: 2 events;
  - 2-7 days: 2 events;
  - 15-30 days: 3 events;
  - 31-181 days: 9 events.
- Duration of event: n = 2[127]: 4 days and 13 days.
- Event outcome: resolved/resolving (14), not resolved (2).

Post-Authorization Data

- Number of cases: 530 (0.2% of 327,125 cases, the total PM dataset).
- MC cases (191), NMC cases (339).
- Country of incidence (≥2%): US (482).
- Subjects' gender: female (243), male (258) and unknown (29).
- Subjects' age in years (n = 530), range: 12 – 15, mean 13.6, median 14.
- Medical history (n = 131): the most frequently (>2) reported medical conditions included Asthma (26), Food allergy (18), Attention deficit hyperactivity disorder (14), Autism spectrum disorder, Hypersensitivity (13 each), Epilepsy (9), Allergy to animal, COVID-19 (8 each) Seasonal allergy (7), Drug hypersensitivity (6), Anxiety, Depression (5 each), Migraine (4), Cystic fibrosis, Disability, Lactose intolerance, Immunodeficiency, Mycotic allergy, Seizure and Type 1 diabetes mellitus (3 each).

[126] Out of the 9 cases reporting PTs included in the SOC Psychiatric disorders (Anxiety, Conversion disorder, Depression and Suicidal ideation), in 8 cases the subjects suffered from underlying psychiatric disorders (ie, anxiety, depression and attention deficit hyperactivity disorder).

[127] This number does not include 3 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- COVID-19 Medical history (n = 8): the reported medical conditions included COVID-19 (8).

- Co-suspects: COVID-19 Moderna (mRNA-1273) vaccine (2), COVID-19 vaccine NRVV AD26 JNJ 78436735, diphtheria vaccine toxoid, HPV vaccine, oxymetazoline, pertussis vaccine acellular and tetanus vaccine toxoid (1 each).

- Number of events: 1496.

- Event seriousness: serious (264), non-serious (1232).

- Most frequently reported PTs (≥2%): Pyrexia (87), Headache (70), Off label use[125] (65), Fatigue (62), Pain in extremity (51), Product administered to patient of inappropriate age[125] (47), Poor quality product administered[128] (39), Product use issue[125], Vomiting (35 each) and Nausea (34).

- Time to event onset (n = 892)[129], range: <24 hours to 23 days, median 1 day.

  - <24 hours: 415 events;
  - 1 day: 281 events;
  - 2-7 days: 153 events;
  - 8-14 days: 24 events;
  - 15-23 days: 19 events.

- Duration of event (n = 41)[130], range: <24 hours to 15 days, median 1 day.

  - <24 hours: 8 events;
  - 1 day: 18 events;
  - 2-7 days: 12 events;
  - 8-14 days: 1 event;
  - 15 days: 2 events.

- Relevant event outcome[34]: resolved/resolving (368), resolved with sequelae (1), not resolved (176), unknown (956).

16.3.5.2.3. Paediatric Subjects ≥ 16 Years of Age

Clinical Trial Data

[128] This event was associated to PTs describing storage error and/or incorrect preparation.

[129] This number does not include 604 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[130] This number does not include 1455 events for which time to event onset partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- Number of cases: 13, originated from Protocols C4591001 (7), C4591001-OPEN LABEL (5) and C4591017 (1) [1.9% of 702 cases, the total CT dataset; these cases involved blinded therapy (5) and BNT162b2 (8)].

- Country of incidence: US (13).

- Subjects' gender: female (7) and male (6).

- Subjects' age in years (n = 13), range: 16 – 17, mean 16.7, median 17.

- Medical history (n = 12): the most frequently (>2) reported medical conditions included Asthma (4), Attention deficit hyperactivity disorder, Anxiety, Depression, Major depression, Migraine, Seasonal allergy (3 each), Anxiety disorder and Insomnia (2 each).

- COVID-19 Medical history: no data in these 13 cases.

- Co-suspects: escitalopram (1).

- PTs (13): Major depression (2), Abdominal pain, Anaphylactoid reaction, Appendicitis, Asthma, Bipolar I disorder, Chest pain, Deep vein thrombosis, Malnutrition, Overdose[131], Status migrainosus and Suicidal ideation (1 each, all assessed unrelated to BNT162b2 or blinded therapy, but the AE Anaphylactoid reaction that was assessed related to BNT162b2).

- Time to event onset (n = 12), range: from 1 day to 181 days, median 40.5 days.

  – 1 day: 1 event;
  – 2-7 days: 3 events;
  – 8-14 days: 1 event;
  – 15-30 days: 1 event;
  – 31-181 days: 6 events.

- Duration of event (n = 6)[132], range: from 5 hours to 10 days, median 4.5 days.

  – <1 day: 2 events (5 hours and 11 hours);
  – 3-7 days: 3 events;
  – 10 days: 1 event.

- Event outcome: resolved/resolving (11), not resolved (2).

Post-Authorization Data

[131] Overdose of anti-depressive medications, not of vaccine was reported.

[132] This number does not include 7 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- Number of cases: 914 (0.3% of 327,125 cases, the total PM dataset).
- MC cases (398), NMC cases (516).
- Country of incidence (≥2%): US (464), UK (201), Austria (96), Germany (37) and Israel (34).
- Subjects' gender: female (521), male (370) and unknown (23).
- Subjects' age in years (n = 806), range: 16 - 17, mean 16.5, median 16.
- Medical history (n = 337): the most frequently (≥2%) reported medical conditions included Suppressed lactation[133] (52), Asthma (41), Food allergy (26), Drug hypersensitivity (19), Epilepsy (17), Immunodeficiency (16), Acne, Attention deficit hyperactivity disorder, Suspected COVID-19 (15 each), Anxiety (14), Hypersensitivity, Type 1 diabetes mellitus (13 each), Depression (12), Autism spectrum disorder, Pregnancy[133] (11 each), COVID-19, Migraine (10 each), Seasonal allergy (9), Diabetes mellitus and Seizure, (8 each).
- COVID-19 Medical history (n = 30): the reported medical conditions included Suspected COVID-19 (15), COVID-19 (10), COVID-19 immunisation, Exposure to SARS-CoV-2 (2 each), Asymptomatic COVID-19 and SARS-CoV-2 test positive (1 each).
- Co-suspects: COVID-19 Moderna (mRNA-1273) vaccine, ibuprofen (3 each), cannabidiol, infliximab, medroxyprogesterone, meningococcal group B RLP2086, meningococcal vaccine, mycophenolate mofetil, paracetamol, tacrolimus, tofacitinib and zonisamide (1 each).
- Number of events: 3035.
- Relevant event seriousness[62]: serious (972), non-serious (2065).
- Most frequently reported PTs (≥2%): Headache (197), Fatigue (160), Pyrexia (155), Chills (93), Nausea (87), Dizziness (83), Pain in extremity (69) and Myalgia (64).
- Time to event onset: n = 2125[134], range: from <24 hours to 51 days, median 0 day.
  - <24 hours: 1163 events;
  - 1 day: 537 events;
  - 2-7 days: 309 events;

[133] These are not maternal cases, since they concern female patients aged 16 or 17 years with medical history of suppressed lactation or pregnancy.

[134] This number does not include 910 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- 8-14 days: 68 events;
- 15-30 days: 39 events;
- 31-181 days: 9 events.

- Duration of event: n = 274[135], range: from <24 hours to 29 days, median 1 day.

  - <24 hours: 33 events;
  - 1 day: 111 events;
  - 2-7 days: 112 events;
  - 8-14 days: 12 events;
  - 15-29 days: 6 events.

- Relevant event outcome[34]: fatal (3), resolved/resolving (1413), not resolved (518), resolved with sequelae (10), unknown (1100).

Lot/Batch Number

Lot/Batch Number (#) information by country was available in 789 cases of the total paediatric dataset with no related quality issues identified during investigations of the impacted lot/batch numbers.

Analysis by age group

- CT: Paediatric (27) and Non-Paediatric (675).

  - A meaningful comparison between the different age groups is not possible due to the low number of paediatric cases.

- PM: Paediatric (1577) and Non-Paediatric (325,548).

  Upon review, case seriousness and case outcomes were generally similar between the overall paediatric dataset and the non-paediatric dataset.

  No significant differences in the reporting proportion of the most frequently reported AEs were noted between the paediatric dataset and the non-paediatric dataset, apart from the following PTs describing inappropriate administration of the vaccine, for which the reporting proportion is higher in the paediatric population: Off label use (7.8% vs 1.3%), Product administered to patient of inappropriate age (5.8% vs 0.0%) and Product use issue (4.4% vs 0.6%). This increase is explicable due to the fact that the vaccine was not authorized for subjects aged < 12 years by EMA until 31 May 2021 for subjects aged between 12 and 15 years.

[135] This number does not include 2761 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

A slight increase in the reporting proportion for the paediatric subjects compared to the non-paediatric subjects was identified also for the following PTs: Poor quality product administered[136] (6.0% vs 1.6%), Application site pain[137] (3.5% vs 0.3%) and Myocarditis[138] (3.1% vs 0.1%).

Analysis by presence of comorbidities[22,57]

- Number of subjects with comorbidities: 181 (11.3% of 1604 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.

Analysis by dose

- Number of vaccine doses administered at the time of the event onset: 1 dose in 703 cases, 2 doses in 441 cases and number of doses was not specified in 460 cases.
- The comparison between the reporting proportion of the most commonly reported AEs in the overall paediatric population after administration of 1 dose or 2 doses of vaccine did not reveal significant differences, with the exception of the following PTs, for which increased reporting proportion was identified upon administration of the second dose of vaccine:
  - Pyrexia (10.1% after 1 dose vs. 26.7% after 2 doses);
  - Chills (4.7% after 1 dose vs. 10.7% after 2 doses);
  - Pain (4.7% after 1 dose vs. 9.1% after 2 doses);
  - Chest pain (3.4% after 1 dose vs. 10.2% after 2 doses);
  - Myalgia (1.8% after 1 dose vs. 5.2% after 2 doses);
  - Myocarditis (1.3% after 1 dose vs. 8.9% after 2 doses).

  Pyrexia, chills, pain and myalgia are events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 *Undesirable effects* of the CDS. Myocarditis[138] was an ongoing signal during the reporting period and evaluation completed after the reporting period. Depending on the clinical picture, chest pain can be considered

[136] The administration of poor quality product was due to product temperature excursion issues, product preparation issues and/or product storage issues.

[137] This is an AE listed in in Section 4.8 *Undesirable effects* of the CDS.

[138] After DLP, the CDS and EU SmPC were updated on 14 July 2021 and on 12 July 2021, respectively, to include in Section 4.4 *Special warnings and precautions for use* a warning about very rare cases of myocarditis and pericarditis that have occurred more often in younger men and shortly after the second dose of vaccine.

consistent with the events listed in Section 4.8 *Undesirable effects* of the CDS, as pain of musculoskeletal origin or be a symptom of myocarditis or pericarditis.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 in paediatric patients.

Conclusion

No new significant safety information was identified based on the review of the cases reported in the overall paediatric population. The most commonly reported AEs[139] other than PTs involving inappropriate/unapproved administration of the vaccine or administration of product with quality issues (due to temperature excursions, storage and/or preparation errors) were events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 *Undesirable effects* of the CDS and a warning about very rare cases of myocarditis and pericarditis that have occurred more often in younger men and shortly after the second dose of vaccine was added to Section 4.4 *Special warnings and precautions for use* of the CDS and of the EU SmPC on 14 July 2021 and 12 July 2021, respectively, after DLP.

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.

16.3.5.3. Use in Pregnant/Lactating Women[140]

As part of the approval letter for the emergency use of Tozinameran - COVID-19 mRNA vaccine (nucleoside modified) - COMIRNATY®, the WHO requested the MAH to present the outcome of the cases of pregnancy observed in the clinical studies.

In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested to present data according to the "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)".

- Search Criteria: "Selects Pregnancy cases from the data set. Pregnancy cases are identified as cases where:
  - Patient Pregnant Flag is "Yes";
  - If there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly;
  - If Delivery Notes are available;
  - If any of the valid events on the case contains one of the following:"

[139] For the CT cases, the analysis was focused on AEs assessed as related to BNT162b2 or blinded therapy.

[140] EIU cases are included.

- SOC Pregnancy, puerperium and perinatal conditions, or
  HLT Exposures associated with pregnancy, delivery and lactation; Lactation disorders, or
  PT Exposure via body fluid.

Clinical Trial Data

Cumulative review (Pregnancy Cases)

- Number of pregnancy cases: 152 (14.5% of the total 1048 cases from the CT dataset). These 152 cases represent 149 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 2 pregnancies). Cases originated from clinical studies C4591001 (141), C4591015 (9), BNT162-01 and C4591017 (1 each) and study treatment was reported as blinded therapy (79), BNT162b2 (43), and placebo (30).

- Country of incidence: US (101), Argentina (28), Brazil (15), South Africa (5), Germany (2) and Turkey (1).

- Of the 145 mother cases, 94 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure before pregnancy (65), Maternal exposure during pregnancy (25) and Exposure during pregnancy (4).

- Fifty-one (51) mother cases, 26 serious and 25 non-serious, reported additional clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases were coded to the PTs Abortion spontaneous (17), Maternal exposure before pregnancy (16), Maternal exposure during pregnancy (13), Abortion incomplete, Abortion spontaneous incomplete, Benign hydatidiform mole, Exposure during pregnancy, Hyperemesis gravidarum, Miscarriage of partner, Pre-eclampsia, Premature separation of placenta, Retained products of conception, Vaginal haemorrhage (1 each). Other reported clinical events coded to the PTs Dyspnoea and Pruritus (1 each). Of the 21 cases reporting spontaneous abortion or abortion related events in 10 cases, mother had a medical history of spontaneous abortion, alcohol/ tobacco use during pregnancy, obesity or gestational hypertension which might have contributed to the event and in 11 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Six (6) serious baby/foetal cases. Cases are classified according to pregnancy outcome.

  – Pregnancy outcome: Live birth with congenital anomaly: Four (4) of these cases reported 11 congenital anomalies that coded to the PTs Hypoxic-ischaemic encephalopathy, Neonatal respiratory failure, Shock, Intestinal perforation, Newborn persistent pulmonary hypertension, Non-reassuring foetal heart rate pattern, Pneumoperitoneum, Renal tubular necrosis, Metabolic acidosis, Foetal heart rate abnormal, Neonatal pneumothorax (1 each). Of these 4 cases, in 3 cases foetus was exposed during 3rd trimester and in 1 case exposure occurred during 2nd trimester. Of

these 4 cases, in 1 case reporting hypoxic-ischaemic encephalopathy, shock, newborn persistent pulmonary hypertension, metabolic acidosis, renal tubular necrosis, pneumoperitoneum, and intestinal perforation mother had a medical history of premature separation of placenta which might have contributed to the development of the events. In the remaining 3 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Pregnancy outcome: Livebirth without congenital anomaly: Two (2) cases reported live birth babies without congenital anomaly but one case was reported with perinatal complication/post-natal complications. Of these 2 cases, in 1 case, foetus was exposed during 1st trimester and in 1 case exposure occurred during 3rd trimester. The events reported in these 2 cases were coded to PTs Foetal hypokinesia, Hyperbilirubinaemia neonatal, Dehydration, and Hypernatraemia (1 each). Of these 2 cases, in 1 case mother was on multiple concomitant medications ie, bupropion, escitalopram and paracetamol and in the remaining case there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 152 cases, 149 cases provided pregnancy outcomes which are provided in Table 38 below. Pregnancy outcome was pending or not provided in the remaining 3 cases.

Table 38. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval

Pregnancy outcome	Prospective cases 144 (94.7% of pregnancy cases)					Retrospective cases 5 (3.3% of pregnancy cases)				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	0
Spontaneous abortion	0	12	0	0	5	0	3	0	0	1
Elective termination (foetal defects)	0	0	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	9	0	0	3	0	0	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	0	0	0	0	0	0	0
Live birth with congenital anomaly	0	1	5	0	0	0	0	0	0	0
Live birth without congenital anomaly	0	51	4	0	54	0	1	0	0	0
Total	***0***	***73***	***9***	***0***	***62***	***0***	***4***	***0***	***0***	***1***

Cumulative review (Lactation case)

- Number of lactation case: 1 (0.1% of the total 702 cases from the CT dataset). This non-serious case reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events.

Incremental review (CT cases)

- Number of pregnancy cases: 26 (3.7% of the total 702 cases from the CT dataset). These 26 cases represent 23 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 2 pregnancies). Cases originated from clinical studies C4591001 (16), C4591015 (9) and C4591017 (1) and study treatment was reported as blinded therapy (17), BNT162b2 (5), and placebo (4).

- Country of incidence: US (18), Argentina (6), Brazil (2).

- Twenty (20) serious mother cases reported additional clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases were coded to the PTs Abortion spontaneous (12), Maternal exposure during pregnancy (6), Abortion incomplete, Benign hydatidiform mole, Hyperemesis gravidarum, Miscarriage of partner, Pre-eclampsia, Premature separation of placenta, Vaginal haemorrhage (1 each). Other reported clinical events coded to the PTs Dyspnoea and Pruritus (1 each). Of the 15 cases reporting spontaneous abortion or abortion related events in 6 cases, mother had a medical history of spontaneous abortion, diabetes mellitus and/ or age ≥40 years which might have contributed to the event and in the remaining 9 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

- Six (6) serious baby/ foetal cases. Cases are classified according to pregnancy outcome.

  - Pregnancy outcome: Live birth with congenital anomaly: Four (4) of these cases reported 11 congenital anomalies that coded to the PTs Hypoxic-ischaemic encephalopathy, Neonatal respiratory failure, Shock, Intestinal perforation, Newborn persistent pulmonary hypertension, Non-reassuring foetal heart rate pattern, Pneumoperitoneum, Renal tubular necrosis, Metabolic acidosis, Foetal heart rate abnormal, Neonatal pneumothorax (1 each). Of these 4 cases, in 3 cases foetus was exposed during 3rd trimester and in 1 case exposure occurred during 2nd trimester. Of these 4 cases, in 1 case reporting hypoxic-ischaemic encephalopathy, shock, newborn persistent pulmonary hypertension, metabolic acidosis, renal tubular necrosis, pneumoperitoneum, and intestinal perforation mother had a medical history of premature separation of placenta which might have contributed to the development of the events. In the remaining 3 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

  - Pregnancy outcome: Livebirth without congenital anomaly: Two (2) cases reported live birth babies without congenital anomaly but one case was reported with perinatal

complication/post-natal complications. Of these 2 cases, in 1 case, foetus was exposed during 1st trimester and in 1 case exposure occurred during 3rd trimester. The events reported in these 2 cases were coded to PTs Foetal hypokinesia, Hyperbilirubinaemia neonatal, Dehydration, and Hypernatraemia (1 each). Of these 2 cases, in 1 case mother was on multiple concomitant medications ie, bupropion, escitalopram and paracetamol and in the remaining case there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

The pregnancy outcomes for these 26 cases are provided in Table 39.

Table 39. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval

Pregnancy outcome	Prospective cases 22 (84.6% of pregnancy cases)					Retrospective cases 4 (15.4% of pregnancy cases)				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	0
Spontaneous abortion	0	9	0	0	3	0	2	0	0	1
Elective termination (foetal defects)	0	0	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	0	0	0	0
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	0	0	0	0	0	0	0
Live birth with congenital anomaly	0	0	5	0	0	0	0	0	0	0
Live birth without congenital anomaly	0	2	3	0	0	0	1	0	0	0
Total	***0***	***11***	***8***	***0***	***3***	***0***	***3***	***0***	***0***	***1***

Post-Authorization Data

Incremental review (Pregnancy)

- Number of pregnancy cases: 1661 (0.5% of the total 327,125 cases from the PM dataset). These 1661 cases represent 1607 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 53 pregnancies).

- Country of incidence (≥10 occurrences): US (472), UK (392), Germany (130), France (71), Canada (69), Mexico (61), Italy (60), Ireland (47), Portugal (42), Spain (37), Israel, Netherlands (30 each), Estonia (25), Brazil (20), Hungary (15), Japan (13), Romania (12), Poland (11), Australia, Austria (10 each).

- Of the 1604 mother cases, 659 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (383), Exposure during pregnancy (208), Maternal exposure timing unspecified (43), Maternal exposure before pregnancy (16), Pregnancy (9), Drug exposure before pregnancy (2), Foetal exposure during pregnancy (1).

- Nine hundred and forty-five (945) mother cases, 635 serious and 310 non-serious, reported additional clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases (≥5 occurrences) were coded to the PTs Abortion spontaneous (275), Vaginal haemorrhage (27), Abortion missed (21), Foetal death (16), Abortion (9), Gestational diabetes (7), Premature labour (6), Stillbirth, Uterine contractions during pregnancy (5 each)[141]. Other frequently reported (≥15 occurrences) clinical events coded to the PTs Headache (154), Fatigue (114), Pain in extremity (95), Pyrexia (83), Vaccination site pain (81), Myalgia (64), Chills (60), Pain (57), Nausea (55), Dizziness (42), Asthenia (34), Arthralgia (33), Vomiting (31), Lymphadenopathy (26), Oropharyngeal pain (25), COVID-19, Malaise (23 each), Diarrhoea (19), Cough (17), Influenza like illness (15). The distribution of clinical events (≥15 occurrences) was similar in the pregnant mothers when compared with the general population.

- Fifty-seven (57) baby/foetal cases, 54 serious and 3 non-serious. Cases are classified according to pregnancy outcome.

  – Pregnancy outcome: Live birth with congenital anomaly: Nine (9) of these cases reported 9 congenital anomalies that coded to the PTs Anencephaly, Cerebrovascular accident, Congenital anomaly, Foetal cystic hygroma, Foetal malformation, Hydrops foetalis, Kidney duplex, Trisomy 21, Ventricular septal defect (1 each). Other clinical events reported in these cases coded to the PTs Premature baby, Tachycardia foetal, Ultrasound foetal abnormal (1 each). Of these 9 cases, information regarding trimester of exposure was provided in 2 cases. Of these 2 cases, in 1 case foetus was exposed during 1st trimester and in 1 case exposure occurred during 3rd trimester. In

[141] Few additional events reported were coded to PTs Pre-eclampsia (3), Amniotic cavity infection (1).

these 9 cases, there was limited information regarding obstetric history/ medical history of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Livebirth without congenital anomaly: Eighteen (18) cases reported live birth babies without congenital anomaly. Of these 18 cases, 2 cases reported normal newborn and 16 cases reported perinatal complication/post-natal complications. Of these 18 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 1 case, foetus was exposed during 1st trimester and in 7 cases exposure occurred during 3rd trimester. The clinical events reported in these 18 cases were coded to PTs Premature baby (11), Foetal growth restriction (3), Foetal hypokinesia (2), Foetal heart rate increased, Foetal heart rate disorder, Ductus arteriosus premature closure, Umbilical cord thrombosis, Pulmonary arterial pressure abnormal, Respiratory disorder neonatal, Neutropenia neonatal, Ventricular hypertrophy, Bradycardia foetal and Neonatal respiratory acidosis (1 each). In these 18 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Stillbirth: Nine (9) cases reported foetal death/ neonatal death. Of these 9 cases, 5 cases reported stillbirth with foetal defects and remaining 4 cases reported stillbirth without foetal defect. Of these 9 cases, information regarding trimester of exposure was provided in 2 cases and the exposure happened during the 1st trimester of the pregnancy. The events reported in these 9 cases were coded to PTs Premature baby (3), Foetal heart rate abnormal, Foetal death, Stillbirth (2 each), Neonatal respiratory distress, Meconium aspiration syndrome, Foetal hypokinesia, PTEN gene mutation, Neonatal pneumothorax, Syndactyly, Foetal heart rate decreased, Macrocephaly, Death neonatal, Foetal movement disorder, Death and Hamartoma (1 each). In these 9 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Elective termination: Seven (7) cases reported elective termination of pregnancy. Of these 7 cases, 6 cases reported elective termination due to foetal defects and 1 case reported elective termination without foetal defects or unknown. Of these 7 cases, information regarding trimester of exposure was provided in 4 cases and the exposure happened during the 1st trimester of the pregnancy. The events reported in these 7 cases were coded to PTs Foetal growth restriction (3), Foetal heart rate abnormal (2), Anencephaly, Cleft palate, Congenital absence of cranial vault, Heart disease congenital, Hydrops foetalis, Foetal cystic hygroma, Trisomy 21, (1 each). In these 9 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: Fourteen (14) cases reported spontaneous abortion. Of these 14 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 7 cases, foetus was exposed during 1st trimester and in 1 case exposure occurred during 2nd trimester. The events reported in

these 14 cases were coded to PTs Foetal growth restriction (5), Congenital anomaly, Anembryonic gestation (2 each), Foetal malformation, Foetal heart rate abnormal, Spine malformation, Small for dates baby, Foetal cystic hygroma, Abortion spontaneous and Foetal death (1 each). In these 14 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

Of the 1661 cases, 1089 cases provided pregnancy outcomes which are provided in Table 40. Pregnancy outcome was pending or not provided in the remaining 572 cases.

Table 40. Post-Authorization Data: Pregnancy Outcome during the Reporting Interval[a]

Pregnancy outcome	Prospective cases 841 (50.6% of pregnancy cases)					Retrospective cases 248 (14.9% of pregnancy cases)				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	1	0	1	0	0	0
Spontaneous abortion	0	26	0	0	26	0	60	5	0	106
Elective termination (foetal defects)	0	2	0	0	3	0	3	0	0	1
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	1	0	0	0
Stillbirth with foetal defects	0	2	0	0	0	0	2	0	0	6
Stillbirth without foetal defects	0	1	0	0	4	0	0	2	0	6
Live birth with congenital anomaly	0	2	0	0	1	0	0	1	0	2
Live birth without congenital anomaly	0	115	91	0	567	0	0	15	0	37
Total	***0***	***148***	***91***	***0***	***602***	***0***	***67***	***23***	***0***	***158***

a. 19 December 2020 through 18 June 2021.

Incremental review (Lactation)

- Number of lactation cases: 966 (0.3% of the total 327,125 cases from the PM dataset).
  - Breast feeding baby cases: 802, of which:
    - Six hundred and fifty-five (655) cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk and Maternal exposure during breast feeding) without the occurrence of any clinical events.
    - One hundred and forty-seven (147) cases, 61 serious and 86 non-serious, reported clinical events that occurred in the infant/child exposed to vaccine via breastfeeding (PT Exposure via breast milk and Maternal exposure during breast feeding); the frequently reported clinical events (≥5 occurrences) were coded to the PTs Pyrexia (32), Rash (19), Diarrhoea, Infant irritability (11 each), Malaise (10), Crying, Infantile vomiting, Irritability (7 each), Poor feeding infant, Vomiting (6 each), Cough, Decreased appetite, Fatigue, Illness, Insomnia, Rhinorrhoea (5 each).
  - Breast feeding mother cases: 164, of which:
    - Five (5) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
    - One hundred and fifty-nine (159) cases, 95 serious and 64 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>10 occurrences) were coded to the PTs Fatigue (36), Headache (29), Pain in extremity (22), Pyrexia (19), Nausea (17), Chills, Myalgia (15 each), Dizziness, Pain (14 each), Breast pain, Lymphadenopathy (11 each).

Literature

Literature article review (Section 11) supports the use of COVID-19 mRNA vaccine in pregnant and breast-feeding women; the vaccine was immunogenic in pregnant women and vaccine-elicited antibodies were transported to infant cord blood and breast milk receipt. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern. Furthermore, antenatal COVID-19 mRNA vaccination induces a robust maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination.

Conclusion

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

16.3.5.4. Use in Patients with Co-Morbidities [22]

- Search criteria for immunocompromised patients: Patients with Medical history PTs included in SMQ Malignancy related conditions (Narrow and Broad Scope); SMQ Malignancy related therapeutic and diagnostic procedures (Narrow and Broad Scope); SMQ Malignant or unspecified tumours (Narrow and Broad Scope); HLGT (Primary Path): Immunodeficiency syndromes; HLT (Primary Path): Retroviral infections; PTs: Allogenic bone marrow transplantation therapy, Allogenic stem cell transplantation, Autologous bone marrow transplantation therapy, Autologous haematopoietic stem cell transplant, Bone marrow transplant, Cord blood transplant therapy, Heart transplant, Liver transplant, Lung transplant, Pancreas islet cell transplant, Renal transplant, Small intestine transplant, Stem cell transplant.

- Search criteria for patients with autoimmune or inflammatory disorders: Patients with Medical history PTs included in HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction.

- Search criteria for frail patients with co-morbidities (eg, COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis): Patients with Medical history of PTs included in HLGTs (Primary Path) Bronchial disorders (excl neoplasms), Heart failures, Mental impairment disorders, Movement disorders (incl parkinsonism), Nephropathies, Pulmonary vascular disorders, Renal disorders (excl nephropathies); HLTs (Primary Path) Autonomic nervous system disorders, Diabetes mellitus (incl subtypes), Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis, Motor neurone diseases, Muscle tone abnormal, Neuromuscular disorders NEC, Pulmonary hypertensions, Respiratory failures (excl. neonatal); patients with Medical history of ongoing Tuberculosis.

Clinical Trial Data

- Number of cases: 314 (44.7% of 702 cases, the total CT dataset; 220 cases involved blinded therapy; while 94 cases involved BNT162b2).

- Country of incidence: US (251), Argentina (33), Brazil (11), Germany (7), South Africa (5), China (4), and Turkey (3).

- Subjects' gender: female (148) and male (166).

- Subjects' age in years (n = 314), range: 12 - 85, mean 53.7, median 55 years.

- Medical history (n = 314): the most frequently (≥ 20 occurrences) reported medical conditions included Hypertension (148), Type 2 diabetes mellitus (92), Gastrooesophageal reflux disease (75), Hypothyroidism (61), Hypercholesterolaemia (59), Depression (52), Hyperlipidaemia (48), Osteoarthritis (47), Obesity (44), Asthma (39), Coronary artery disease, Insomnia, Sleep apnoea syndrome (35 each), Seasonal allergy (34), Anxiety (31), Benign prostatic hyperplasia (26), Postmenopause (25), Chronic obstructive pulmonary disease, Hysterectomy (23 each), Back pain, Dyslipidaemia (22 each), and Neuropathy peripheral (21).

- COVID-19 Medical history (n = 9): COVID-19 immunisation (5), COVID-19 (3) and COVID-19 pneumonia (1).

- Co-suspects (n = 193): blinded therapy (162), placebo (22), insulin detemir, BNT162b1(2 each), BNT162b3, allopurinol, alprazolam, atorvastatin calcium, azithromycin, calcium folinate, cyclobenzaprine HCl, dapsone, disulfiram, doxycycline hyclate, estrogens conjugated, ethinylestradiol/levonorgestrel, fluorouracil, glibenclamide, indometacin, irinotecan HCl, naproxen, oxaliplatin, sertraline HCl, valsartan, and warfarin (1 each).

- Number of events: 389 reported (of which 7 were events of interest).

- Most frequently reported relevant PTs (≥2%): Condition aggravated (13, 4.1%), Acute myocardial infarction (9, 2.9%), and Pneumonia (7, 2.2%). All the frequently reported serious adverse events were assessed as unrelated to BNT162b2 by the Sponsor.

- Time to event onset: (n = 333), range: <24 hours to 181 days, median 87 days.

  - <24 hours: 4 events;
  - 1 day: 7 events;
  - 2-7 days: 18 events;
  - 8-14 days: 15 events;
  - 15-30 days: 33 events;
  - 31-181 days: 256 events.

- Duration of event: (n = 242), range: < 24 hours to 171 days.

  - < 24 hours: 11 events;
  - 1 day: 27 events;
  - 2-7 days: 108 events;
  - 8-14 days: 28 events;
  - 15-30 days: 23 events;
  - 31-181 days: 40 events.

- Reported event outcome: fatal (35), resolved/resolving (298), resolved with sequelae (18), not resolved (38), and unknown (1).

Analysis by age group

- ≤ 17 years (11), 18-30 years (3), 31-50 years (55), 51-64 years (93), 65-74 years (93), and ≥ 75 years (59);

- Upon review, all most frequently (≥2%) reported events Acute myocardial infarction, Condition aggravated, and Pneumonia were reported in adult and elderly population (4.5% in adult vs 4.8% in elderly). No cases reported most frequently reported events in the paediatric population.

Post-Authorization Data

- Number of cases: 51,076 (15.6% of 327,125 cases, the total PM dataset).
- MC cases (25,242), NMC cases (25,834).
- Country of incidence (≥ 100 occurrences): UK (13,950), US (13,145), France (6,357), Italy (3,209), Japan (1,801), Spain (1,411), Germany (1,380), Czech Republic (1,102), Sweden (1,023), Austria (734), Netherlands (727), Denmark (645), Norway (520), Canada (506), Ireland (450), Belgium (419), Portugal (416), Finland (378), Mexico (308), Israel (302), Greece (283), Hungary (278), Switzerland (277), Croatia, Romania (146 each), Poland (129), and Luxembourg (106).
- Subjects' gender: female (37,360), male (12,940) and unknown (776).
- Subjects' age in years (n = 48,473), range: 0.17-105, mean 58.9, median 59.
- Medical history (n = 51,076): the most frequently (≥1,000 occurrences) reported medical conditions included Asthma (10,569), Hypertension (10,066), Diabetes mellitus (5,385), Hypothyroidism (4,895), Type 2 diabetes mellitus (3,240), Drug hypersensitivity (3,170), COVID-19 (2,410), Suppressed lactation (2,357), Rheumatoid arthritis (2,284), Chronic obstructive pulmonary disease (2,219), Hypersensitivity (1,923), Atrial fibrillation (1,912), Immunodeficiency (1,889), Food allergy (1,837), Depression (1,791), Arthritis (1,763), Breast cancer (1,686), Suspected COVID-19 (1,681), Seasonal allergy (1,598), Autoimmune thyroiditis (1,429), Obesity (1,360), Gastrooesophageal reflux disease (1,323), Chronic kidney disease (1,322), Anxiety (1,204), Cardiac failure (1,201), Dementia (1,147), Thyroid disorder (1,063), and Migraine (1,060).
- COVID-19 Medical history: the most frequently (≥10 occurrences) reported COVID-19 medical conditions included COVID-19 (2,410), Suspected COVID-19 (1,681), SARS-CoV-2 test positive (149), COVID-19 pneumonia (101), Exposure to SARS-CoV-2 (46), Asymptomatic COVID-19 (28), COVID-19 immunisation (16), Occupational exposure to SARS-CoV-2 (11), and SARS-CoV-2 test (10).
- Co-suspects (n = 989): the most frequently (≥10 occurrences) reported co-suspect medications included apixaban (53), adalimumab (37), paracetamol (32), COVID-19 AstraZeneca vaccine (30), tofacitinib citrate (26), Lenvatinib mesylate, treprostinil sodium (23 each), etanercept (21), ibuprofen (20), methotrexate sodium (19), acetylsalicylate lysine (17), COVID-19 Moderna (mRNA 1273) vaccine, levothyroxine sodium (16 each), acetylsalicylic acid (15), prednisone (14), colecalciferol, pregabalin (12 each), palbociclib (11), and infliximab (10).
- Number of events: 207,959 (of which 1,414 were events of interest);
- Reported event seriousness: serious (92,550), non-serious (115,477).

- Most frequently reported relevant PTs (≥3%): Headache (10,501, 20.6%), Fatigue (8,852, 17.3%), Pyrexia (7788, 15.3%), Nausea (5,674, 11.1%), Pain in extremity (5,239, 10.3%), Chills (5,111, 10.0%), Myalgia (4,819, 9.4%), Arthralgia (4,523, 8.9%), Vaccination site pain (4,062, 8.0%), Pain (4,042, 7.9%), Dizziness (3,951, 7.7%), Malaise (3,630, 7.1%), Dyspnoea (3,380, 6.6%), Asthenia (3,127, 6.1%), Diarrhoea (2,496, 4.9%), Lymphadenopathy (2,422, 4.7%), Vomiting (2,249, 4.4%), Pruritus (2,232, 4.4%), Rash (1,991, 3.9%), Cough (1,681, 3.3%), Paraesthesia (1,679, 3.3%), and Influenza like illness (1,628, 3.2%).

- Time to event onset: (n = 147,953), range < 24 hours to 174 days, median 72.5 days.

  - < 24 hours: 47,422 events;
  - 1 day: 46,514 events;
  - 2-7 days: 31,855 events;
  - 8-14 days: 8,592 events;
  - 15-30 days: 9,055 events;
  - 31-181 days: 4,515 events.

- Duration of event (n = 31,254),[142] < 24 hours to 156 days.

  - <24 hours: 4,037 events;
  - 1 day: 9,056 events;
  - 2-7 days: 14,858 events;
  - 8-14 days: 1,921 events;
  - 15-30 days: 986 events;
  - 31-181 days: 396 events.

- Reported event outcome34: fatal (6,617), resolved/resolving (100,011), resolved with sequelae (2,878), not resolved (44,420), unknown (55,194);

- Lot/Batch Number (> 1,000 occurrences): EM0477 (1,410) and EK9788 (1,091).

Analysis by age group

- CT: ≤ 17 years (11), 18-30 years (3), 31-50 years (55), 51-64 years (93), 65-74 years (93), and ≥ 75 years (59);

  - Upon review, all most frequently (≥2%) reported events Acute myocardial infarction, Condition aggravated, and Pneumonia were reported in adult and elderly population (4.5% in adult vs 4.8% in elderly). No cases reported most frequently reported events in the paediatric population.

[142] This number does not include 176,705 events for which partial administration or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

- PM: ≤ 17 years (191), 18-30 years (3,351), 31-50 years (13,412), 51-64 years (12,277), 65-74 years (7,886), ≥ 75 years (11,815), and unknown (2,458);

  – Upon review, there are no differences between different age groups.

Conclusion

The reporting proportion of not resolved cases (31.9%), cases resolved with sequelae (1.8%), and fatal cases (5.4%) in patients with comorbidities is slightly higher than the reporting proportion observed in the overall population (23.5% for outcome of not resolved, 1.0% for outcome of resolved with sequelae, and 1.5% for fatal outcome). This is expected, considering that most of the cases reporting patients with underlying diseases and/or poor intercurrent conditions.

No safety signals have emerged that would be considered specific to this population. Evaluation of cases reporting use in patients with comorbidities did not reveal any significant new safety information. Surveillance will continue. Data about each individual special sub-population are summarized in Section 16.3.5.5, Section 16.3.5.6. and Section 16.3.5.7.

16.3.5.5. Use in Immunocompromised Patients

- Search criteria: Patients with Medical history of 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: 105 (15.0% of 702 cases, the total CT dataset; blinded therapy [51], BNT162b2 [43], BNT162b1 [1]; placebo [10]).

- Country of incidence: US (82), Argentina (15), Brazil, Germany, South Africa, and Turkey (2 each).

- Subjects' gender: female (61), and male (44).

- Subjects' age in years (n = 105), range: 17 – 85, mean 63.3, median 66.

- Medical history (n = 105): the most frequently (≥2%) reported relevant medical conditions included Hysterectomy (23), Breast cancer, Prostate cancer (13 each), Benign prostatic hyperplasia, Cholecystectomy (7 each), Basal cell carcinoma, Prostatectomy (6 each), Neoplasm malignant, Thyroidectomy (5 each), Appendicectomy, Breast

conserving surgery, Cancer surgery, Colon cancer, Malignant melanoma, Tonsillectomy (4 each), Gastrectomy, Lung lobectomy, Lymphadenectomy, Mammoplasty, Sigmoidectomy, Spinal fusion surgery (3 each), Adenocarcinoma pancreas, Biopsy prostate, Colectomy, Leukaemia, Lung adenocarcinoma, Prostatomegaly, Radical prostatectomy, Skin cancer, Squamous cell carcinoma of skin, Testis cancer, Thyroid cancer, Thyroid mass (2 each). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 Medical history: None.
- Co-suspects (n = 3): The reported co-suspect agents included alprazolam, azithromycin, calcium folinate, cyclobenzaprine, doxycycline, fluorouracil, irinotecan, oxaliplatin and sertraline (1 each).
- Number of events: 129.
- Most frequently reported clinical PTs (>2 occurrences): Breast cancer (6), Acute respiratory failure, Condition aggravated (4 each), Myocardial infarction (3).
- BNT162b2 related events coded to the PT: Acute myeloid leukaemia (1). Time to onset of event is 38 days and the event outcome is reported is not resolved. None of the events were related to blinded therapy.

Post-Authorization Data

- Number of cases: 11,995 (3.7% of 327,125 cases, the total PM dataset).
- MC cases (5651), NMC cases (6344).
- Country of incidence: UK (3585), US (2831), France (2008), Italy (673), Czech Republic (476), Spain (300), Germany (263); the remaining 1859 cases were distributed among 56 countries.
- Subjects' gender: female (8282), male (3541) and unknown (172).
- Subjects' age in years (n = 11,287),[143] range: 12 – 105, mean 62.8, median 64.
- Medical history (n = 11,995). The most frequently (≥2%) reported relevant medical conditions included Immunodeficiency (1889), Breast cancer (1686), Neoplasm malignant (776), Prostate cancer (642), Thyroidectomy (568), Hysterectomy (567), Chemotherapy (451), Radiotherapy (443), Renal transplant (386), Neoplasm (343), Lung neoplasm malignant (270), Chronic lymphocytic leukaemia (267), Mastectomy (242), Thyroid cancer (237), Cholecystectomy (227), Splenectomy (218), Breast cancer female

[143] Excluded 5 cases with contradictory demographic information (physical characteristics not matching with the reported age value) from reported minimum age calculation.

(205), Colon cancer (203), Malignant melanoma (190). Of note, more than 1 relevant medical history was reported in some cases.

- COVID-19 Medical history (n = 936): COVID-19 (531), Suspected COVID-19 (367), COVID-19 pneumonia (28), Asymptomatic COVID-19 (9), Post-acute COVID-19 syndrome (1).

- Co-suspects (n = 324): The most frequently (≥5 cases) reported co-suspect agents included lenvatinib (23), apixaban (17), palbociclib (10), pembrolizumab (9), COVID-19 Vaccine NRVV AD (8), trimethoprim/sulfamethoxazole (7), carboplatin, cisplatin, gemcitabine, ibuprofen (6 each), acetylsalicylate, levothyroxine, nivolumab, paclitaxel (5 each).

- Number of events: 46,821.

- Relevant event seriousness[62]: serious (23,127), non-serious (23,718).

- Most frequently reported clinical PTs (≥3%): Headache (2207), Fatigue (2048), Pyrexia (1660), Pain in extremity (1250), Nausea (1223), Chills (1067), Myalgia (1009), Arthralgia (959), Vaccination site pain (910), Pain (896), Malaise (848), Dizziness (807), Asthenia (731), Dyspnoea (702), Lymphadenopathy (624), Diarrhoea (594), Vomiting (554), Pruritus (453), Influenza like illness (433), Rash (408), COVID-19 (369), and Paraesthesia (354).

- Time to event onset (n = 34,557 events),[144] range: <24 hours to 121 days, median 1 day.

  - < 24 hours: 11,816 events;
  - 1 day: 9060 events;
  - 2-7 days: 8628 events;
  - 8-14 days: 2526 events;
  - 15-30 days: 1681 events;
  - 31-181 days: 846 events.

- Duration of event (n = 6424 of 14,222 events with outcome of resolved/resolved with sequelae)[145]

  - < 24 hours: 661 events;
  - 1 day: 2040 events;
  - 2-7 days: 3012 events;
  - 8-14 days: 448 events;

[144] This number does not include 134 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

[145] This number does not include 19 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

- 15-30 days: 173 events;
- 31-181 days: 90 events.

- Relevant event outcome[34]: fatal (1498), resolved/resolving (21,566), resolved with sequelae (654), not resolved (10,164), unknown (13,232).

- The lot/batch number which reported ≥3% of cases reporting ADRs following use in immunocompromised patients is #EM0477 (325 cases). No quality issues identified during investigations of the impacted lot/batch number.

Analysis by age group

- CT Data: Paediatric (1), Adults (47) and Elderly (57).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (34), Adults (5714), Elderly (5578) and Unknown (669).
  - 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 and Lymphadenopathy. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (1.5% [85 cases] in adults vs 4.5% [250 cases] in elderly). In majority of the elderly cases (172 of 250 cases) that reported the event coded to PT COVID-19, the co-reported events was coded to the PTs Drug ineffective (74 cases) and Vaccination failure (98 cases). These cases are also summarized in Section 16.3.4.5 *Lack of Therapeutic Efficacy*).
  - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (8.2% [466 cases] in adults vs 2.0% [113 cases] in elderly) compared to the elderly population.
  - No comparison was made to the paediatric population considering limited number of cases.

Conclusion

No new significant safety information was identified based on a review of these cases.

16.3.5.6. Use in Patients with Autoimmune or Inflammatory Disorders

- Search Criteria: Patients with Medical history PTs included in HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction.

- Of the 26,352 cases, the most frequently reported PTs (≥3%) included: Headache (5847), Fatigue (4916), Pyrexia (3948), Nausea (3107), Pain in extremity (3017), Chills (2818),

Arthralgia (2743), Myalgia (2657), Pain (2351), Vaccination site pain (2201), Dizziness (2166), Malaise (1874), Asthenia (1594), Dyspnoea (1415), Diarrhoea (1390), Lymphadenopathy (1337), Pruritus (1185), Rash (1140), Vomiting (1095), Paraesthesia (990), Influenza like illness (833), Feeling abnormal (800).

- MC cases (11,811), NMC cases (14,664).
- Event seriousness: serious (45,555), non-serious (64,832).
- Event outcome: fatal (2248), resolved/resolving (52,605), resolved with sequelae (1594), not resolved (24,603), unknown (29,896).

The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

During the reporting interval, the focus of the analysis has been narrowed to include exacerbation or flare of PTs of interest (ie, condition aggravated, disease progression), rather than all events.

- Of the 845 cases, 473 cases were determined to be non-contributory and are 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 (eg, atrial fibrillation, kidney disease, deep vein thrombosis, abdominal pain, throat swelling).

Therefore, 372 cases are included in the analysis below.

Clinical Trial Data

- Number of cases: 1 (0.1% of 702 cases, the total CT dataset; 1 blinded therapy).
- A [redacted] case, involving a 33-year-old male subject with a history of eosinophilic oesophagitis, experienced an eosinophilic oesophagitis flare (PT Condition aggravated) the same day he received his second dose of BNT162b2. The event resolved after 1 day and was considered unrelated to BNT162b2.

Post-Authorization Data

- Number of cases: 371 (0.1% of 327,125 cases, the total PM dataset).
- MC cases (156), NMC cases (215).
- Country of incidence (≥2%): UK (109), US (97), France (58), Germany, Italy (14 each), Spain (10), Canada, Netherlands (8 each).
- Subjects' gender: female (273), male (90) and unknown (8).

- Subjects' age I years (n = 341), range: 17 - 95, mean 57.4, median 57.

- Relevant medical history: the most frequently (≥3%) reported medical conditions included: Rheumatoid arthritis (42), Hypothyroidism (31), Arthritis (26), Autoimmune disorder, Diabetes mellitus (25 each), Immunodeficiency (21), Colitis ulcerative (20), Sjogren's syndrome (18), Psoriasis (15), Ankylosing spondylitis, Immune thrombocytopenia (14 each), Autoimmune thyroiditis, Type 1 diabetes mellitus (12 each).

- COVID-19 Medical history (n = 21): COVID-19 (11), Suspected COVID-19 (9), SARS-CoV-2 test positive (1).

- Co-suspects: adalimumab, tofacitinib (2 each), acetylsalicylic acid, acitretin, amoxicillin, enalapril, estradiol, hydrochlorothiazide, latanoprost, methotrexate, patisiran, pregabalin, ramipril, rituximab (1 each).

- Number of events: 2128 (of which 376 were events of interest ie, exacerbation/flare AEs).

- Relevant event seriousness: serious (264), non-serious (114).

- Most frequently reported relevant PTs (≥2%): Condition aggravated (247), Disease recurrence (118).

- Time to event onset (n = 224), range: 0 - 65 days, median 2 days.

  - <24 hours: 47 cases;
  - 1 day: 55 cases;
  - 2-7 days: 83 cases;
  - 8-14 days: 21 cases;
  - 15-30 days: 14 cases;
  - 31-181 days: 5 cases.

- Duration of event (n = 22), range: 0 - 21.5 days, median 5 days.

  - <24 hours: 2 cases;
  - 1 day: 2 cases;
  - 2-7 days: 11 cases;
  - 8-14 days: 5 cases;
  - 15-30 days: 2 cases.

- Relevant event outcome: fatal (2), resolved/resolving (140), resolved with sequelae (4), not resolved (116), unknown (115).

- Lot/Batch Number (n = 234): The most frequently reported lot number (≥10 cases): EM0477 (14), ER1741 (10).

Analysis by age group

- CT: Adult (1).
- PM: Paediatric (1), Adults (217), Elderly (124) and Unknown (29).
  - 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 198 cases, 2 doses in 132 cases; in 76 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.

Conclusion

Overall, there were 372 cases (1 CT case and 371 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.

16.3.5.7. Use in Frail Patients with Co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis)

- Search criteria for frail patients with co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis): Patients with Medical history of PTs included in HLGTs (Primary Path) Bronchial disorders (excl neoplasms), Heart failures, Mental impairment disorders, Movement disorders (incl parkinsonism), Nephropathies, Pulmonary vascular disorders, Renal disorders (excl nephropathies); HLTs (Primary Path) Autonomic nervous system disorders, Diabetes mellitus (incl subtypes), Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis, Motor neurone diseases, Muscle tone abnormal, Neuromuscular disorders NEC, Pulmonary hypertensions, Respiratory failures (excl. neonatal); patients with Medical history of ongoing Tuberculosis.
- Number of cases: 28,023 (8.6 % of 327,125, the total PM dataset).
- MC cases (15,348), NMC cases (12,675).
- Case seriousness: serious (15,247), non-serious (12,776).

- Country of incidence: UK (6,889), US (6,708), France (3,694), Italy (1,503), Japan (1,415), Spain (986), Germany (874), Sweden (716), Czech Republic (691), Netherlands (485), Denmark (435), Austria (390), Norway (363), Finland (268), Ireland (254), Portugal (251), Belgium (249), Canada (221), Mexico (208), Switzerland (177), Hungary (166), Greece, Israel (145 each), Romania (69), Croatia (67), Panama (61), Poland (60), Estonia (51), Costa Rica (40), Brazil (36), Luxembourg, Malta (29 each), Slovenia (27), Singapore (26), Iceland, Slovakia (25 each), Australia (22), Bulgaria, Latvia (20 each), Puerto Rico (17), South Africa (16), Lithuania (15), Chile, Cyprus (14 each), Colombia, Serbia, Turkey (13 each), Saudi Arabia (8), Ecuador (6), Iraq, United Arab Emirates (5 each), Jordan, Peru, Philippines (4 each), Bermuda, Lebanon, New Zealand, Tunisia (3 each), Kuwait, Malaysia, Qatar (2 each), Albania, Argentina, Curacao, French Guiana, French Polynesia, Georgia, Guyana, Hong Kong, India, Korea, Republic of (South Korea), Oman, Ukraine, Uruguay, and Virgin Islands, U.S. (1 each).

- Subject's gender: female (19,139), male (8,506), and unknown (378).

- Subject's age in years (n = 26,891), range: 0.17-104, mean 61, median 61.

- Relevant subjects' medical histories most frequently reported (≥1,000 cases) coded to the PTs: Asthma (10,608), Hypertension (7,276), Diabetes mellitus (5,399), Type 2 diabetes mellitus (3,332), Chronic obstructive pulmonary disease (2,242), Drug hypersensitivity (1,783), Atrial fibrillation (1,489), COVID-19 (1,483), Chronic kidney disease, Hypersensitivity (1,335 each), Hypothyroidism (1,290), Cardiac failure (1,202), Depression (1,183), Food allergy (1,159), Seasonal allergy (1,151), Dementia (1,149), Obesity (1,119), and Suppressed lactation (1,064).

- Of the 114,369 events overall reported, the most frequent clinical events (≥1,000 occurrences) coded to the PTs: Headache (5,256), Fatigue (4,547), Pyrexia (4,323), Nausea (2,956), Chills (2,674), Pain in extremity (2,579), Myalgia (2,422), Dyspnoea (2,351), Dizziness (2,118), Vaccination site pain (2,087), Arthralgia (2,062), Pain (2,018), Malaise (1,995), Asthenia (1,779), Vomiting (1,338), Diarrhoea (1,333), Pruritus (1,264), Cough (1,168), Lymphadenopathy (1,035), and Rash (1,029); all these 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.

- Case outcome: fatal (2346, see Section 16.3.4.1 *Death*), resolved/resolving (13,875), resolved with sequelae (482), not resolved (8,336) and unknown (2984).

Conclusion

The reporting proportion of not resolved cases (29.7%) and cases resolved with sequelae (1.7%) in frail subjects is similar to the reporting proportion observed in the overall population (23.5% for outcome of not resolved, 1.0% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (8.4%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (1.5%). This is expected, considering that most of the cases reporting a fatal outcome (80%) 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 (eg, 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.

16.3.5.8. Interactions with other Vaccines

- Search criteria: HLT Interactions.

- Of the 253 cases, 251 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

  - In 107 cases, the subject did not experience a drug interaction, but rather the reporters were inquiring about whether or not a drug interaction could potentially occur.

  - In 144 cases (of which 65 were serious), the subjects experienced drug interactions with the following concomitant medications warfarin (7), alcohol, clozapine (5 each), apixaban, clopidogrel, methotrexate, steroids (unspecified) (4 each), adalimumab, lamotrigine, prednisone, sertraline, unspecified medications (3 each), acetaminophen, atorvastatin, blood thinners (unspecified), botulinum, diphenhydramine, glatiramer, guselkumab, hydroxyurea, ibuprofen, insulin, lithium, phenprocoumon, pregabalin, trazodone, rituximab (2 each), acenocoumarol, acetylsalicylic acid, acetylsalicylate lysine, amphetamine/dextroamphetamine, amitriptyline, amoxicillin/clavulanate, anaesthesia (unspecified), antibiotics (unspecified), allergy shot (unspecified), aripiprazole, atenolol, budesonide/formoterol/glycopyrronium, bupropion, cannabis, carbidopa/levodopa, cefuroxime, cephalexin, ciprofloxacin, clonazepam, contraceptive (unspecified), contrast medium, cortisone, denosumab, dexamethasone, diabetes medication (unspecified), diltiazem, dulaglutide, eletriptan, esomeprazole, fiorinal, fluindione, fluoxetine, food, gammaplex, gabapentin, ginseng, golimumab, heparin, hormone replacement therapy (unspecified), immunoglobin, immunosuppressant, immunotherapy, infliximab, interferon, ketoprofen, lanreotide, levodopa, levothyroxine, lisdexamfetamine, local anaesthetic, meclizine, mesalamine, methylprednisolone, metoprolol, metronidazole, mirtazapine, montelukast, movicol, mycophenolic acid, ocrelizumab, octocog alfa, olanzapine, omeprazole, osimertinib, oxycodone, oxycodone/paracetamol, palbociclib, pantoprazole, paroxetine, penicillin, psychiatric medication (unspecified), quetiapine, ropinirole, tadalafil, tafenoquine, tamsulosin, temazepam, tenofovir, tofacitinib, trimethoprim, ustekinumab, vitamin B12, zonisamide (1 each).

Two of the 253 cases reported an interaction with another vaccine and are discussed below.

Clinical Trial Data

There were no serious clinical trial cases reported during the reporting period.

Post-Authorization Data

- Number of cases: 2 (0.0% of 327,125 cases, the total PM dataset).
- MC case (1), NMC case (1).
- Country of incidence: Germany, US (1 each).
- Subjects' gender: female (1), male (1).
- Subjects' age (n = 1): 57 years.
- Medical history (n = 1): Pertussis.
- COVID-19 Medical history: None.
- Co-suspects (n = 1): Diphtheria vaccine toxoid, pertussis vaccine acellular 5- component, polio vaccine inact 3V (vero), tetanus vaccine toxoid.
- Number of events: 8 (of which 2 were events of interest).
- Relevant event seriousness: non-serious (2).
- Relevant PT: Drug interaction (2).
- Co-reported AEs: Circumstance or information capable of leading to medication error, Induration, Influenza like illness, Myalgia, Pain, Vaccination site swelling (1 each).
- Time to event onset: n = 1, <24 hours.
- Duration of event: Unknown (2).
- Relevant event outcome: Unknown (2).

Analysis by age group comorbidities [22,57] and dose

No comparison between the different age groups and presence of comorbidities can be done due to the limited number of cases.

Conclusion

Overall, of the 253 cases, 107 were no relevant as a drug interaction did not occur and in 144 cases, the drug interaction occurred with a concomitant medication rather than another vaccine. The were 2 cases in the overall post-marketing dataset that reported a vaccine interaction. In general, the most frequently co-reported events observed in subjects with vaccine interaction was consistent with those observed in the overall population. There is no indication of a safety signal of interference of immune response of vaccines noted based on a review of these cases. In one of the 2 cases, it was reported that BNT162b2 increased the

vaccination reaction to diphtheria vaccine toxoid, pertussis vaccine acellular 5- component, polio vaccine inact 3V (vero), tetanus vaccine toxoid.

16.4. Characterisation of Risks

After DLP, 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 (see Section 14).

The MAH proposes the following list of safety concerns for the next reporting period, subject to the PRAC approval of the EU-RMP version 2.3.

Table 41. Ongoing Safety Concerns

Important identified risks	Anaphylaxis Myocarditis and pericarditis[a]
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. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory Disorders
	Interaction with other vaccines
	Long-term safety data

a. Search criteria: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

16.4.1. Characterisation of Important Identified and Potential Risks

A typical medicinal product has multiple risks associated with it and individual risks vary in terms of severity, effect on individual patients, and public health impact.

What constitutes an important risk depends upon several factors including the impact on the individual patient, the seriousness of the risk and its severity, and the impact on public health. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered. Risks may be related to nonclinical or clinical safety or quality issues. The intended purpose and impact of the product eg, whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease must also be considered when characterising risks.

The following were considered in characterising risk(s) of this product:

- frequency of risk;
- public health impact (severity and seriousness/reversibility/outcomes);

- impact on the individual patient (effect on quality of life or could lead to serious consequences if left untreated);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (ie, predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

Internal and external datasets were used to populate the table below with available data. In addition to literature searches for the drug itself and its class, external data sources were consulted.

Table 42 characterises the important identified and potential risks of BNT162b2.

Table 42. Characterisation of Important Risks

Important Identified Risk: Anaphylaxis *Search: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock*	
Characterisation	*Potential mechanisms, evidence source and strength of evidence* Interaction of an allergen with IgE on basophils and mast cells triggers release of histamine, leukotrienes and other mediators that cause diffuse smooth muscle contraction and vasodilation with plasma leakage. This can manifest clinically with dyspnea, hypotension, swelling (sometimes leading to airway compromise), and rash (including hives). *Risk factors and risk groups* Known hypersensitivity to any components of the vaccine. *Preventability* Prevention of anaphylaxis may not be possible, particularly with the 1st dose of a vaccine; therefore, healthcare professionals administering the vaccine must be vigilant for early signs and symptoms. *Impact on the risk-benefit balance of the biologic product* Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening event requiring medical intervention. *Public health impact* Minimal due to rarity of the event. Although the potential clinical consequences of an anaphylactic reaction are severe, this is a known risk of vaccines to healthcare professionals with negligible public health impact.
Cumulative Case Characterisation (through 18 June 2021)	***Post-marketing sources:*** - No. of cases: 3836. - Relevant PTs: Anaphylactic reaction (3,425), Anaphylactic shock (421), Anaphylactoid reaction (77), Anaphylactoid shock (5).[51] - Frequently reported additional PTs (≥100 occurrences): Dyspnoea (697), Nausea (450), Pruritus (434), Headache (392), Dizziness (379), Cough (375), Erythema (370), Rash (314), Tachycardia (302), Urticaria (296), Malaise (256), Throat tightness (227), Pyrexia (225), Vomiting (213), Blood pressure increased (193),

Table 42. Characterisation of Important Risks

Cumulative Case Characterisation (through 18 June 2021) *Cont'd*	Oropharyngeal discomfort (187), Fatigue (179), Palpitations (176), Feeling abnormal (166), Paraesthesia (161), Chills (157), Chest discomfort, Hypoaesthesia (142 each), Asthenia, Flushing, Wheezing (130 each), Swollen tongue (129), Pharyngeal swelling, Tremor (126 each), Heart rate increased (123), Dysphonia (122), Hypersensitivity (119), Hypertension (115), Respiratory distress (109), Throat irritation (108), Blood pressure decreased (107), Paraesthesia oral (106), Diarrhoea (105), Lip swelling (103), Loss of consciousness (101), Hypotension (100). - Subjects' gender: female (3192), male (455), unknown (189) - Subjects' age in years (n = 3440), range: 12 – 104, mean 45.6, median 44. - Age group: Paediatric (23), Adults (3030), Elderly (395) and Unknown (388). - Case source: Spontaneous (3756), Literature (74), Non-interventional study (6) - Event seriousness: serious (3882), non-serious (46) - Event outcome: Fatal (28), Not resolved (173), Resolved with sequelae (56), Resolved/resolving (2967), Unknown data (707). ***Clinical trials:*** - No. of cases: 3 (of which 2 involved blinded therapy) - No. of SAEs: 3 - The most common PTs: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction (1 each) - Related SAEs: Anaphylactoid reaction (1). Based on the cumulative post-marketing and clinical trials data, no new safety information was identified for BNT162b2 and anaphylaxis.

Table 42. Characterisation of Important Risks

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) ***Search:*** PTs Vaccine associated enhanced respiratory disease OR Vaccine associated enhanced disease OR 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.	
Characterisation	*Potential mechanisms, evidence source and strength of evidence* This potential risk is theoretical because it has not been described in association with the COVID-19 mRNA vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. Animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunisation, whereas cellular immunopathology has been demonstrated after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) vaccines.[146,147] This potential risk has been included based on these animal data with these related betacoronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine.[148] Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favouring Th2 over Th1] and antibody-mediated immune responses (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells).[149] *Risk factors and risk groups* It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.[149] *Preventability* An effective vaccine against COVID-19 that produces high neutralizing titers and a T_H1 predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected

[146] Lambert PH, Ambrosino DM, Andersen SR, et al. Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine 2020;38(31):4783-91.

[147] Law B, Sturkenboom M. D2.3 priority list of adverse events of special interest: COVID-19. In: WP2 standards and tools. V2.0. 25-05-2020. Brighton Collaboration. Decatur, GA: Safety Platform for Emergency vACcines; 2020: 52 pages.

[148] Openshaw PJ, Culley FJ, Olszewska W. Immunopathogenesis of vaccine-enhanced RSV disease. Vaccine 2001;20(Suppl 1):S27-31.

[149] Graham BS. Rapid COVID-19 vaccine development. Science 2020;368(6494):945-6.

Table 42. Characterisation of Important Risks

Characterisation *Cont'd*	to mitigate the risk of VAED/VAERD;[146,149] that immune profile is elicited by COVID-19 mRNA vaccine in clinical and preclinical studies.[150,151] *Impact on the risk-benefit balance of the biologic product* If there were an unfavourable balance in COVID-19 cases, including severe cases, in the pivotal clinical study between the vaccine and placebo groups, that may signal VAED/VAERD. *Public health impact* The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.
Cumulative Case Characterisation (through 18 June 2021)	***Post-marketing sources:*** Number of cases potentially indicative of VAED-VAERD: 584 (same cases retrieved in the interval period - see Table 23). ***Clinical trials:*** There were no cases reporting COVID-19 infection associated to one of the PTs utilized to identify potential severe or atypical cases of COVID-19.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer. The risks for BNT162b2 are well managed. No special investigations to further characterise any of these risks are necessary.

16.4.2. Description of Missing Information

Table 43 describes missing information associated with the use of BNT162b2.

Table 43. Description of Missing Information

Topic	Description
Use in pregnancy and while breast feeding	The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated despite the lack of safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at

[150] Sahin U, Muik A, Derhovanessian E, et al. Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine. medRxiv 2020.07.17.20140533.

[151] Vogel AB, Kanevsky I, Che Ye, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. bioRxiv 2020.09.08.280818.

Table 43. Description of Missing Information

Topic	Description
Use in pregnancy and while breast feeding *Cont'd*	risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarized in Section 16.3.5.3 *Use in Pregnant/Lactating Women.*
Use in immunocompromised patients	The vaccine has not been studied in individuals with overt immunocompromised conditions. Therefore, further safety data will be sought in this population. Cases involving use of BNT162b2 in immunocompromised patients received during the reporting interval are summarized in Section 16.3.5.5. *Use in Immunocompromised Patients.*
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	The vaccine has been studied in individuals with stable chronic diseases (eg, 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. Cases involving use of BNT162b2 in frail patients with comorbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) received during the reporting interval are summarized in Section 16.3.5.7. *Use in Frail Patients with Co-morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis).*
Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. Cases involving use of BNT162b2 in patients with autoimmune or inflammatory disorders received during the reporting interval are summarized in Section 16.3.5.6 *Use in Patients with Autoimmune or Inflammatory Disorders.*
Interaction with other vaccines	There are no data on interaction of BNT162b2 mRNA vaccine with other vaccines at this time. Cases involving interactions with other vaccines received during the reporting interval are summarized in Section 16.3.5.8 *Interactions with other Vaccines.*
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.

16.5. Effectiveness of Risk Minimisation (if applicable)

No new information for risk minimisation activities became available during the reporting interval.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

BNT162b2 is indicated in the EEA countries for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. In other countries it is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

Study C4591001 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[152] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[152] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[153] were included as were participants with known stable infection with HIV, HCV, or HBV.[152]

Efficacy analyses were performed with confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through 13 March 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population, see table below.

[152] Ref #12 of the CDS. Global Emergency Use Authorization Application, Section 6.2.1.2

[153] Ref #21 of the CDS. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

Table 44. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[154]			
Subgroup	**TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[155]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

[154] Ref#53 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[155] Ref#54 of the CDS. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 44. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 45 and Table 46.

Table 45. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[156]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2 [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk [g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)

[156] Ref #55 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 45. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[156]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese [h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).

h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 46. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2 [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk [g]			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese [h]			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Table 46. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).

h. Obese is defined as BMI ≥30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 47) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the TRADENAME and placebo groups.

Table 47. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition[157,158]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After Dose 1 [d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2 [f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition[159,160]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After Dose 1 [d]	1 8.427[e] (22,473)	45 8.269[e] (22,394)	97.8 (87.2, 99.9)
7 days after Dose 2 [f]	0 6.514[g] (21,620)	32 6.391[g] (21,693)	100 (88.0, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[161]

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[157] Ref #57 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[158] Ref #58 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population.

[159] Ref #59 of the CDS. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population.

[160] Ref #60 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[161] Ref #61 of the CDS. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy.

Table 47. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[161]

- Hospitalization;
- Admission to the ICU;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[162]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[162]
g. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age

Vaccine efficacy in adolescents 12 to 15 years of age is presented in Table 48.

[162] Ref#62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 48. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 to 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*,[163]			
	TRADENAME N[a]=1005 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=978 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Adolescents 12 to 15 Years of Age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection[164]			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1110 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Adolescents 12 to 15 Years of Age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In C4591001 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses comparing

[163] Ref#46 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

[164] Ref#47 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 to 25 years of age (n = 170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The GMT ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the GMR >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[165]

17.2. Newly Identified Information on Efficacy and Effectiveness

Antibody waning, the need for a booster dose or revaccination

Neutralizing SARS-CoV-2 antibody titers and S1-binding IgG antibodies were evaluated at 6 months after Dose 2 for Study C4591001 Phase 1 participants who received BNT162b2 at 30 µg and the corresponding placebo recipients. Data were analyzed for both younger (18 to 55 years of age) and older (65 to 85 years of age) Phase 1 age groups, which included N =15 each randomized in a 4:1 vaccine:placebo ratio.

Overall, SARS-CoV-2 serum 50% neutralizing GMTs and S1-binding IgG GMCs at 6 months after Dose 2 showed a decline relative to the peak levels observed at 1-month after Dose 2, but still remained higher than both pre-vaccination and placebo control levels.

For both younger and older age groups, the observed neutralizing GMTs declined from 1 month after Dose 2 (Day 52) to 6 months after Dose 2 (Day 202) (Figure 17). In the younger age group, GMTs were 179.2 at 1 month after Dose 2 and 54.7 at 6 months after Dose 2; in the older age group, GMTs declined from 151.6 to 29.0 over this same interval.

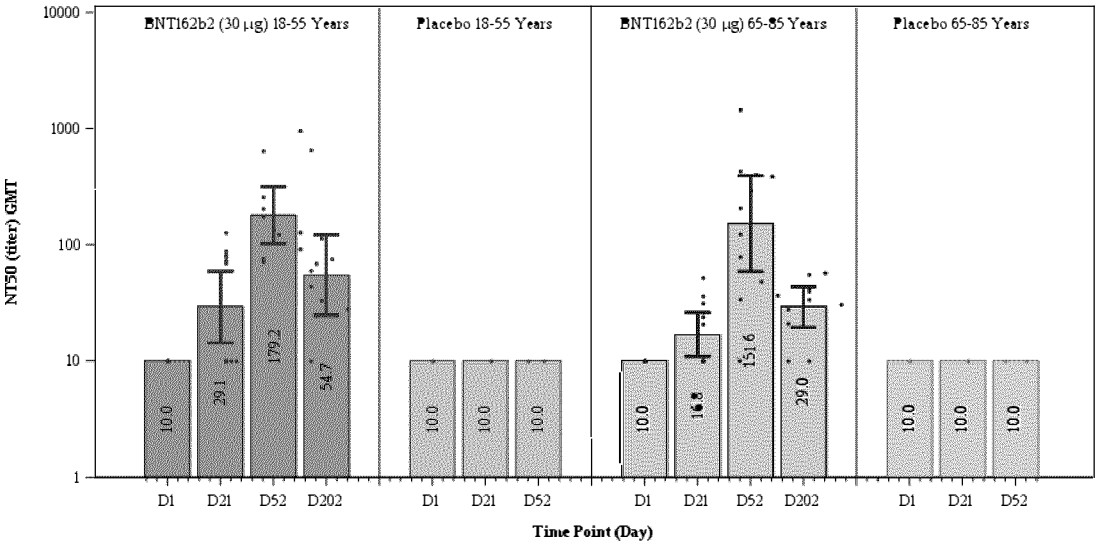
Observed S1-binding GMCs at 6 months after Dose 2 also declined from peak values at 1 month after Dose 2, in both age groups (Figure 18).

These Phase 1 data show persistence of a robust immune response elicited by BNT162b2 30 µg vaccination in adults for up to 6 months; and also suggest, based on the modest decline in GMTs and GMCs from 1 month to 6 months after receiving Dose 2, that vaccinees may benefit from a booster dose at 6 months or thereafter.

Booster groups are currently being evaluated in Study C4591001 for safety and immunogenicity of a third dose of BNT162b2 30 µg administered to adults 18 to 55 years of age, at approximately 6 months after completing the initial 2-dose series.

[165] Ref #48 of the CDS. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population.

Figure 17. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Phase 1, 2 Doses, 21 Days Apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population



Abbreviations: D = day; GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

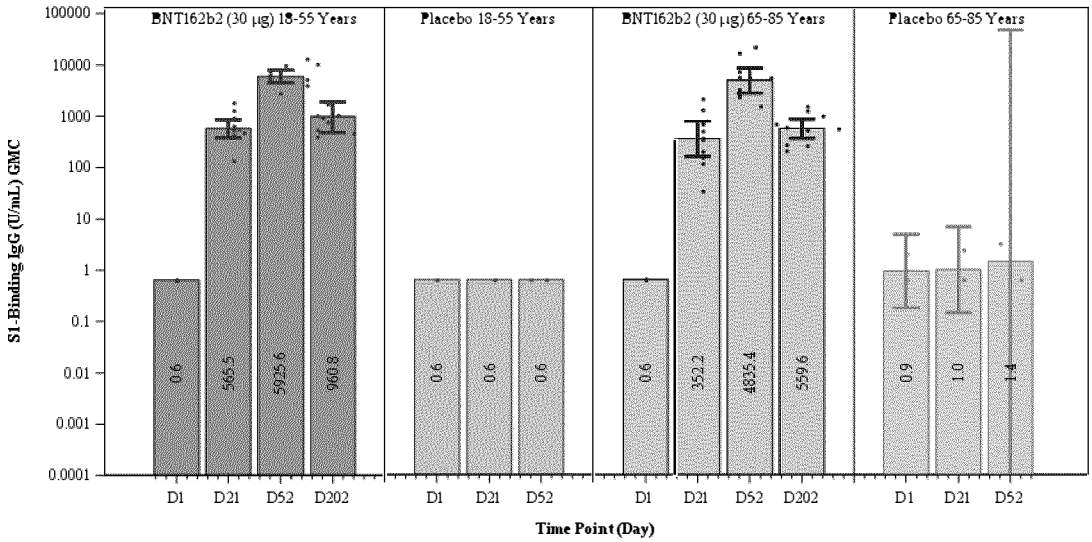
Note: Blood samples from the Day 7 and Day 14 post–Dose 2 visits are not included since these samples were not retested with the 6-month post–Dose 2 samples.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean titer.

PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:25) Source Data: adva Table Generation: 01APR2021 (02:17)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2_unblinded/C4591001_BLA1/adva_f002_sars_50_b2_p1

Figure 18. Geometric Mean Concentrations and 95% CIs: S1-Binding IgG Level Assay – Phase 1, 2 Doses, 21 Days Apart – BNT162b2 (30 µg)/Placebo – Evaluable Immunogenicity Population



Abbreviations: D = day; GMC = geometric mean concentration; IgG= immunoglobulin G; S1 = spike protein S1 subunit.
Note: Blood samples from the Day 7 and Day 14 post–Dose 2 visits are not included since these samples were not retested with the 6-month post–Dose 2 samples.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:25) Source Data: adva Table Generation: 01APR2021 (02:19)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2_unblinded/C4591001_BLA1/adva_f002_s1_b2_p1

17.3. Characterisation of Benefits

Data in Section 17.1 demonstrates a high degree of efficacy against symptomatic and severe COVID-19 in non-immunocompromised people over 12 years of age, during the period at least 7 days following the second dose of vaccine. Efficacy is evident separately and at a similar level in people 12-15 years of age, 16-64 years of age, 65 to 74 years of age and 75 years of age. Efficacy also appears largely independent of risk factors (having at least 1 of the CMI categories) and obesity. Efficacy is also high against severe disease after the first dose. This is anticipated to deliver effective prevention of COVID-19 in the community and reduced hospitalisation, severe morbidity and death from COVID-19. Section 17.2 describes a reduction in viral geometric mean neutralizing titres at 6 months after the second dose of vaccine to a similar level to that observed 21 days after the first dose of vaccine. The implications of this reduction in circulating antibody will be followed up in the ongoing efficacy study.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

BNT162b2 indications are provided in Section 1.

The COVID-19 is caused by a novel coronavirus labelled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause

was recognised in Wuhan City, Hubei Province, China.[166] The number of infected cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[167]

Incidence

Estimates of SARS-CoV-2 incidence change rapidly. The MAH obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organisation that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.[168]

As of 03 March 2021, the overall number of people who had been infected with SARS-CoV-2 was over 115 million worldwide,[169] an increase of nearly 100 million in the 7 months since 28 July 2020.[170]

Table 49 shows the incidence and prevalence as of 03 March 2021 for the US, UK, and EU-27 countries. In the EU and the UK, by 03 March 2021 the total number of confirmed cases had accumulated to almost 27 million people, or 5,226 per 100,000 people (from 1.7 million, or 337 per 100,000 by 28 July 2020). Across countries in the EU, the number of confirmed cases ranged from 1,072 to 11,836 cases per 100,000 people. Finland and Greece reported the lowest incidence rates while Czech Republic, Slovenia, and Luxembourg reported the highest.[169]

In the US, the number of confirmed cases had reached over 29 million cases (8,864 per 100,000 people) by 03 March 2021.[169] This is an increase from 4.5 million (1,357 per 100,000) by 28 July 2020.[170]

Table 49. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021[169]

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases[a]	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	115,760,943	1,485	21,707,680	278	2,571,518	33	7,794,824,793
EU-27	22,642,536	5,083	6,113,464	1,462	553,363	124	445,424,167
UK	4,194,785	6,157	1,065,282	1,564	123,783	182	68,125,249

[166] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33.

[167] World Health Organization. 2020. Coronavirus Disease 2019 (COVID-19) Situation Report – 11.

[168] Worldometers.info. Dover, Delaware, USA. Accessed on 06 March 2021.

[169] Worldometers.info. Reported Cases and Deaths by Country or Territory. 03 March 2021. Dover, Delaware, U.S.A. https://www.worldometers.info/coronavirus/#countries. Accessed on 03 March 2021.

[170] Worldometers.info. Reported Cases and Deaths by Country or Territory. 28 July 2020. Dover, Delaware, U.S.A. https://www.worldometers.info/coronavirus/#countries. Accessed on 28 July 2020.

Table 49. Incidence, Prevalence, and Mortality of COVID-19 as of 03 March 2021[169]

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases[a]	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
EU-27 + UK	26,837,321	5,226	7,178,746	1,398	677,146	132	513,549,416
US	29,456,377	8,864	8,921,400	2,685	531,652	160	332,304,437
EU-27 Countries							
Austria	465,322	5,147	21,028	233	8,625	95	9,040,866
Belgium	774,344	6,662	699,566	6,019	22,141	191	11,623,476
Bulgaria	253,183	3,662	33,770	488	10,413	151	6,913,156
Croatia	244,205	5,973	3,322	81	5,555	136	4,088,197
Cyprus	35,620	2,936	33,331	2,747	232	19	1,213,250
Czech Republic	1,269,058	11,836	154,580	1,442	20,941	195	10,722,330
Denmark	212,798	3,665	6,995	120	2,370	41	5,805,897
Estonia	69,193	5,214	17,938	1,352	615	46	1,327,135
Finland	59,442	1,072	12,683	229	759	14	5,546,504
France	3,810,316	5,829	3,461,485	5,295	87,542	134	65,370,546
Germany	2,472,896	2,945	126,785	151	71,711	85	83,963,843
Greece	197,279	1,899	21,157	204	6,597	64	10,388,744
Hungary	439,900	4,561	98,361	1,020	15,324	159	9,643,837
Ireland	221,189	4,446	193,468	3,889	4,357	88	4,974,683
Italy	2,976,274	4,927	437,421	724	98,635	163	60,401,999
Latvia	88,022	4,702	9,233	493	1,654	88	1,872,109
Lithuania	200,349	7,430	10,859	403	3,281	122	2,696,596
Luxembourg	55,902	8,834	3,074	486	643	102	632,773
Malta	23,226	5,251	3,000	678	321	73	442,333
Netherlands	1,101,430	6,418	-	-	15,697	92	17,160,343
Poland	1,735,406	4,589	249,567	660	44,360	117	37,818,722
Portugal	806,626	7,926	64,797	637	16,430	161	10,176,690
Romania	812,318	4,242	44,953	235	20,586	108	19,151,141
Slovakia	314,359	5,756	51,570	944	7,489	137	5,461,420
Slovenia	192,266	9,247	10,751	517	3,874	186	2,079,130
Spain	3,136,321	6,706	343,770	735	70,247	150	46,766,954
Sweden	675,292	6,659	-	-	12,964	128	10,141,493

a. Active case counts were not available for Netherlands and Sweden; therefore, those two countries are excluded from the overall prevalence calculations for EU-27 and EU-27 + UK.

The reported numbers refer only to cases that have been tested and confirmed to be carrying the virus. There are large geographic variations in the proportion of the population tested as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported. The numbers should therefore be interpreted with caution.[170]

The main existing treatment options:

Through 18 June 2021, other COVID-19 vaccines were authorised[171] in the European Union including vaccines from Moderna (EU/1/20/1507), Janssen (EU/1/20/1525) and AstraZeneca (EU/1/21/1529). Others are reported to be currently under review and may subsequently be approved.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Symptoms of COVID-19

The clinical manifestations of COVID-19 vary widely, from asymptomatic infection in 17-20%,[172,173] to critical illness and death.

Progression and Timeline of Mild to Moderate Disease

Mild to moderate disease is defined as the absence of viral pneumonia and hypoxia. For those who develop symptoms, the incubation period is usually 4 to 5 days, with 97.5% experiencing symptoms within 11 days of exposure.[174,175] Those with mild COVID-19 recover at home with supportive care and guidance to self-isolate. Those with moderate disease are monitored at home and are sometimes recommended to be hospitalised if conditions worsen.[175] Data on rates of re-infection are limited but variants that are not neutralized by immune antisera, such as the recent South African variant, may lead to increased risk of re-infection in the future.[174]

Progression and Timeline of Severe Disease Requiring Hospitalisation

Those with severe disease will require hospitalisation to manage their illness. Based on data that have been systematically collected for the US by the CDC between 01 August 2020 and 02 March 2021, there were 1,814,606 new hospital admissions for patients with confirmed

[171] According to the Union Register of Medicinal Products https://ec.europa.eu/health/documents/community-register/html/ Accessed on 18 July 2021.

[172] Pollock A M, Lancaster J. Asymptomatic transmission of COVID-19. BMJ 2020; 371:m4851 doi:10.1136/bmj.m4851.

[173] Toba N, Gupta S, Ali AY, et al. COVID-19 under 19: A meta-analysis. Pediatr Pulmonol 2021 Feb 25. doi: 10.1002/ppul.25312. Epub ahead of print. PMID: 33631060.

[174] CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed on 07 March 2021.

[175] Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. N Engl J Med 2020; 383(18):1757-1766. doi: 10.1056/NEJMcp2009249. Epub 2020 Apr 24. PMID: 32329974.

COVID-19 in the US.[176] For the week ending 28 February 2021, 10 patients per 100,000 population were hospitalised due to COVID-19 in 22 countries of the EU/EEA with available data.[177]

The most common symptoms in patients are fever (42-80%), shortness of breath (35-71%), fatigue (33-62%), cough (77-84%), chills (63%), myalgias (63%), headache (59%), and diarrhea (33%).[178,179,180,181] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care.[182,183,178] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[184]

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 days and time from onset of illness to ICU admission was 9.5–12 days.[174] In 17 countries of the EU/EEA with available data, 1.8 patients per 100,000 population were in the ICU due to COVID-19 for the week ending 28 February 2021.[177] A recent meta-analysis found that, of patients <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.[173]

Mortality

As of 07 March 2021, there were 522,973 deaths reported in the US for all age groups among 28,771,749 cases (1.8% of cases).[176] As of 28 February 2021 there were 547,267 deaths

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[176] CDC. COVID Data Tracker as of 07 Mar 2021. https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed on 08 March 2021.

[177] ECDC. Weekly Surveillance Summary, Week 08, 2021. https://covid19-surveillance-report.ecdc.europa.eu/. Accessed on 07 March 2021.

[178] Hur K, Price CPE, Gray EL, et al. Factors associated with intubation and prolonged intubation in hospitalized patients with COVID-19. [published correction appears in Otolaryngol Head Neck Surg. 2020 Jul;163(1):NP1]. Otolaryngol Head Neck Surg 2020;163(1):170-8.

[179] Burke RM, Killerby ME, Newton S, et al. Case Investigation Form Working Group. Symptom profiles of a convenience sample of patients with COVID-19 - United States, January-April 2020. MMWR Morb Mortal Wkly Rep 2020; 69(28):904-8. doi: 10.15585/mmwr.mm6928a2. PMID: 32673296; PMCID: PMC7366851.

[180] Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020;69(18):545-50.

[181] Nowak B, Szymański P, Pańkowski I, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med 2020;130(5):407-11.

[182] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763-70.

[183] Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. Health Aff (Millwood) 2020;39(7):1253-62.

[184] Iaccarino, G, Grassi G, Borghi C, et al. Age and multimorbidity predict death among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension 2020;76(2):366-72.

reported for all age groups in the EU/EEA among 22,527,370 cases (2.4% of cases).[185] As of 7 March 2021, the UK has seen 124,736 deaths from COVID-19 in all age groups among 4,231,166 cases (2.9% of cases).[186] According to a recent meta-analysis of paediatric studies published through October 2020, the mortality for patients <19 years of age is 2%.[173]

Mortality data are also presented from Worldometer, an independent organisation that publishes current, reliable COVID-19 statistics online.[170] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 03 March 2021, the overall SARS-CoV-2 mortality for the EU + UK was 677,146 deaths, or 132 per 100,000 people. Reported mortality among EU countries and the UK ranged from 14 to 195 deaths per 100,000 (Table 49). Finland and Cyprus reported the lowest mortality; Czech Republic, Belgium and Slovenia reported the highest.[169]

In the US, as of 03 March 2021, the mortality was 531,652 deaths (160 per 100,000 people). Mortality in the US was similar to that of EU countries Hungary, Portugal, and Italy.[169]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK.[183,180,187,188] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[187,189]

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

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[185] ECDC. Situation Report Week 8 2021. https://www.ecdc.europa.eu/en/covid-19. Accessed on 08 March 2021.

[186] JHU COVID Map 2021. https://coronavirus.jhu.edu/map.html. Accessed on 08 March 2021.

[187] Jones S, Mason N, Palser T, et al. Trends in risk-adjusted 28-day mortality rates for patients hospitalized with COVID-19 in England. J Hosp Med. Published Online First February 5, 2021. DOI: 10.12788/jhm.3599.

[188] Rao GG, Allen A, Papineni P, et al. London North West Healthcare Trust COVID-19 Research Group. Cross-sectional observational study of epidemiology of COVID-19 and clinical outcomes of hospitalised patients in North West London during March and April 2020. BMJ Open 2021;11(2):e044384. doi: 10.1136/bmjopen-2020-044384. PMID: 33602712; PMCID: PMC7896375.

[189] Horwitz LI, Jones SA, Cerfolio RJ, et al. Trends in COVID-19 risk-adjusted mortality rates. J Hosp Med 2021;2:90-2. Published Online First October 23, 2020. doi:10.12788/jhm.3552.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarized below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The subjects in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

Non-interventional (observational) study data:

a) There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.

b) Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also inherent limitations.

Post-marketing data:

a) Reports originate from multiple sources (consumer and healthcare professional) and they can be poorly characterised from a medical perspective.

b) Limited or incomplete information is common, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.

c) Difficult to contextualize quantitatively, as voluntary and sporadic reporting do not allow complete knowledge of total exposure or total number of events ever experienced in the exposed population. These data are generally not suitable to make between-drug comparisons.

18.2.1. Benefits

Please refer to Section 17.

18.2.2. Risks

An assessment of the important risks, identified and potential, was performed using the following data sources: pre-clinical studies, clinical studies, post-marketing experience, and literature as applicable. Interval findings are summarized in Table 50.

Based on pharmacovigilance monitoring activities, there has been no new safety information contributing importantly to the risk of BNT162b2.

Table 50. Summary of Important Risks

Risks	Clinical Study Data	Post-Marketing Data	Literature Sources	Conclusion
Important Identified Risks				
Anaphylaxis	No new data from clinical studies were identified during the reporting interval.	Based on the review of post-marketing data, no new safety information was identified for BNT162b2 and anaphylaxis.	No new significant data received from literature sources.	Anaphylaxis is an adverse reaction in Section 4.8 of the EU SmPC, in the CDS and local labels/fact sheets. It is also included as an Important identified risk in the EU RMP and in the US PVP. Based upon review of the available information, no additional change to the RSI is warranted at this time.
Important Potential Risks				
VAED VAERD	No new data from clinical studies were identified during the reporting interval.	Based on the review of post-marketing data, no new safety information was identified for BNT162b2 and VAED-VAERD.	No new significant data received from literature sources.	VAED-VAERD is theoretical because it has not been described in association with the COVID-19 mRNA vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. It is included as an Important Potential Risk in the EU-RMP and in the US-PVP. Based upon review of the available information, no additional change to the RSI is warranted at this time.

18.2.3. Overall Benefit-Risk

The important risks associated with the use of BNT162b2 are minimized through provision of relevant product information in the RSI to support safe use of the product. Risks have been evaluated in the context of the enumerated benefits of the product. Based on the available safety and efficacy data for BNT162b2, the overall benefit-risk profile of BNT162b2 remains favourable.

Table 51. Overall Benefit-Risk for BNT162b2

Consideration	Favourable Benefit-Risk	Non Contributory	Unfavourable Benefit-Risk
Severity of condition	The severity of the condition being treated, as well as comorbidities and outcomes in the population to be treated were considered. (See Section 18.1)	NA	NA
Unmet medical need	BNT162b2 meets an unmet medical need, because there is - lack of alternative therapies, or - although alternative products are available in this class, this product may be the preferred therapeutic option or preferred in a select group of patients. (See Section 18.1)	NA	NA
Clinical benefit	The nature, clinical importance, duration, and generalizability of benefits were considered. (See Section 18.1)	NA	NA
Risk associated with treatment	The nature, seriousness, frequency, predictability, reversibility, impact on patients and public health of the product's risks were considered. (See Section 18.2.2)	NA	NA
Risk management	Risk minimisation measures currently in place for this product support a favorable benefit-risk balance. (See Section 18.2.2)	NA	NA

Table was adapted from European Medicines Agency. Benefit-risk Methodology Project – Working package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010.

19. CONCLUSION AND ACTIONS

Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2, the benefit-risk profile of BNT162b2 remains favourable. No additional changes to the BNT162b2 RSI or additional risk minimisation activities are warranted in addition to those above mentioned.

The MAH will continue to review the safety of BNT162b2, including all reports of adverse experiences and will revise the product documents if an evaluation of the safety data yields significant new information.