PERIODIC SAFETY UPDATE REPORT #2
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (nucleoside modified) (BNT162b2)

ATC CODE: J07BX03[1]

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD)[2]: 19 DECEMBER 2020

EUROPEAN UNION REFERENCE DATE (EURD): 19 DECEMBER 2020

INTERVAL COVERED BY THIS REPORT:

19 JUNE 2021 through 18 DECEMBER 2021

DATE OF THIS REPORT: 18 FEBRUARY 2022

SIGNATURE:____________________**Date: 18 February 2022**

NAME AND CONTACT DETAILS OF THE QPPV:	
EU Qualified Person Worldwide Medical & Safety Pfizer srl Via Anna Maria Mozzoni 12 20152 Milan (Italy)	telephone: fax numbe email:
EU Qualified Person Deputy Worldwide Medical & Safety Pfizer srl Via Anna Maria Mozzoni 12 20152 Milan (Italy)	telephone: fax numbe email:

Marketing Authorisation Holder:
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

Please note that this report may contain unblinded clinical trial information.

The information contained in this document is proprietary and confidential. Any disclosure, reproduction, distribution, or other dissemination of this information outside of Pfizer and BioNTech, its Affiliates, its Licensees, or Regulatory Agencies is strictly prohibited. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor to use it for unauthorized purposes.

---

[1] Implementation as new ATC code starting from 01 January 2022.

[2] Earliest conditional approval date.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

EXECUTIVE SUMMARY

This is the 2nd Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (nucleoside modified) (Coronavirus disease 2019 [COVID-19] mRNA Vaccine, COMIRNATY®, also referred to as BNT162b2)[3], covering the reporting interval 19 June 2021 through 18 December 2021.

The active substance of the COVID-19 mRNA vaccine is a highly purified single-stranded, 5'-capped messenger ribonucleic acid (mRNA) produced using a cell-free *in vitro* transcription from the corresponding deoxyribonucleic acid (DNA) template, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

BNT162b2 is a white to off-white frozen solution, provided as

- Concentrate for dispersion for injection; PBS/Sucrose[4] presentation – Purple cap – 30 µg/dose as multidose vial and must be diluted before use. One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution. One dose (0.3 mL) contains 30 µg of BNT162b2 (embedded in lipid nanoparticles [LNPs]).

  The vaccine contains as excipients

  - (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, sucrose, water for injections,
  - potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate.
- Dispersion for injection; Tris/Sucrose[5] presentation – Grey cap – 30 µg/dose as multidose vial (not to be diluted before use). One vial (2.25 mL) contains 6 doses of 0.3 mL. One dose (0.3 mL) contains 30 µg of BNT162b2 (embedded in LNPs).

  The vaccine contains as excipients

  - ALC-0315,
  - ALC-0159,
  - DSPC,

---

[3] Also referred to as Pfizer-BioNTech COVID-19 vaccine in other Company's documents.

[4] This is the first formulation used since 19 December 2020 and approved for 12-year and older.

[5] The Tris/Sucrose (tromethamine) presentation for 12 years of age and older received the corrected CHMP' positive opinion on 14 October 2021 and EC decision on 03 November 2021. This presentation is not yet marketed as of 18 December 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- cholesterol, sucrose, water for injections,
- tromethamine, tromethamine hydrochloride.

- Concentrate for dispersion for injection; Tris/Sucrose[6] presentation – Orange cap – 10 µg/dose as multidose vial and must be diluted before use. One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution. One dose (0.2 mL) contains 10 µg of BNT162b2 (embedded in LNPs).

  The vaccine contains as excipients

  - ALC-0315,
  - ALC-0159,
  - DSPC,
  - cholesterol, sucrose, water for injections,
  - tromethamine, tromethamine hydrochloride.

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.

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.[6]

It is administered intramuscularly in the deltoid muscle.

- For individuals aged 12 years and older, the 2 formulations (PBS/Sucrose and Tris/Sucrose) are administered as 30 µg/dose intramuscularly as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose (third dose) may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.
  - PBS/Sucrose presentation – Purple cap: dilute before use.
  - Tris/Sucrose presentation – Grey cap: do not dilute before use.

- For individuals aged 5 through 11 years, the Tris/Sucrose formulation – Orange cap - is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.

[6] The Tris/Sucrose (tromethamine) paediatric presentation for 5 – 11 years received the CHMP' positive opinion on 25 November 2021 and EC corrigendum decision on 03 December 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Cumulatively, it is estimated that 61,098[7] participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with 54,755 participants exposed to BNT162b2, 1085 participants exposed to clinical candidates developed as variant vaccines based on BNT162b2 (BNT162b2 [B.1.351], BNT162b2 [B.1.1.7 + B.1.617.2], BNT162b2 [B.1.617.2] and BNT162b2 [B.1.1.7]) and 633 participants exposed to other early development candidates (including BNT162a1 [30], BNT162b1 [411] to, BNT162b3 and BNT162c2 [96 participants each]). There were 6469 participants exposed to blinded therapy and 3430 to placebo.

There were 372 participants who received BNT162b2 as a study drug or as a comparator in another Pfizer clinical development program (B747).[8]

From the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 December 2021, approximately 2,443,245,455 doses of BNT162b2 were shipped from BioNTech and Pfizer worldwide, corresponding to 2,100,134,815 estimated administered doses.

During the current reporting interval (19 June 2021 through 18 December 2021), approximately 1,661,566,580 doses of BNT162b2 were shipped from BioNTech and Pfizer worldwide, corresponding to 1,430,363,611 estimated administered doses.

Overall, through 18 December 2021, a total of 47,038,200 paediatric Tris/Sucrose doses were shipped worldwide.

Additionally, as per data provided by LP in Hong Kong, Macau, and Taiwan, 16,034,012 doses of BNT162b2 were administered cumulatively through 15 December 2021 and 14,203,352 were administered from 19 June 2021 through 15 December 2021.

Details about BNT162b2 marketing authorisation by type of formulation, and population include:

- The PBS 30 µg formulation in individuals aged 16 years and older has received approvals in 99 countries including full (3), conditional (48), EUA and other type of approvals (48).
- The PBS 30 µg formulation in individuals aged between 12 and 15 years has received approvals in 81 countries including full (3), conditional (46), EUA and other type of approvals (32).
- The Tris/Sucrose 30 µg formulation in individuals aged 12 years and older has received approvals in 52 countries including full (1), conditional (36), EUA and other type of approvals (15).

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

[8] In PSUR #1, 557 blinded therapy participants were exposed; the database was unblinded on 21 December 2021 and 187 participants who had received 20vPnC and Placebo are excluded from the calculation for the current reporting interval; 2 new participants received BNT162b2.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- The Tris/Sucrose 10 µg formulation in individuals aged between 5 and 11 years has received approvals in 59 countries including full (2), conditional (36), EUA and other type of approvals (21).
- The booster dose has received approvals in 66 countries including full (2), conditional (40), EUA and other type of approvals (24).

The use of BNT162b2 in individuals aged 12 years and older is under a special import permit in Macau, Hong Kong, and Taiwan. In these countries only the PBS formulation was is approved.

BioNTech is the MAH in 55 countries; Pfizer is the MAH in 40 countries, the local Ministry of Health (MoH) is the MAH in 3 countries, the LP Hemas and the local Government are the MAH in 1 country each.

In addition, WHO had approved the Emergency Use Listing (EUL) of BNT162b2.

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

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

- The EMA and other Health Authorities have requested updates to the labels as well as the distribution of a direct healthcare professional communication (DHPC) on 19 July 2021 to address findings on myocarditis and pericarditis cases following vaccination with BNT162b2.
- On 12 August 2021, Swissmedic requested a joint DHPC (Pfizer, Moderna) on myocarditis/pericarditis.
- On 08 December 2021, following the Brazilian Health Authority (ANVISA) request, a DHPC was issued to ensure that HCPs are aware of the risk for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use.

The reference safety information (RSI) for this PSUR is the COVID 19 mRNA vaccine Core Data Sheet (CDS) version 9.0 dated 02 December 2021, in effect at the end of the reporting period. Five previous CDS versions (19 May 2021 version 4.0, 14 July 2021 version 5.0, 11 August 2021 version 6.0, 08 September 2021 version 7.0, 19 October 2021 version 8.0) were also in effect during the reporting period. Safety-related changes included updates of the following sections: 4.2 Posology and method of administration (version 8.0), 4.4 Special warnings and precautions for use (version 5.0), 4.8 Undesirable effects (versions 7.0 and 8.0), 5.1 Pharmacodynamic properties (version 8.0), Appendix A, Appendix B (version 7.0 and 8.0).

During the reporting period, the following signals were addressed:

- Signals determined not to be risks:

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Appendicitis, Herpes Zoster including ophthalmic herpes zoster, Immune thrombocytopenia, Myasthenia gravis, Thrombocytopenia Thrombosis Syndrome (TTS), Erythema Multiforme, Glomerulonephritis and Nephrotic Syndrome, Hypoaesthesia / Paraesthesia, Rhabdomyolysis, Uveitis, Multisystem inflammatory syndrome (MIS) in adults (MIS-A) and children (MIS-C), Liver Injury/Autoimmune Hepatitis.

- Signals determined to be risks:

  Myocarditis and pericarditis.

- Ongoing signals:

  Vasculitis, Cerebral Venous Sinus Thrombosis (CVST).

Commitments to be addressed in this PSUR were received from EMA and WHO. The Pharmacovigilance Risk Assessment Committee (PRAC) requests were included in the Assessment Reports (ARs) of the Summary Monthly Safety Reports (SMSRs/MSSR), in the Final AR of PSUR #1 and in signals' AR. The WHO requests were included in the EUL Procedure. Topics covered in these commitments are summarized below:

HA	Commitment(s)
PRAC	Activities to manage all the AE reports received and prioritization of pregnancy cases among the unlocked cases.
	Observed vs Expected (O/E) sensitivity analysis to consider backlog cases and list of terms evaluated for Adverse Events of Special Interest (AESIs) background incidence estimate. Updated age stratified O/E analysis for herpes zoster.
	Use of follow-up questionnaire.
	Safety profile of homologous vaccination schedule when administered at time interval different from the recommended posology and safety profile of heterologous vaccination schedule.
	Safety evaluation of exacerbation of pre-existing autoimmune/anti-inflammatory disorders, chronic urticaria and polymyalgia rheumatica.
	Safety evaluation of glomerulonephritis, nephrotic syndrome, subacute thyroiditis, and MIS-C/A.
	Routine pharmacovigilance monitoring of erythema multiforme.
	Estimate of the exposure of "third doses" in EEA countries and by age group.
	Handling and dosing errors as result of different BNT162b2 formulations on the market.
WHO	Pregnancy outcome in CT.
	Data on LMICs populations with HIV, malnutrition and tuberculosis and other infectious diseases.

According to the European Risk Management Plan (EU-RMP) version 2.0 adopted on 31 May 2021, 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. During the reporting period, on 05 August 2021, the MAH submitted the 2.3 version of the EU-RMP including

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

myocarditis/pericarditis as important identified risk; this version received a positive CHMP opinion on 30 September 2021.

A summary of the EU-RMP versions and associated procedures, submitted during the reporting period, is summarized below. Version number of the EU-RMPs was agreed with EMA.

Procedure and description	Procedure submission date	Submitted EU-RMP[a]	Approval date
EMEA/H/C/005735/II/0036 PI update based on interim study C4591001 results for all participants ≥16 years of age and including participants with confirmed stable HIV disease	18 May 2021	• RMP v2.1: 18 May 2021 • Consolidated RMP v2.2 (v2.0 + v2.1): 29 July 2021	• CHMP opinion for v2.2: 16 September 2021 • EC decision: 23 September 2021
EMEA/H/C/005735/II/0059 RMP v2.3 update as outcome of myocarditis/pericarditis signal PAM-SDA-032 (EPITT ref. No. 19712)	05 August 2021	• RMP v2.3: 27 September 2021 (Eudralink)	• CHMP opinion: 30 September 2021
EMEA/H/C/005735/X/0044 Line extension Tris/Sucrose Adult (0.1 mg/ml dispersion for injection)	17 June 2021 (CMC) 21 September 2021 (Clinical)	• RMP v2.4: 21 September 2021 • Consolidated RMP v2.5 (v2.3 + v2.4): 12 November 2021	• CHMP opinion (corrected): 14 October 2021 • EC decision: 03 November 2021
EMEA/H/C/005735/X/0077 Line extension 5-11 years old Tris/Sucrose Paediatrics (0.1 mg/ml Concentrate for dispersion for injection)	15 October 2021	• RMP v3.0: 15 October 2021 • Consolidated RMP v3.1 (v2.5 + v3.0 including study C4591007 as SOB and changed CSR due date for study C4591001: 25 November 2021 (Eudralink) • Up-versioned RMP v4.0: 26 November 2021 (Eudralink) and on 15 December 2021 (Gateway)	• CHMP opinion: 25 November 2021 • EC corrigendum decision: 03 December 2021
EMEA/H/C/005735/II/0087 • RMP version 2.6 update related to procedures EMEA/H/C/005735/II/0062 (third booster) and EMEA/H/C/005735/II/0067 (booster in immunocompromised) • discontinuation of enrolment in study C4591015 (PAM-MEA-012)	15 November 2021	• RMP v2.6: 15 November 2021	RSI: 13 January 2022

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Procedure and description	Procedure submission date	Submitted EU-RMP[a]	Approval date

a. The submission of the EU-RMP v3.0 for line-extension to 5-11 years of age had higher priority respect the EU-RMP v2.6 in agreement with EMA.

After DLP, an updated COVID-19 mRNA Vaccine CDS that was made effective on 21 December 2021 for the addition of the Booster Dose Study C4591031 information. The overall safety profile for the booster dose was similar to that seen after 2 doses. A higher frequency of lymphadenopathy was observed in participants receiving a booster dose in C4591031 (2.8%) compared to participants receiving 2 doses (0.4%).

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 MAH has updated the benefit-risk profile of BNT162b2 which remains favourable. No additional changes to the BNT162b2 RSI or additional risk minimisation activities are warranted in addition to those above mentioned.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

TABLE OF CONTENTS

EXECUTIVE SUMMARY 2
LIST OF TABLES 13
LIST OF FIGURES 17
APPENDICES 18
LIST OF ABBREVIATIONS 20
1. INTRODUCTION 25
2. WORLDWIDE MARKETING APPROVAL STATUS 26
3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS 27
4. CHANGES TO REFERENCE SAFETY INFORMATION 27
5. ESTIMATED EXPOSURE AND USE PATTERNS 28
5.1. Cumulative Subject Exposure in Clinical Trials 28
5.2. Cumulative and Interval Patient Exposure from Marketing Experience 29
6. DATA IN SUMMARY TABULATIONS 36
6.1. Reference Information 36
6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials 36
6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources 36
6.3.1. General Overview 37
6.3.1.1. General Overview of the Safety Database – All Cases 40
6.3.1.2. General Overview of the Safety Database - Unlocked Cases 76
7. SUMMARIES OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL 78
7.1. Completed Clinical Trials 78
7.2. Ongoing Clinical Trials 79
7.3. Long-term Follow-up 80
7.4. Other Therapeutic Use of Medicinal Product 81
7.5. New Safety Data Related to Fixed Combination Therapies 81
8. FINDINGS FROM NON-INTERVENTIONAL STUDIES 81
9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES 82
9.1. Other Clinical Trials 82
9.2. Medication Errors 82

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

10. NON-CLINICAL DATA 94
11. LITERATURE 94
12. OTHER PERIODIC REPORTS 94
13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS 95
14. LATE-BREAKING INFORMATION 95
15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED 95
15.1. Exacerbation (flare-up) of pre-existing AI/Inflammatory Disorders 97
15.2. Pregnancy and Lactation 98
15.3. Chronic Urticaria/Worsening of Pre-Existing Chronic Urticaria 99
15.4. Polymyalgia Rheumatica and Exacerbation or Flare-up 99
15.5. Subacute Thyroiditis 100
15.6. Glomerulonephritis and Nephrotic Syndrome 100
15.7. Multisystem Inflammatory Syndrome in Children and Adult 101
15.8. Erythema Multiforme 102
16. SIGNAL AND RISK EVALUATION 102
16.1. Summary of Safety Concerns 102
16.2. Signal Evaluation 103
16.2.1. Evaluation of Closed Signals 103
16.2.1.1. Evaluation of Closed Signals During the Reporting Interval Assessed under any Regulatory Procedure 103
16.2.1.2. Evaluation of Closed Signals During the Reporting Interval not Assessed as part of any Regulatory Procedure 111
16.2.2. Signal Evaluation Plan for Ongoing Signals 111
16.3. Evaluation of Risks and New Information 111
16.3.1. Evaluation of Important Identified Risks 111
16.3.1.1. Important Identified Risks – Anaphylaxis 111
16.3.1.2. Important Identified Risks – Myocarditis and Pericarditis 115
16.3.2. Evaluation of Important Potential Risks 160
16.3.3. Evaluation of Other Risks (not categorised as important) 166
16.3.3.1. Adverse Events of Special Interest (AESIs) 166
16.3.3.2. Clinical Reactogenicity Data on Individuals Previously exposed or not to SARS-COV-2 222
16.3.3.3. Local Adverse Reactions 223

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16.3.3.4. Systemic Adverse Reactions 226
16.3.3.5. Severe Reactogenicity 235
16.3.3.6. Age-Related Adverse Reactions 237
16.3.3.7. Vaccination Stress/Anxiety related ADRs 243
16.3.4. Evaluation of Special Situations 246
16.3.4.1. Death 246
16.3.4.2. Overdose 255
16.3.4.3. Abuse, Misuse, and Drug Dependency 257
16.3.4.4. Occupational Exposure 260
16.3.4.5. Lack of Therapeutic Efficacy 261
16.3.4.6. Off-Label Use 268
16.3.4.7. Unexpected Therapeutic Effect 270
16.3.5. Update on Special Patient Populations 272
16.3.5.1. Use in Elderly Patients 272
16.3.5.2. Use in Paediatric Patients 275
16.3.5.3. Use in Pregnant/Lactating Women 287
16.3.5.4. Use in Patients with Comorbidities 300
16.3.5.5. Use in Immunocompromised Patients 302
16.3.5.6. Use in Patients with Autoimmune or Inflammatory Disorders 306
16.3.5.7. Use in Frail Patients with Comorbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis) 310
16.3.5.8. Interactions with other Vaccines 314
16.4. Characterisation of Risks 316
16.4.1. Characterisation of Important Identified and Potential Risks 316
16.4.2. Description of Missing Information 323
16.5. Effectiveness of Risk Minimisation (if applicable) 324
17. BENEFIT EVALUATION 324
17.1. Important Baseline Efficacy and Effectiveness Information 324
17.2. Newly Identified Information on Efficacy and Effectiveness 333
17.3. Characterisation of Benefits 341
18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS 342

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

18.1. Benefit-Risk Context – Medical Need and Important Alternatives 342
18.2. Benefit-Risk Analysis Evaluation 349
18.2.1. Benefits 350
18.2.2. Risks 350
18.2.3. Overall Benefit-Risk 352
19. CONCLUSION AND ACTIONS 352

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

LIST OF TABLES

Table 1. List of PSURs 26
Table 2. Regulatory Actions Taken During the Reporting Period for Safety Reasons 27
Table 3. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide 30
Table 4. Cumulative Administered Doses of BNT162b2 – License Partner Data 31
Table 5. Interval Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide 32
Table 6. Interval Administered Doses of BNT162b2 – License Partner Data 32
Table 7. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Dose Number 33
Table 8. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Country 34
Table 9. Japan - Cumulative Number of BNT162b2 Administered Doses 35
Table 10. US - Cumulative Number of BNT162b2 Administered Doses 35
Table 11. EU/EEA – Interval Number of BNT162b2 Administered Doses by Age Group and Dose Number 36
Table 12. Demographic Information - All Cases Received during the Reporting Interval 41
Table 13. Clinical Trial Data: Medical History and Co-Suspects 47
Table 14. Clinical Trial Data: Serious Events Reported in ≥2% Cases 49
Table 15. Post-Authorisation Data: Medical History and Co-Suspects 54
Table 16. Post-Authorisation Data: Events Reported in ≥2% Cases 55
Table 17. Demographic Information – Tris/Sucrose Cases – Orange Cap Received during the Reporting Interval 65
Table 18. Demographic Information – Comparison of Paediatric Tris/Sucrose versus Paediatric PBS/Sucrose Cases 66
Table 19. Events Reported in ≥2%* Cases - Comparison of Paediatric Tris/Sucrose – Orange Cap versus PBS/Sucrose Cases – Purple Cap 66
Table 20. Comparison of clinical AEs reported in ≥2% Booster Dose or Third Dose Cases vs Primary Series Cases 74
Table 21. Most Frequently Reported Lot Numbers 75
Table 22. Demographic Information - Unlocked Cases at the End of the Reporting Interval 76
Table 23. Post-Authorisation Data: Events Reported in ≥2% of Unlocked Cases 77
Table 24. Overview of Signals 96

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 25. Ongoing Safety Concerns 102
Table 26. Signal Evaluation Plan for Ongoing Signals 111
Table 27. Myocarditis in Subjects aged 5 – 11 Years (N=10)....119
Table 28. Myocarditis in Subjects aged 12 – 15 Years (N=488)....121
Table 29. Myocarditis in Subjects aged 16 – 17 Years (N=470)....123
Table 30. Myocarditis in Subjects aged 18 – 24 Years (N=1187)....125
Table 31. Myocarditis in Subjects aged 25 – 29 Years (N=589)....127
Table 32. Myocarditis in Subjects aged 30 – 39 Years (N=995)....129
Table 33. Myocarditis in Subjects aged ≥40 Years (N=1876) 131
Table 34. Myocarditis in Subjects of Unknown Age (N=732)....133
Table 35. Myocarditis in Subjects who Received a Booster dose....135
Table 36. Pericarditis in Subjects aged 5-11 years (N=4) 140
Table 37. Pericarditis in Subjects aged 12-15 years (N=215) 141
Table 38. Pericarditis in Subjects aged 16-17 years (N=174) 142
Table 39. Pericarditis in Subjects aged 18-24 years (N=659) 144
Table 40. Pericarditis in Subjects aged 25-29 years (N=614) 145
Table 41. Pericarditis in Subjects aged 30-39 years (N=1222) 148
Table 42. Pericarditis in Subjects aged ≥ 40 years (N=2059) 152
Table 43. Pericarditis in Subjects with Unknown Age (N=363)....153
Table 44. Pericarditis in Subjects who Received a Booster dose....155
Table 45. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome....229
Table 46. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome 231
Table 47. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome 233
Table 48. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups....239
Table 49. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups....239
Table 50. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups....239

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 51. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups 241

Table 52. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups 241

Table 53. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups 242

Table 54. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval 252

Table 55. Post-Authorisation- Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group during the Reporting Interval 252

Table 56. Clinical Trial Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval 254

Table 57. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval 254

Table 58. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval 291

Table 59. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval 294

Table 60. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval 298

Table 61. Characterisation of Important Risks 317

Table 62. Description of Missing Information 323

Table 63. 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 325

Table 64. 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 326

Table 65. 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 328

Table 66. 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 330

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 67. 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 332

Table 68. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through 11 Years of Age Evaluable Efficacy Population 336

Table 69. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through Less Than 12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population 337

Table 70. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population 338

Table 71. Incidence, Prevalence, and Mortality of COVID-19 as of 16 January 2022....343

Table 72. Summary of Important Risks 351

Table 73. Overall Benefit-Risk for BNT162b2 352

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

LIST OF FIGURES

Figure 1. Clinical Trial Data: Number of SAEs by Age Group and Gender 43
Figure 2. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities 44
Figure 3. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities and Gender....................45
Figure 4. Clinical Trial Data: Case Outcome by Age Group in Presence of Comorbidities 46
Figure 5. Clinical Trial Data: Case Outcome by Age Group in Absence of Comorbidities 47
Figure 6. Post-Authorisation Data: Number of Cases by Age Group and Gender 50
Figure 7. Post-Authorisation Data: Case Outcome by Presence/Absence of Comorbidities 51
Figure 8. Post-Authorisation Data: Case Outcome by Presence/Absence of Comorbidities and Gender....................52
Figure 9. Post-Authorisation Data: Case Outcome by Age Group in Presence of Comorbidities 53
Figure 10. Post-Authorisation Data: Case Outcome by Age Group in Absence of Comorbidities 54
Figure 11. Post-Authorisation Data: Event Seriousness of the PTs ≥2% of Cases................57
Figure 12. Post-Authorisation Data: Clinical AEs reported in ≥2 % of Cases by Age Group 58
Figure 13. Events Reported in ≥2% of All Clinical Trial Cases by Age Group 240
Figure 14. Events Reported in ≥ 2% of All Post-marketing Cases by Age Group 242

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

APPENDICES

APPENDIX 1 REFERENCE INFORMATION (02 DECEMBER 2021) 353
APPENDIX 1.1 SAFETY RELATED CHANGES TO RSI 417
APPENDIX 1.2 CORE DATA SHEET (19 MAY 2021)...435
APPENDIX 1.3 CORE DATA SHEET (14 JULY 2021) 476
APPENDIX 1.4 CORE DATA SHEET (11 AUGUST 2021)...518
APPENDIX 1.5 CORE DATA SHEET (08 SEPTEMBER 2021).......................................560
APPENDIX 1.6 CORE DATA SHEET (19 OCTOBER 2021) 607
APPENDIX 2.1 CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS 671
APPENDIX 2.1.1 CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS FROM NON-PFIZER (LICENSING PARTNER) CLINICAL TRIALS 710
APPENDIX 2.2 CUMULATIVE AND INTERVAL SUMMARY TABULATION OF SERIOUS AND NON-SERIOUS ADVERSE REACTIONS FROM POST-MARKETING DATA SOURCES 714
APPENDIX 2.3 CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA 1051
APPENDIX 2.3B CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM BIONTECH DEVELOPMENT PROGRAMS 1053
APPENDIX 2.3C CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM FOSUN DEVELOPMENT PROGRAMS 1054
APPENDIX 2.3.1 CUMULATIVE CLINICAL TRIAL EXPOSURE WITH DEMOGRAPHIC DATA FROM OTHER PFIZER DEVELOPMENT PROGRAMS 1055
APPENDIX 3 TABULAR SUMMARY OF SAFETY SIGNALS 1056
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 1078
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 1080
APPENDIX 5 LIST OF SOURCES OF INFORMATION USED TO PREPARE THE PSUR (LITERATURE ABSTRACTS) 1085
APPENDIX 6A LIST OF REGULATORY AUTHORITIES REQUEST(S).....................1136

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

APPENDIX 6A.1 EXACERBATION (FLARE-UP) OF PRE-EXISTING AI/INFLAMMATORY DISORDERS 1170
APPENDIX 6A.2 CHRONIC URTICARIA/WORSENING OF PRE-EXISTING CHRONIC URTICARIA....1213
APPENDIX 6A.3 POLYMYALGIA RHEUMATICA CUMULATIVE REVIEW....1224
APPENDIX 6A.4 GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME CUMULATIVE REVIEW 1282
APPENDIX 6A.5 MIS-C / MIS-A 1299
APPENDIX 6B OBSERVED VERSUS EXPECTED ANALYSES FOR ADVERSE EVENTS OF SPECIAL INTEREST....1309
APPENDIX 6C.1 INTERVAL SUMMARY TABULATION OF FATAL REPORTS....1354
APPENDIX 6C.2 CUMULATIVE SUMMARY TABULATION OF FATAL REPORTS....1406
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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

LIST OF ABBREVIATIONS

Abbreviation	Term
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
AI	auto-immune
AIIRD	autoimmune inflammatory rheumatoid diseases
ALC-0315	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ANVISA	Agência Nacional de Vigilância Sanitária (Brazilian Health Regulatory Agency)
AR	assessment report
ARDS	acute respiratory distress syndrome
aRR	adjusted relative risk
AT	Austria
ATC	anatomical therapeutic chemical
BC	Brighton Collaboration
BE	Belgium
BG	Bulgaria
BMI	body mass index
CAR-T	chimeric antigen receptor T
CD	cluster of differentiation
CDC	Centres for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CMI	Charlson comorbidity index
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
COVID-19 vaccine mRNA (mRNA 1273)	Spikevax COVID-19 Moderna vaccine
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial
CTD	connective tissues disease
CU	chronic urticaria
CVST	cerebral venous sinus thrombosis
CY	Cyprus

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Abbreviation	Term
CZ	Czechia
DE	Germany
DHPC	direct healthcare professional communication
DK	Denmark
DLCO	diffusing capacity of the lungs for carbon monoxide
DLP	data lock point
DMTs	disease-modifying therapies
DNA	deoxyribonucleic acid
DR	Democratic Republic
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
D2	Dose 2
EC	European Commission
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EE	Estonia
EEA	European economic area
EIU	exposure in utero
EL	Greece
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMG	electromyogram
EPITT	European pharmacovigilance issues tracking tool
ES	Spain
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	emergency use authorization
EUL	emergency use listing
EURD	European Union reference dates
F	female
FAR	final assessment report
FDA	Food and Drug Administration
FI	Finland
FR	France
GBS	Guillan-Barrè syndrome
GC	glucocorticoids
GMR	geometric mean ratio
GMT	geometric mean titers
GVHD	graft versus host disease
GVP	Good pharmacovigilance practices
HA	Health Authority
HCP	healthcare professional
HBV	hepatitis B virus
HCV	hepatitis C virus

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Abbreviation	Term
HCT	haematopoietic stem cell transplantation
HIV	human immunodeficiency virus
HLGT	(MedDRA) high level group term
HLT	(MedDRA) high level term
HR	Croatia
HU	Hungary
HZ	herpes zoster
IBD	International Birth Date
ICH	International Council on Harmonisation
ICSR	individual case safety report
ICU	Intensive care unit
IE	Ireland
Ig	immunoglobulin
IRR	incidence rate ratio
IS	Iceland
IT	Italy
JIA	juvenile idiopathic arthritis
COVID-19 J&J vaccine	Janssen COVID-19 Vaccine
JST	Japan Science and Technology
LFT	liver function test
LI	Liechtenstein
LLOQ	lower limit of quantitation
LMIC	low- and middle-income countries
LNP	lipid nanoparticles
LOE	lack of efficacy
LP	license partner
LT	Lithuania
LU	Luxembourg
LV	Latvia
M	male
MAH	marketing authorisation holder
MC	medically confirmed
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	middle East respiratory syndrome coronavirus
MHRA	(UK) Medicines and Healthcare products Regulatory Agency
MIS	multisystem inflammatory syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MG	myasthenia gravis
MMF	mycophenolate mofetil
mod	modified
MoH	ministry of health

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Abbreviation	Term
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSSR/SMSR	summary monthly safety report
MT	Malta
NAAT	nucleic acid amplification test
NEC	not elsewhere classified
NICE	National Institute for Health and Care Excellence
NL	Netherlands
NMC	non-medically confirmed
NO	Norway
NT50	50% neutralizing titer 50
O/E	observed versus expected
PASS	post-authorisation safety study
PBS	phosphate buffered saline
PC	product complaint
PCR	polymerase chain reaction
PEG	polyethylene glycol
PF4	platelet factor 4
PhV	pharmacovigilance
PL	Poland
PM	post-marketing
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	polymyalgia rheumatica
PBS	phosphate buffered saline
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	(MedDRA) Preferred Term, Portugal
PVP	pharmacovigilance plan
PWE	patients with epilepsy
QPPV	qualified person for pharmacovigilance
RA	rheumatoid arthritis
RBD	receptor binding domain
RMP	risk management plan
RO	Romania
ROW	rest of world
RNA	ribonucleic acid
RSI	reference safety information
RSV	respiratory syncytial virus
RT-PCR	reverse transcription-polymerase chain reaction
RVE	relative vaccine efficacy
S	spike
SAE	serious adverse event

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Abbreviation	Term
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBSR	summary bimonthly safety report
SE	Sweden
SI	Slovenia
SK	Slovakia
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SOB	specific obligations
SOC	(MedDRA) system organ class
SOT	solid organ transplantation
SPEAC	Safety Platform for Emergency vACcines
Th1	T helper cell type 1
Th2	T helper cell type 2
TGA	Therapeutic Goods Administration
TME	targeted medical event
TTO	time to onset
TTS	thrombocytopenia thrombosis syndrome
U	unknown
UK	United Kingdom
US	United States
USG	United States Government
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
VSD	Vaccine Safety Datalink
WHO	World Health Organization

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

1. INTRODUCTION

This is the 2nd Periodic Safety Update Report (PSUR) for COVID-19 mRNA vaccine (nucleoside modified) (Coronavirus disease 2019 [COVID-19] mRNA Vaccine, COMIRNATY®, also referred to as BNT162b2),[3] covering the reporting interval 19 June 2021 through 18 December 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 highly purified single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral S protein of SARS-CoV-2. The nucleoside-modified mRNA is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19.

All the BNT162b2 formulations contain: ALC-0315, ALC-0159, DSPC, cholesterol, sucrose and water for injections.

The PBS/Sucrose formulation includes additionally potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, as excipients. The Tris/Sucrose formulation includes additionally tromethamine, tromethamine hydrochloride as excipients.

BNT162b2 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older. It is administered intramuscularly in the deltoid muscle.

- For individuals aged 12 years and older, the 2 formulations (PBS/Sucrose and Tris/Sucrose) are administered as 30 µg/dose intramuscularly as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose (third dose) may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.
  - PBS/Sucrose presentation – Purple cap: dilute before use.
  - Tris/Sucrose presentation – Grey cap: do not dilute before use.
- For individuals aged 5 through 11 years, the Tris/Sucrose formulation – Orange cap - is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.

The list of the PSURs prepared for BNT162b2 is presented in Table 1.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 1. List of PSURs

PSUR Number	Reporting Period
1	19 December 2020 Through 18 June 2021

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 temporary authorisation for emergency supply under Regulation 174 in the UK[9] on 01 December 2020.

BNT162b2 received first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020.

BNT162b2 is authorised for the following formulations:

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

BioNTech is the MAH in 55 countries; Pfizer is the MAH in 40 countries, the local MoH is the MAH in 3 countries, the LP Hemas and the local Government are the MAH in 1 country each.

In addition, WHO had approved the EUL of BNT162b2.

[9] 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 authorisation approval are currently active.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

The use of BNT162b2 in individuals aged 12 years and older is under a special import permit in Hong Kong, Macau, and Taiwan. In these countries only the PBS/Sucrose – Purple cap formulation was approved.

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

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

Table 2 summarises the actions taken for safety reasons during the reporting interval.

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

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

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

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID 19 mRNA vaccine CDS version 9.0 dated 02 December 2021, in effect at the end of the reporting period and included in Appendix 1. The 5 previous CDS versions (19 May 2021 version 4.0, 14 July 2021 version 5.0, 11 August 2021 version 6.0, 08 September 2021 version 7.0, 19 October 2021 version 8.0), which were also in effect during the reporting period, are included in Appendix 1.2 through Appendix 1.6. Safety-related changes included updates of the following sections: 4.2 Posology and method of administration (version 8.0), 4.4 Special warnings and precautions for use (version 5.0), 4.8 Undesirable effects (versions 7.0 and 8.0), 5.1 Pharmacodynamic properties (version 8.0), Appendix A, Appendix B (version 7.0 and 8.0).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 61,098[7] participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

- BNT162b2: 54,755 participants of which
  - 27,814 had received BNT162b2;
  - 25,110 had received BNT162b2 post-unblinding and had received placebo before;
  - 959 had received BNT162b2/placebo;
  - 872 had received BNT162b2 and blinded booster.
- Variant vaccines based on BNT162b2: 1085 participants of which
  - 374 had received BNT162b2 (B.1.351)[10];
  - 392 had received BNT162b2 (B.1.617.2);
  - 299 had received BNT162b2 (B.1.1.7 + B.1.617.2);
  - 20 had received BNT162b2 (B.1.1.7).
- Early development candidates: 633 participants of which
  - 30 had received BNT162a1;
  - 411 had received BNT162b1;
  - 96 had received BNT162b3;
  - 96 had received BNT162c2.
- Blinded therapy: 6469 participants.
- Placebo: 3430 participants.

Participant 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 utilised in another Pfizer clinical development program (B747): 372 participants[8] received BNT162b2 as a study vaccine or as a comparator in the

[10] BNT162b2 (B.1.351), which is also referred as BNT162b2s01 and $BNT162b2_{SA}$.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

clinical study B7471026[11]. Participant demographics data (eg, age, gender, race) by treatment groups are presented in Appendix 2.3.1.

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

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

- EMEA/H/C/005735/MEA/002.8 (9th SMSR), "*The MAH should provide an estimate of the exposure of "third doses" in future PSURs separately (reporting period and cumulatively), if applicable.*", and
- EMEA/H/C/005735/MEA/002.10 (11th SMSR), "2. *The MAH is requested to report the total number of administered Comirnaty dose 3 in the EU/EEA, per country, and by age group.*"

Response

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

The total number of the BNT162b2 third doses administered, downloaded from the HA's websites (EMA, PMDA and FDA) is provided in Table 7 through Table 11. Details for the cumulative number of third doses administered by age group cumulatively and during the interval period in the EU/EEA countries are shown in Table 7 and in Table 11.

Cumulative exposure – MAH and LP Data

The worldwide number of shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 86% of the shipped doses were administered. This ratio represents the proportion of doses cumulatively administered (as per public available

[11] A phase 3, randomised, 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

data for the EEA[12] countries and the US[13]) out of those cumulatively shipped (based on MAH data, according to the shipment tracker [Order Book][14]).

With these caveats in mind, it is estimated that:

- approximately 2,443,245,455 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 December 2021, corresponding to 2,100,134,815 estimated administered doses.
- approximately 1,661,566,580 doses of BNT162b2 were shipped worldwide during the current reporting interval from 19 June 2021 through 18 December 2021, corresponding to 1,430,363,611 estimated administered doses.[15]
- overall, through 18 December 2021, a total of 47,038,200 paediatric Tris/Sucrose doses were shipped worldwide.

Cumulative worldwide estimated exposure by dose and region based on or extrapolated from internal data (number of shipped doses) is displayed in Table 3.

Table 3. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide

Region/Country	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	34.8	**849861180**	**748038353**
European Union (27)	24.6	601128915	534009280
European Economic Area Countries (3)	0.4	8675175	7706540
Other Countries[a]	9.8	240057090	206322533
North America	17.1	**418517795**	**342330709**
US	14.9	363479395	295026702
Canada	2.3	55038400	47304006
Central and South America[b]	14.7	**360146940**	**309536490**
Asia	26.6	649874940	558549818
Japan	8.1	198815760	170876733

[12] Approximately 89% 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 17 December 2021.

[13] Approximately 81% 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 18 December 2021.

[14] 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.

[15] License Partner data are not included in the reported amount.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 3. Cumulative Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide

Region/Country	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Other Countries[c]	18.5	451059180	387673085
Oceania	2.0	**48221340**	**41444929**
Australia/New Zealand	2.0	48120720	41358449
Other Countries[d]	0.0	100620	86480
Africa[e]	4.8	**116623260**	**100234517**
Total	**100.0**	**2443245455**	**2100134815**

a. Includes the non-EU countries (Albania, Andorra, Bosnia, Kosovo, Montenegro, North Macedonia, Serbia, Turkey and Vatican City) and the Commonwealth of Independent States (Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Ukraine and Uzbekistan).
b. Includes Antigua & Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St Kitts & Nevis, St. Lucia, StVin & Grenadine, Suriname, Trinidad & Tobago and Uruguay.
c. Includes Bahrain, Bangladesh, Bhutan, Brunei, Indonesia, Iraq, Israel, Jordan, Korea, Kuwait, Laos, Lebanon, Malaysia, Maldives, Mongolia, Nepal, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, Thailand, Timor-Leste, United Arab Emirates and Vietnam.
d. Includes Solomon Islands.
e. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Chad, Congo, DR Congo, Egypt, Eswatini, Ethiopia, Gabon, Ghana, Guinea, Ivory Coast, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda and Zambia.

Out of the cumulative estimated shipped and administered doses, 1,271,146,210 and 1,092,515,560 respectively, were shipped to ROW (Non--EEA countries, Canada, Central and South America, Asian countries [excluding Japan], Oceania and Africa).

Cumulative LP (Fosun) data on the number of BNT162b2 doses administered in Hong Kong, Macau and Taiwan is provided in Table 4.

Table 4. Cumulative Administered Doses of BNT162b2 – License Partner Data[a]

Region/Country	Total Number of Administered Doses
Asia	**16034012**
Hong Kong[b]	6093002
Macau[c]	165058
Taiwan[c]	9775952

a. Cumulative through 15 December 2021.
b. Conditional Authorisation under legislation 599K.
c. Special Import Permit.

Interval exposure – MAH and LP Data

Interval worldwide estimated exposure by dose, and region based on or extrapolated from internal data (number of shipped doses) is displayed in Table 5.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 5. Interval Estimated Shipped and Administered Doses of BNT162b2 by Region Worldwide

Region/Country	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	31.2	**517768380**	**454824798**
European Union (27)	20.2	334910040	297515333
European Economic Area Countries (3)	0.3	5115840	4544626
Other Countries[a]	10.7	177742500	152764840
North America	11.3	**187511900**	**153636773**
US	9.5	157421800	127775151
Canada	1.8	30090100	25861622
Central and South America[b]	18.2	**302502210**	**259992414**
Asia	30.1	**500937840**	**430542435**
Japan	6.3	104645970	89940362
Other Countries[c]	23.9	396291870	340602073
Oceania	2.6	**42539820**	**36561817**
Australia/New Zealand	2.6	42439200	36475337
Other Countries[d]	0.0	100620	86480
Africa[e]	6.6	**110306430**	**94805373**
Total	**100.0**	**1661566580[f]**	**1430363611**

a. Includes the non-EU countries (Albania, Andorra, Bosnia, Kosovo, Montenegro, North Macedonia, Serbia, Turkey, and Vatican City) and the Commonwealth of Independent States (Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Ukraine and Uzbekistan).
b. Includes Antigua & Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St Kitts & Nevis, St. Lucia, St Vin & Grenadine, Suriname, Trinidad & Tobago, and Uruguay.
c. Includes Bahrain, Bangladesh, Bhutan, Brunei, Indonesia, Iraq, Israel, Jordan, Korea, Kuwait, Laos, Lebanon, Malaysia, Maldives, Mongolia, Nepal, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, Thailand, Timor-Leste, United Arab Emirates and Vietnam.
d. Includes Solomon Islands.
e. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Chad, Congo, DR Congo, Egypt, Eswatini, Ethiopia, Gabon, Ghana, Guinea, Ivory Coast, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda, and Zambia.
f. Out of these shipped doses, 27,071,460 doses were shipped for COVAX, 190,716,900 doses were shipped for USG Donation program and 7,420,140 doses were shipped for EC Donation program.

During the reporting interval, out of the estimated shipped and administered doses, 1,059,472,930 and 910,588,139 respectively, were shipped and administered to the ROW.

Interval LP (Fosun) data on the number of BNT162b2 doses administered in Hong Kong, Macau and Taiwan is provided in Table 6.

Table 6. Interval Administered Doses of BNT162b2 – License Partner Data[a]

Region/Country	Total Number of Administered Doses
Asia	**14203352**
Hong Kong[b]	4302577
Macau[c]	124823

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 6. Interval Administered Doses of BNT162b2 – License Partner Data[a]

Region/Country	Total Number of Administered Doses
Taiwan[c]	9775952

a. 19 June 2021 through 15 December 2021.
b. Conditional Authorisation under legislation 599K.
c. Special Import Permit.

Cumulative exposure – Health Authority Public Data

Cumulative data about the number of COMIRNATY® doses administered are published for EEA, Japan, and US in the respective Health Authorities' websites; these data are provided in Table 7 through Table 10.

Table 7 displays the EEA published data with number of doses administered for each age group and by dose number.

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

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

a. Data from 19 countries.
b. Data from 12 countries.
c. Data from 15 countries.
d. Data from 16 countries.
e. Data from 17 countries.
f. Data from 26 countries.
g. Data from 30 countries.
Cumulative period up to week 50, 20 December 2021- as of 17 December 2021
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea

Table 8 provides, as per EMEA/H/C/005735/MEA/002.10 (11th SMSR) commitment, the cumulative total number of administered Comirnaty dose 3 in the EU/EEA, per country, and by age group.

.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 8. EU/EEA – Cumulative Number of BNT162b2 Administered Doses by Age Group and Country

Age Group →	<18 years	18 - 24 years	25 – 49 years	50 – 59 years	60 – 69 years	70 – 79 years	≥80 years	Age Unknown	ALL
Countries ↓									
AT	19592	167407	945814	622236	598376	480515	378439		3192787
BE	7035	78936	497462	473567	756128	715090	498612	0	3019795
BG	0	1687	30605	31570	56354	52028	15035	0	187279
CY	-	1984	58826	39501	45367	45314	24517		215509
CZ	423	12677	213355	206440	487242	537303	244928		1701945
DE	-	-	-	-	-	-	-		17882039
DK	-	18215	298610	372807	416092	487596	221851		1815800
EE	176	4022	43512	35036	51678	50962	35302	0	220512
EL	107	43142	503199	467459	603044	593164	420655	0	2630663
ES	2219	6385	60483	54716	66126	2428927	1989952	0	4606589
FI	590	4804	67251	67460	139750	225475	194929	0	699669
FR	-	-	-	-	-	-	-		15477845
HR	95	2519	44195	46501	97943	103331	53559	2	348048
HU	4365	87137	743774	427939	629434	537068	225976	0	2651328
IE	4222	40210	302499	258749	314225	311536	165080	4	1392299
IS	-	11324	52163	24643	20842	20962	10238	0	139949
IT	5744	152400	1533248	1471255	1604977	1581766	2459283		8802929
LI	-	-	-	-	-	-	-		4267
LT	192	16042	120678	77643	110103	100263	58436	1	483165
LU		5201	17711	10910	19049	12908	17458		83237
LV	1588	3598	25540	12675	12864	7680	3523	0	65880
MT	63	2018	13306	14678	28869	28735	14378	0	101984
NL	0	-	-	-	-	-	-		998957
NO	0	15296	141613	128254	285703	363251	193803		1127920
PL	-	65953	944393	920235	1592554	1501993	653608	3934	5678736
PT	-	18633	198553	180603	497226	736791	565450	2	2197256
RO	3106	38380	280763	184220	231271	143120	46428		924182
SE	-	17551	154363	154622	508030	640464	351722		1826752
SI	116	5285	60514	60441	97313	86006	54381		363940
SK	-	12170	149210	93082	216309	179461	63521	0	713753

Table 9 shows the cumulative number of BNT162b2 dose administered in Japan.

Table 9. Japan - Cumulative Number of BNT162b2 Administered Doses

	Dose Number		
	1st Dose	2nd Dose	3rd Dose
General population[a]	77539045	76719180	NA
Elderly	31977259	31841627	NA
Medical workers[b]	6378205	5709228	203502
All	**83917250**	**82428408**	**203502**

a. Including elderly.
b. Vaccinations for medical workers (1st and 2nd dose) was completed as of 02 August 2021.
Source: Government's website where this data was downloaded:
https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html Download Date: December 22, 2021, 10:00 a.m. [JST]

Table 10 shows the cumulative number of BNT162b2 doses administered in the US.

Table 10. US - Cumulative Number of BNT162b2 Administered Doses

Population	No. of Doses
All	286210683
Fully vaccinated (2 doses)	114237781
With a booster dose	31367565
- Booster dose with BNT162b2 after primary series with BNT162b2 (Homologous Dose Schedule)	26790457
- Booster dose with BNT162b2 after primary series with Moderna (Heterologous Dose Schedule)	1531288
- Booster dose with BNT162b2 after primary series with J&J (Heterologous Dose Schedule)	907712
- Booster dose with BNT162b2 after primary series with other COVID-19 vaccines (Heterologous Dose Schedule)[a]	55009
- Booster dose with BNT162b2 after primary series with unknown COVID-19 vaccines (Heterologous Dose Schedule)	2083099

a. Not BNT162b2, Moderna or J&J vaccine
Source https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 18 December 2021.

Interval exposure – Health Authority Public Data

Interval data about the number of COMIRNATY® doses administered are available only for the EEA countries.

Table 11 displays, as per EMEA/H/C/005735/MEA/002.10 (11th SMSR) commitment, the interval data with number of doses administered for each age group and by dose number in the EEA countries.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

a. Data from 19 countries.
b. Data from 12 countries.
c. Data from 15 countries.
d. Data from 16 countries.
e. Data from 17 countries.
f. Data from 26 countries.
g. Data from 30 countries.
Interval reporting period including week 24 through to week 50, 20 December 2021- as of 17 December 2021
https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea

Currently there are no available public data that allow to estimate the COMIRNATY® exposure by gender.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The MedDRA version 24.1 has been used to code adverse events/reactions in summary tabulations.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 2.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in clinical trial cases received by the MAH. This appendix is organised 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 December 2021 and the interval data are from 19 June 2021 to 18 December 2021. This appendix is organised according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non-interventional sources.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

The list of regulatory commitments received from EMA in the PSUR FAR and from SMSR's ARs, PRAC or signal assessments and from WHO to be addressed in the PSUR is detailed below. Responses are provided in Appendix 6A.

As part of the PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), the PRAC requested the MAH to 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,*

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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.*

As part of the SMSR assessment reports, the PRAC requested:

- EMEA/H/C/005735/MEA/002.6 (7th SMSR)

  The MAH should provide an updated age-stratified O/E analysis of herpes zoster, with a sensitivity analysis to account for the backlog of cases. The MAH is also requested to

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

discuss possible mechanisms that could underpin herpes zoster reactivation following vaccination. (MS1/MS4)

- EMEA/H/C/005735/MEA/002.8 (9th SMSR)

  The MAH should provide an estimate of the exposure of "third doses" in future PSURs separately (reporting period and cumulatively), if applicable.

- EMEA/H/C/005735/MEA/002.10 (11th SMSR)

  1. *The MAH should report on handling and dosing errors as a result of the different Comirnaty formulations on the market.*

  2. *The MAH is requested to report the total number of administered Comirnaty dose 3 in the EU/EEA, per country, and by age group.*

As per signal assessment reports, the PRAC requested:

- Signal assessment report on Glomerulonephritis and nephrotic syndrome with tozinameran EMA/PRAC/416198/2021 EPITT no: 19722 Procedure no: SDA 035

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

- Signal assessment report on multisystem inflammatory syndrome in children for COVID 19 vaccines EMA/PRAC/473788/2021 EPITT no: 19732 Procedure no: SDA 038

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

- WHO approval letter for the emergency use of Tozinameran - COVID-19 mRNA vaccine (nucleoside modified) - COMIRNATY®

  The MAH was requested 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.

  The MAH was requested to present the outcome of the cases of pregnancy observed in the clinical studies.

6.3.1.1. General Overview of the Safety Database – All Cases

As per PRAC commitment (procedure EMEA/H/C/PSUSA/00010898/202106),

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.*"

Response

Please refer to Appendix 6A.

General Overview – All Cases

A total of 658,249 case reports (721 from CT[16] and 657,528 from PM) containing 2,174,419 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 327,827 case reports retrieved in the PSUR #1. Refer to Appendix 2.1 for the cumulative summary tabulation of all CT cases and to Appendix 2.2 for the summary tabulation of all PM cases received during the current reporting period and cumulatively.

---

[16] Clinical Trials cases include

- 695 cases originated from 6 interventional trials (C4591001, C4591001-OPENLABEL, C4591007, C4591007-OPENLABEL, C4591015, C4591020, C4591024, C4591031, C4591031-OPENLABEL) for which BioNTech is the Sponsor and Pfizer acts as lead development party,
- 10 cases from 3 BioNTech interventional trials (BNT162-01 – RN9391R00, BNT162-04 and BNT162-14) and
- 16 cases from 1 Fosun (BioNTech License Partner) interventional trial (BNT162-06) with BioNTech third party acting as lead development party.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Demographic information of all cases included in the safety database and received during the reporting interval are shown in Table 12.

Table 12. Demographic Information - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=658,249	CT No. of Cases (%[a]) N=721	PM No. of Cases (%[a]) N=657,528[b]
EudraVigilance Cases		297,489	0	297,489
MC	Yes	277,041 (42.1)	721 (100)	276,320 (42.0)
	No	381,208 (57.9)	0	381,208 (58.0)
Country of occurrence (*: ≥2% of all cases)	Japan*	110,876 (16.8)	0	110,876 (16.9)
	UK*	81,075 (12.3)	11 (1.5)	81,064 (12.3)
	Netherlands*	79,600 (12.1)	0	79,600 (12.1)
	Germany*	74,910 (11.4)	13 (1.8)	74,897 (11.4)
	France*	55,111 (8.4)	0	55,111 (8.4)
	US*	51,219 (7.8)	525 (72.8)	50,694 (7.7)
	Italy*	31,114 (4.7)	0	31,114 (4.7)
	Austria*	19,645 (3.0)	0	19,645 (3.0)
	Australia*	17,749 (2.7)	0	17,749 (2.7)
	Spain*	17,731 (2.7)	17 (2.4)	17,714 (2.7)
	Other countries	119,219 (18.1)	155 (21.5)	119,064 (18.1)
Gender	Female	450,061 (68.4)	360 (49.9)	449,701 (68.4)
	Male	176,083 (26.8)	350 (48.5)	175,733 (26.7)
	Unknown/No Data	32,105 (4.9)	11 (1.5)	32,094 (4.9)
Age (years)	N	582,152	653	581,499
	Min-Max	0.04 – 121	0.83 – 91	0.04 – 121
	Mean	44.3	52.6	44.3
	Median	42.0	58.0	42.0
Age Range	≤ 17 years	20,871 (3.2) [19,843][c]	117 (16.2) [67]	20,754[f,g] (3.2) [19,776]
	0 to 27 days	187 (<0.1) [6]	46 (6.2) [0]	143[b] (<0.1) [6]
	28 days to 23 months	760 (0.1) [56]	23 (3.2) [19]	737[b] (0.1) [37]
	2-11 years	1431 (0.2) [1291]	24 (3.3) [24]	1407[b] (0.2) [1267]
	12-15 years	10,397 (1.6) [10,397]	14 (1.9) [14]	10,383 (1.6) [10,383]
	16-17 years	8093 (1.2) [8093]	10 (1.4) [10]	8083 (1.2) [8083]
	18-30 years	122,598 (18.6)	51 (7.1)	122,547 (18.6)
	31-50 years	244,082 (37.1)	114 (15.8)	243,968 (37.1)
	51-64 years	110,681 (16.8)	188 (26.1)	110,493 (16.8)
	65-74 years	51,377 (7.8)	147 (20.4)	51,230 (7.8)
	≥ 75 years	36,851 (5.6)	86 (11.9)	36,765 (5.6)
	Unknown	71,500 (10.9)	7 (1.0)	71,493 (10.9)
	N/A[e]	289 (<0.1)	11 (1.5)	278 (<0.1)
Case Seriousness	Serious	173,900 (26.4)	721 (100)	173,179 (26.3)
	Non-serious	484,349 (73.6)	0 (0)	484,349 (73.7)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 12. Demographic Information - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=658,249	CT No. of Cases (%[a]) N=721	PM No. of Cases (%[a]) N=657,528[b]
Case Outcome	Fatal	5413 (0.8)	46 (6.4)	5367 (0.8)
	Not recovered	213,015 (32.4)	116 (16.1)	212,899 (32.4)
	Recovered/ Recovering	300,809 (45.7)	526 (73.0)	300,283 (45.7)
	Recovered with sequelae	7512 (1.1)	29 (4.0)	7483 (1.1)
	Unknown	131,499 (20.0)	4 (0.6)	131,495 (20.0)
Presence of comorbidities [d]	Yes	67,108 (10.2)	290 (40.2)	66,818 (10.2)
	No	591,141 (89.8)	431 (59.8)	590,710 (89.8)

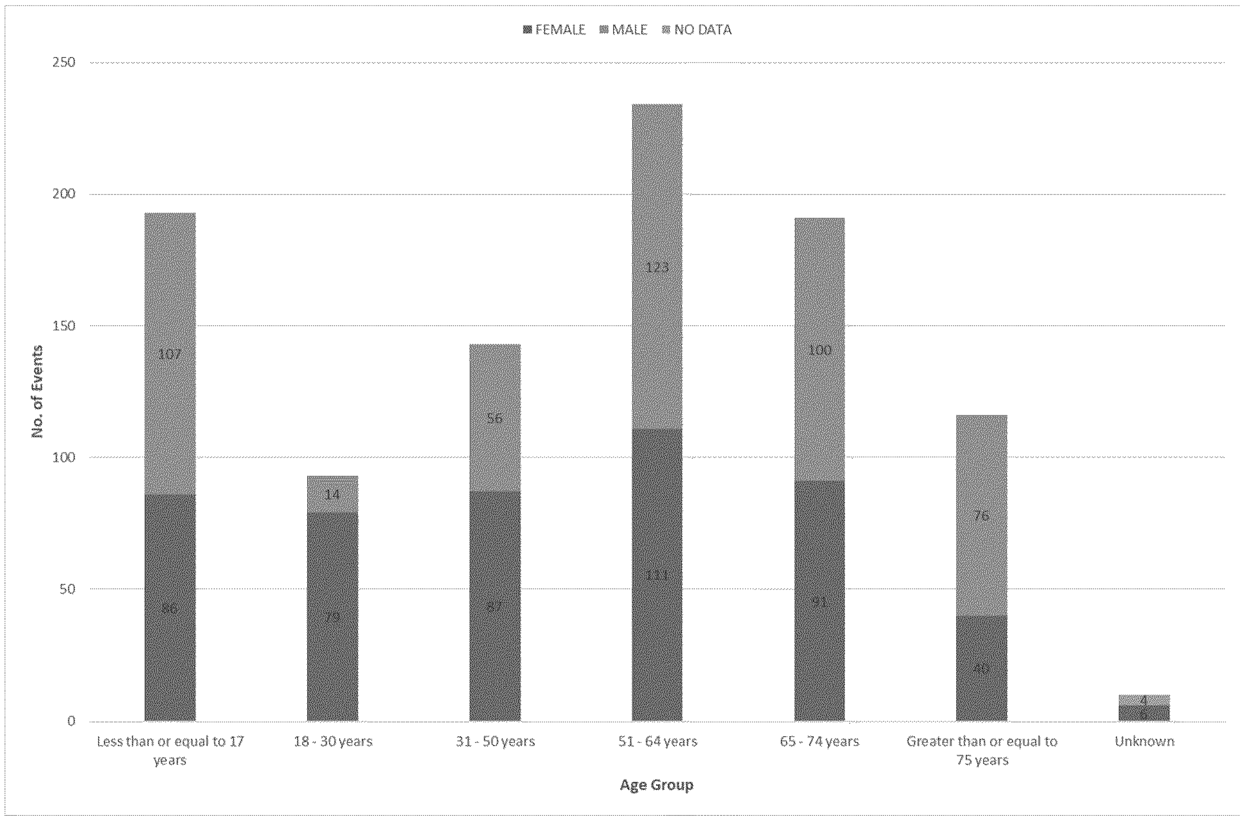
a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. It includes 1 child case that upon review has been reassessed as invalid, since unspecified number of subjects was reported and 2 cases (a [redacted]) with data not consistent with the reported paediatric age. These 3 cases were excluded in Section 16.3.5.2.1 *Paediatric Subjects < 5 Years*.
c. Numbers of squared brackets include number of participants/subjects who received BNT162b2. Numbers of squared brackets do not include non-participants (foetus/neonates) exposed before or during the mother' pregnancy or babies exposed through breastfeeding. Number of cases reported in this table may not match with number of cases evaluated in individual Sections due to case by case review that is not possible to implement in the overall dataset
d. 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 comorbidities (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.
e. Foetus cases-Age range only applies to post-birth subjects.
f. It includes 6 pregnant female subjects aged 12-, 14-, and 15-years and 9 pregnant female subjects aged 16- and 17-years (excluded in Section 16.3.5.2.3 *Paediatric Subjects ≥12 Years of Age*).
g. It includes 427 cases where the age is reported as "Adolescent" and 31 cases where the age is reported in decades.
N: Number of cases.

6.3.1.1.1. General Overview of the Safety Database - Clinical Trials Data

During the reporting period, in the CT dataset the number of female and male participants was balanced (49.9% vs 48.5%); the number of SAEs experienced by female participants is slightly higher than male (500 vs 476); in the 18 - 30 years and the 31 - 50 years age groups, the number of SAEs reported in females was higher than in males, while in the paediatric population, in 51-64 years and in the elderly age groups, the SAEs reported in male participants was higher than in females (Figure 1).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 1. Clinical Trial Data: Number of SAEs by Age Group and Gender

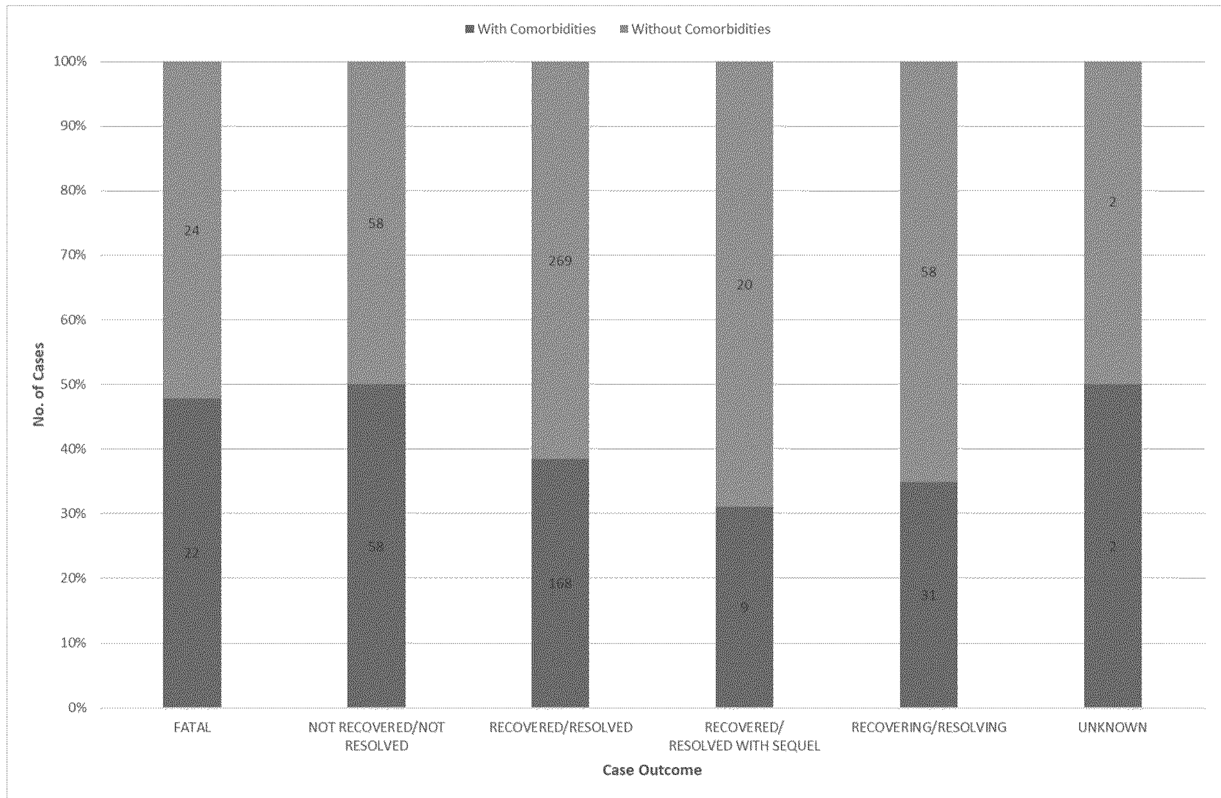


Case outcomes by presence/absence of comorbidities[17], by gender and age group in clinical trial cases are presented in Figure 2 through Figure 5. Overall, the proportion of cases with comorbidities is lower than cases without comorbidities and this is reflected also among the cases with a fatal outcome (Figure 2). A slightly higher number of male participants experienced a fatal outcome in the presence of comorbidities (Figure 3), and more male than female participants experienced a fatal outcome in the absence of comorbidities (Figure 3). When comorbidities are reported, the age group 51-64 years is the most represented across all case outcomes; among the cases with a fatal outcome the same number of occurrences was reported in the age groups 51-64 years and ≥75 years, as shown in Figure 4. In cases without comorbidities (Figure 5), most of the cases had a favourable outcome across all age groups at the time of reporting with the paediatric participants as more represented group; the highest number of fatal outcomes occurred in the 51-64 years followed by the 65-74 years.

[17] 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 comorbidities (eg 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.

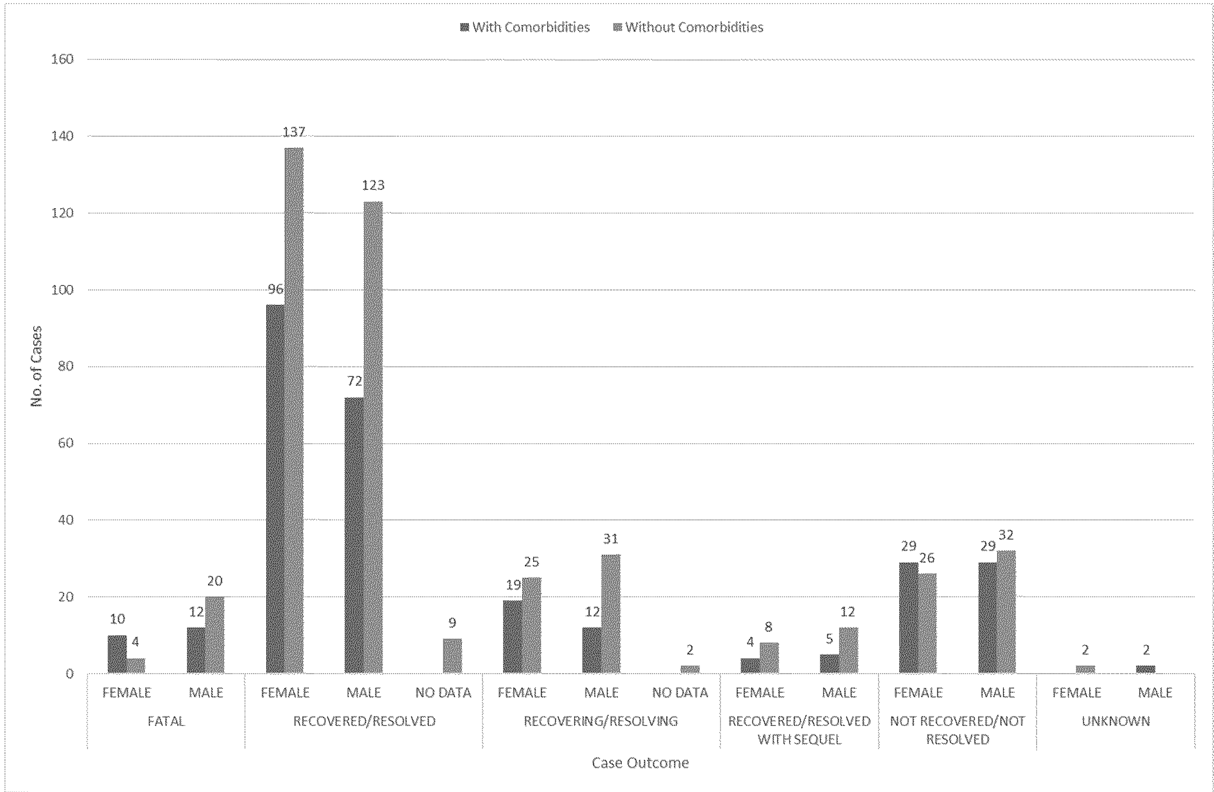
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 2. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities



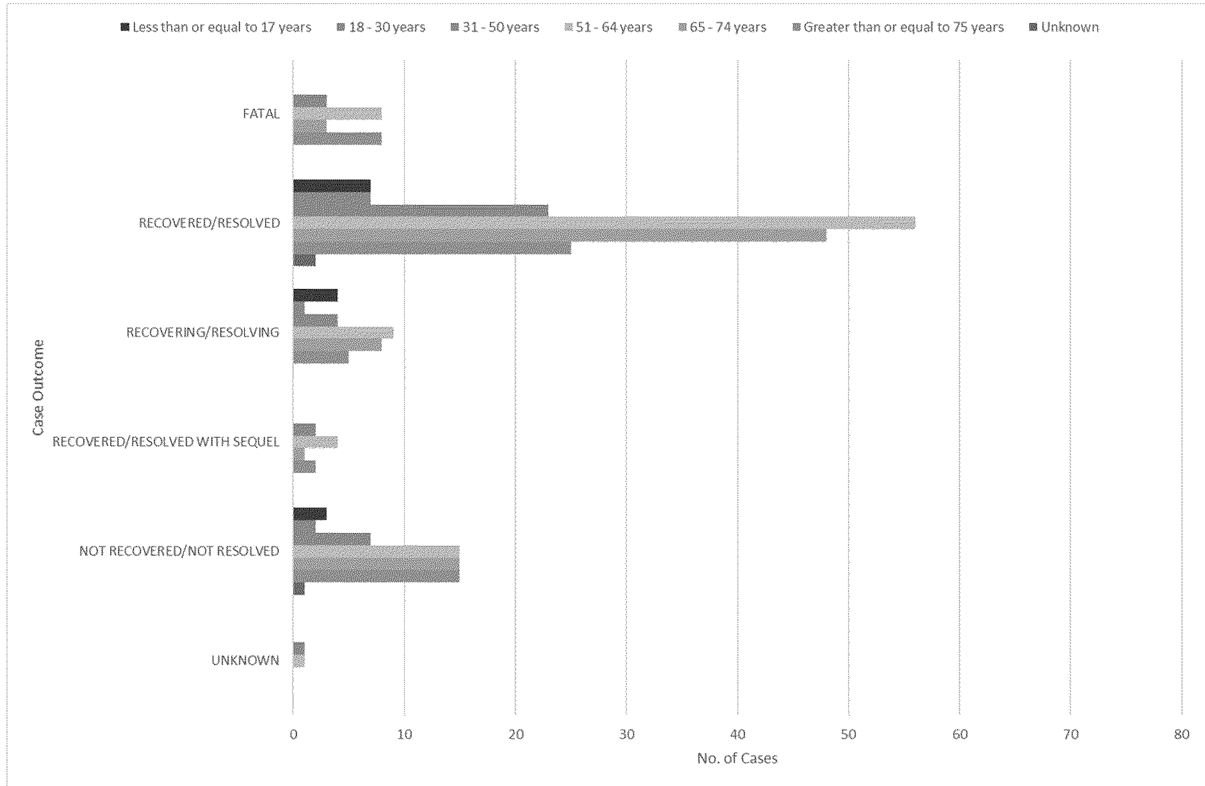
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 3. Clinical Trial Data: Case Outcome by Presence/Absence of Comorbidities and Gender



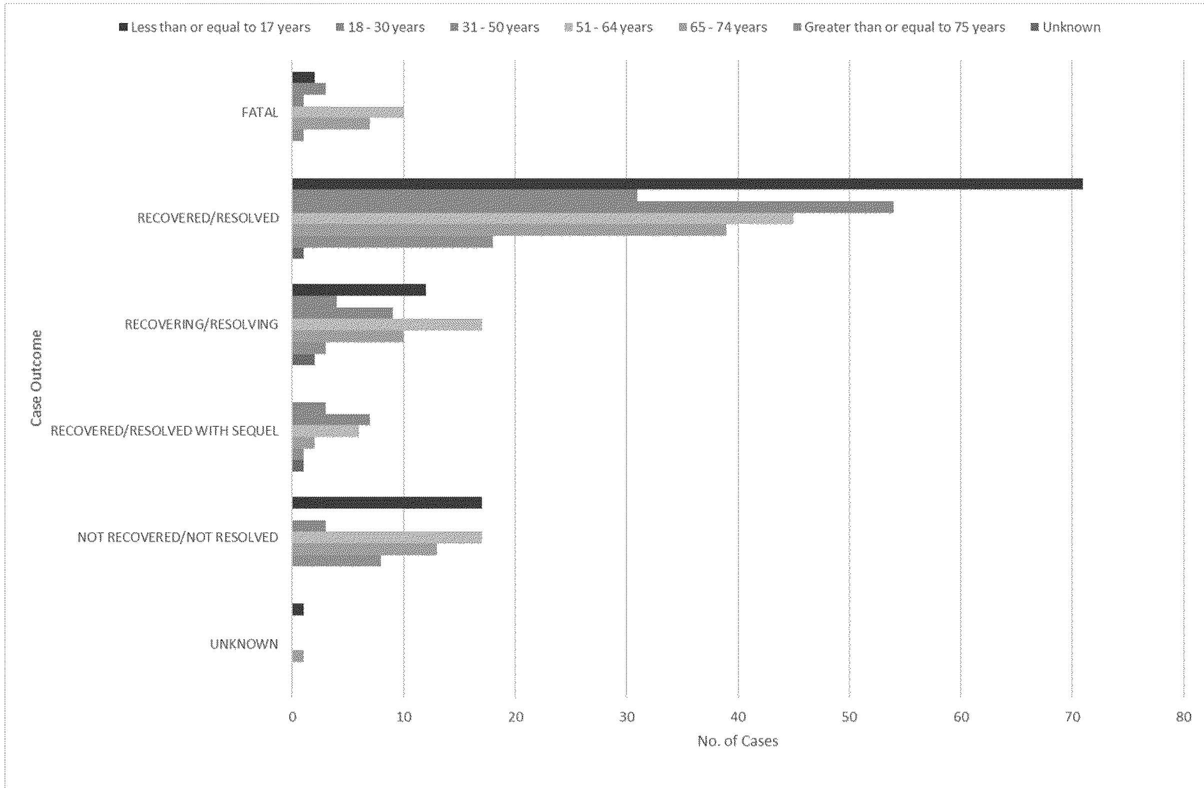
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 4. Clinical Trial Data: Case Outcome by Age Group in Presence of Comorbidities



090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 5. Clinical Trial Data: Case Outcome by Age Group in Absence of Comorbidities



The summary of medical history and co-suspects reported in the CT cases is provided in Table 13.

Table 13. Clinical Trial Data: Medical History and Co-Suspects

Most frequently reported (≥2%) medical history (HLGT): Vascular hypertensive disorders (224), Lipid metabolism disorders (140), Glucose metabolism disorders (incl diabetes mellitus) (100), Lifestyle issues (101), Gastrointestinal motility and defaecation conditions (99), Allergic conditions (96), Joint disorders (95), Appetite and general nutritional disorders (93), Depressed mood disorders and disturbances (86), Anxiety disorders and symptoms (80), Obstetric and gynaecological therapeutic procedures (69), Bronchial disorders (excl neoplasms) (68), Infections – pathogen unspecified (56), Gastrointestinal therapeutic procedures (55), Thyroid gland disorders (52), Sleep disorders and disturbances (50), Cardiac arrhythmias (47), Coronary artery disorders, Headaches, Therapeutic procedures and supportive care NEC (41 each), Musculoskeletal and connective tissue disorders NEC, Prostatic disorders (excl infections and inflammations) (38 each), Bone and joint therapeutic procedures (37), Age related factors (30), Bone disorders (excl congenital and fractures) (29), Pregnancy, labour, delivery and postpartum conditions, Respiratory disorders NEC (28 each), Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders), Viral infectious disorders (26 each), Bone and joint injuries, General system disorders NEC, Lipid analyses, Peripheral neuropathies (25 each), Vascular therapeutic procedures (24), Anterior eye structural change, deposit and degeneration (22), Anaemias nonhaemolytic and marrow depression, Gallbladder disorders, Neurological disorders NEC, Upper respiratory tract disorders (excl infections) (21 each), Epidermal and dermal conditions, Head and neck therapeutic procedures, Hepatobiliary therapeutic procedures, Injuries NEC, Vision disorders (20 each), Abdominal hernias and other abdominal wall conditions, Cardiac therapeutic procedures, Psychiatric disorders NEC (19 each), Renal disorders (excl nephropathies) (18), Central nervous system vascular disorders, Gastrointestinal signs and symptoms, Eye

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 13. Clinical Trial Data: Medical History and Co-Suspects

therapeutic procedures, Urinary tract signs and symptoms (17 each), Abortions and stillbirth, Embolism and thrombosis, Sexual function and fertility disorders (16 each), Nervous system, skull and spine therapeutic procedures, Reproductive neoplasms female benign (15 each). The medical conditions (PTs History) reported in more than 2% of the cases included Hypertension (220), Gastrooesophageal reflux disease (83), Depression and Obesity (77 each), Type 2 diabetes mellitus (76), Seasonal allergy (69), Osteoarthritis (68), Anxiety and Hypercholesterolemia (63 each), Hyperlipidaemia (51), Insomnia (50), Asthma (49), Non-tobacco user (47), Hypothyroidism (46), Benign prostatic hyperplasia, Hysterectomy (35 each), Migraine (33), Back pain (29), Postmenopause and Pregnancy (27 each), Atrial fibrillation and Dyslipidaemia (26 each), Blood cholesterol increased (24), Coronary artery disease (23), COPD (22), Tobacco user (20), Cholecystectomy, Ex-tobacco user (19 each), Cataract and Sleep apnoea syndrome (18 each), Osteoporosis (17), Anaemia, Intervertebral disc protrusion, Irritable bowel syndrome and Live birth (16 each), Drug hypersensitivity and Myocardial infarction (15 each). **COVID-19 medical history (n=6):** COVID-19. **Most frequently reported (≥2) co-suspect medications:** dinoprostone, ibuprofen and oxytocin (2 each).

Adverse Event Data

A total of 1002 SAEs were reported in 721 cases.

The MedDRA SOCs containing the greatest number of reported events[18] (≥2%) from clinical trial data were Injury, poisoning and procedural complications (179), Infections and infestations (159), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (119); Pregnancy, puerperium and perinatal conditions (69), Cardiac disorders (68), Nervous system disorders (59), Respiratory, thoracic and mediastinal disorders (53), Gastrointestinal disorders (52), General disorders and administration site conditions (41), Musculoskeletal and connective tissue disorders (39), Psychiatric disorders (36), and Hepatobiliary disorders (21).

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

[18] Of note, multiple adverse events may be reported in a single case.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

a. Includes BNT162b2 (b2), BNT162b2s01 (b2s01), BNT162b3 (b3), Blinded Therapy (BT) and Placebo.
b. Includes BNT162b1, b2, b2s01, b3, BNT162c2 (c2), BT and Placebo.
c. Reporting proportion calculated as n/N (% of cases) in the current reporting period or cumulatively.
d. Reported as serious occurrence as associated to SAEs. This PT is coded in maternal cases, and in foetal cases when a foetal AE is reported. For associated SAEs, refer to Section 16.3.5.3 *Use in Pregnant/Lactating Women.*
N: Number of cases; n: Number of events.

The most frequently reported serious adverse events in the clinical trials are not expected or consistent with expected events as per the current Investigator's Brochure.

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

- Myocarditis (2), Pain in extremity and Pyrexia (1 each) were assessed as related by both the Investigator and the Sponsor.
- Hepatic enzyme increased and Transient ischaemic attack (2 each), Angioedema, Appendicitis and Tachycardia (1 each) were assessed as related by the Investigator and unrelated by the Sponsor.

Conclusion

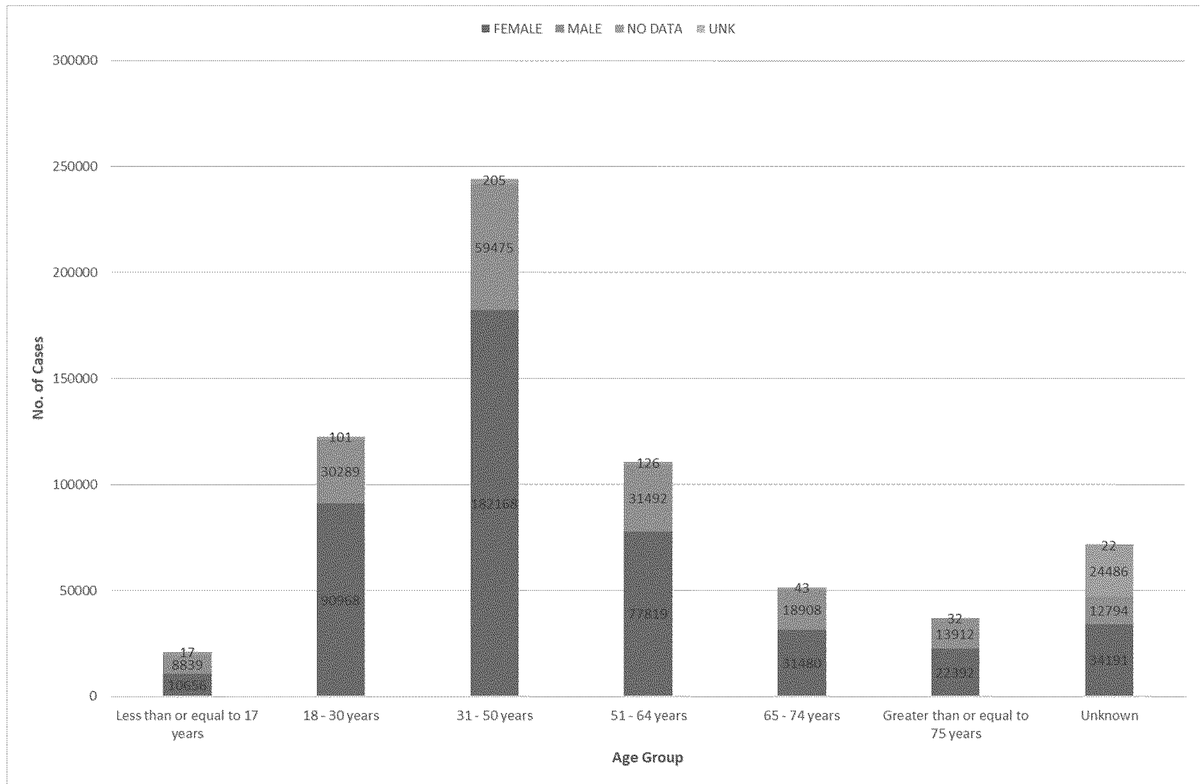
Based on the review of the CT cases, no new safety issues were identified.

6.3.1.1.2. General Overview of the Safety Database - Post-Authorisation Data

During the reporting period, in the PM dataset the number of female subjects was 2.6 times the number of male subjects (68.4% vs 26.7%); across the different age groups the ratio of female/male cases ranged between 1.6 in the elderly aged at least 75 years to 3.0 in the 18-30 years group (Figure 6).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

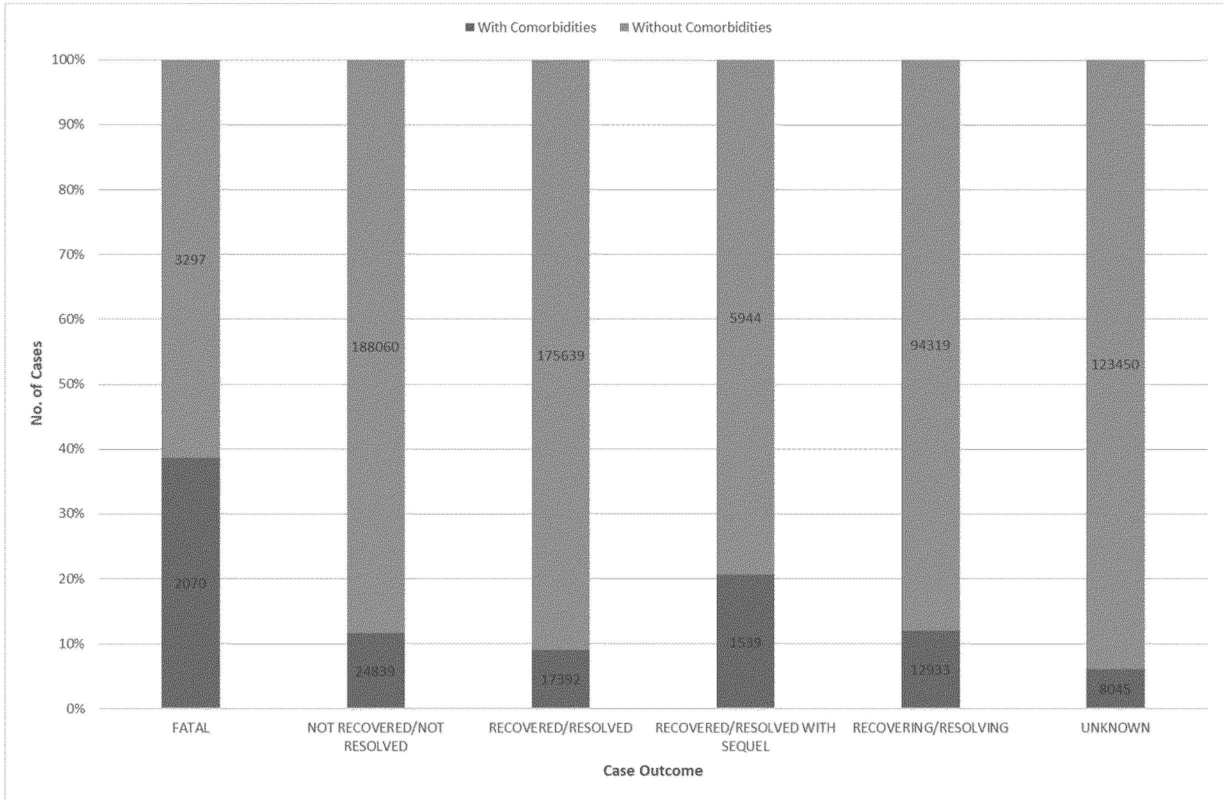
Figure 6. Post-Authorisation Data: Number of Cases by Age Group and Gender



Case outcomes by presence/absence of comorbidities, by gender and age group in PM cases are presented in Figure 7 through Figure 10. Overall, the proportion of cases with comorbidities was 10.2% of the total PM dataset; Figure 7 shows the case outcome by presence/absence of comorbidities.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

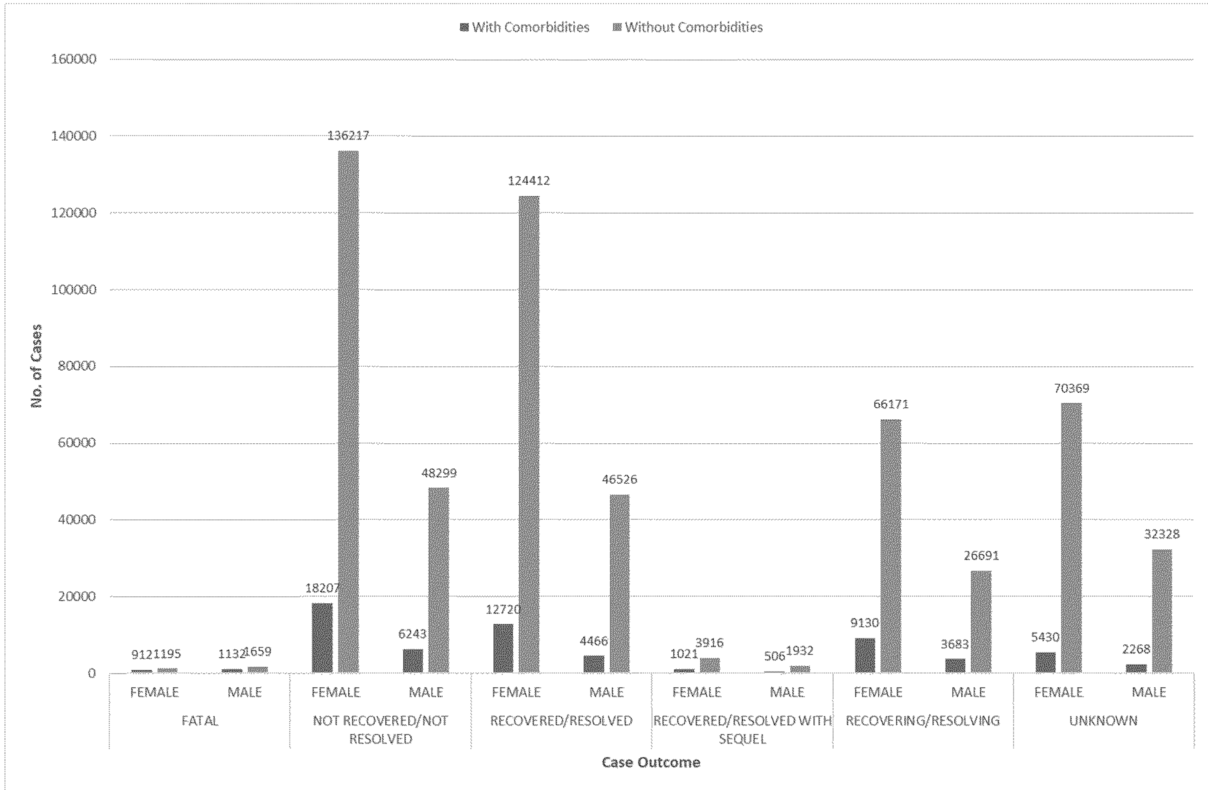
Figure 7. Post-Authorisation Data: Case Outcome by Presence/Absence of Comorbidities



A slightly higher number of male subjects experienced a fatal outcome independently from the presence of comorbidities (Figure 8).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

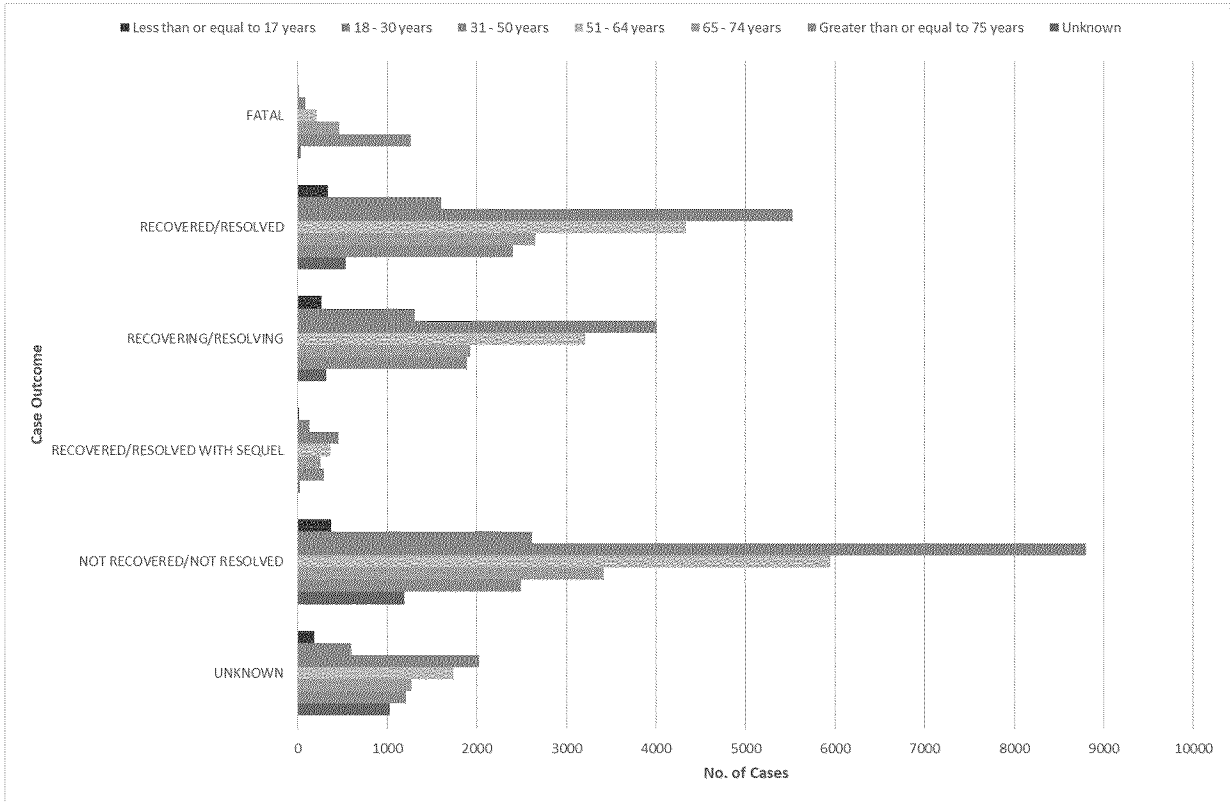
Figure 8. Post-Authorisation Data: Case Outcome by Presence/Absence of Comorbidities and Gender



The age group 31-50 years represents 37% of the PM cases; this age group is the most represented one across all but fatal case outcomes, both in presence and in absence of comorbidities (Figure 9 and Figure 10). Among the cases with a fatal outcome, the age group more represented is the one including elderly aged at least 75 years, both in presence or in absence of comorbidities, as shown in Figure 9 and in Figure 10.

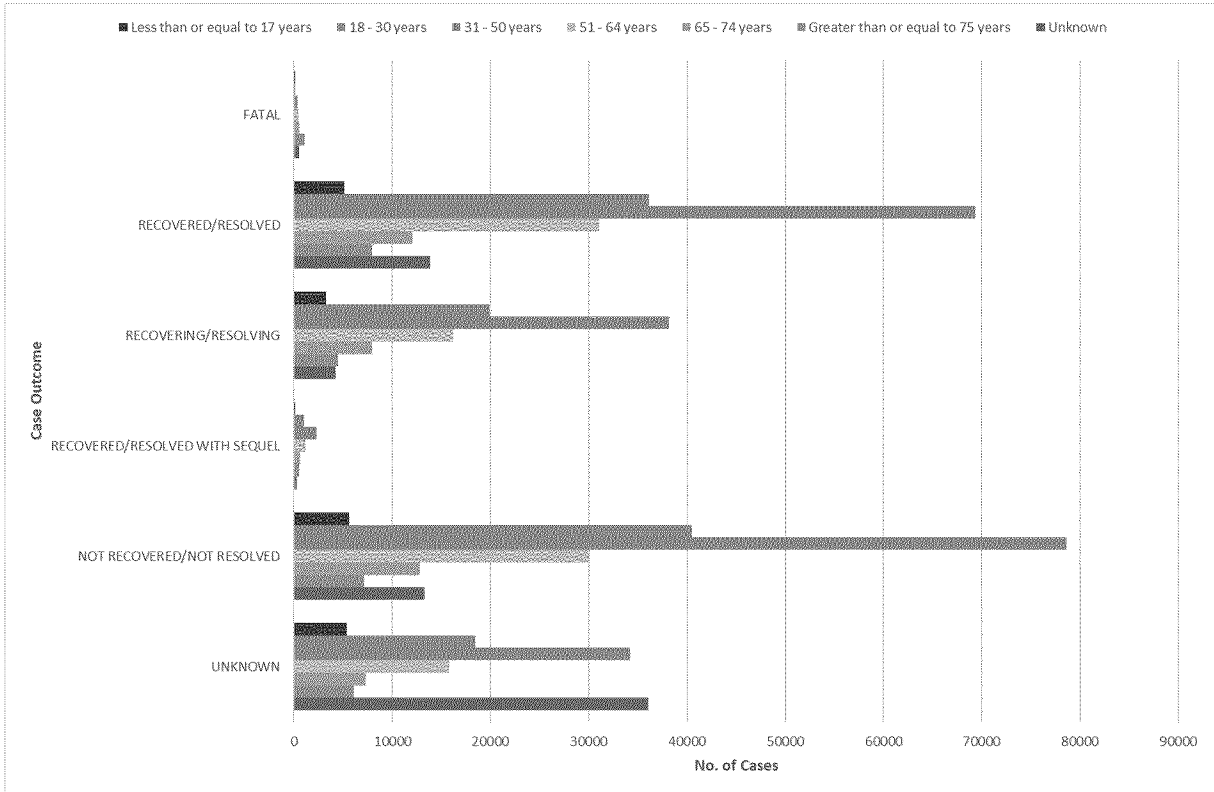
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 9. Post-Authorisation Data: Case Outcome by Age Group in Presence of Comorbidities



090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 10. Post-Authorisation Data: Case Outcome by Age Group in Absence of Comorbidities



The summary of medical history and co-suspects reported in the PM cases is provided in Table 15.

Table 15. Post-Authorisation Data: Medical History and Co-Suspects

Most frequently reported (≥2%) medical history (HLGT): Allergic conditions (40,491), Viral infectious disorders (38,355), Vascular hypertensive disorders (24,697), Breast disorders (20,351), Bronchial disorders (excl neoplasms) (17,185), Lifestyle issues (14,434). The medical conditions (PTs History) reported in more than 2% of the cases included Hypertension (24,096), Suppressed lactation[19] (20,170), and Asthma (14,450). **COVID-19 medical history:** COVID-19 (21,127), Suspected COVID-19 (13,720), SARS-CoV-2 test positive (225), Post-acute COVID-19 syndrome (175), Exposure to SARS-CoV-2 (142), COVID-19 pneumonia (138), Coronavirus infection (110), Asymptomatic COVID-19 (100), Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (17 each), Coronavirus pneumonia and Coronavirus test positive (4 each), COVID-19 treatment (2). **Most frequently reported (≥40) co-suspect vaccines/medications (other than COVID-19 vaccines):** Influenza vaccine (488), hepatitis A vaccine, influenza vaccine (surface antigen, inactivated, adjuvanted) 4V (83), adalimumab (63), tofacitinib citrate (58), influenza vaccine inact split 4V (56), ibuprofen and

[19] All UK cases; this medical history term is being investigated by the HA who forwarded the cases.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 15. Post-Authorisation Data: Medical History and Co-Suspects

paracetamol (52 each), apixaban (46), ethinylestradiol, levonorgestrel and macrogol (45 each), etanercept (41), acetylsalicylic acid (40). **Most frequently reported (≥40) co-suspect COVID-19 vaccines:** COVID-19 AstraZeneca vaccine (409), COVID-19 Moderna vaccine (231), COVID-19 vaccine (38), COVID-19 vaccine J&J (23), COVID-19 vaccine inact (vero) CZ02 (7), COVID-19 vaccine inact (vero) HB02 (2), COVID-19 vaccine Sputnik (1).

Adverse Event Data

A total of 2,173,417 AEs (of which 542,562 were serious and 1,631,402 non-serious[20]) were reported in 657,528 PM cases.

The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (738,521), Nervous system disorders (308,965), Musculoskeletal and connective tissue disorders (242,863), Gastrointestinal disorders (140,894), Skin and subcutaneous tissue disorders (96,458), Injury, poisoning and procedural complications (82,952), Reproductive system and breast disorders (93,828), Respiratory, thoracic and mediastinal disorders (80,334), Infections and infestations (59,737), and Cardiac disorders (52,788).

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

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

MedDRA SOC MedDRA PT	Reporting Period 19 Jun 2021 – 18 Dec 2021		Cumulatively through 18 Dec 2021
	All Cases (N=657,528) AEs (n=2,173,417)	Serious Cases (N=173,179) Serious AEs[a] (n=542,562)	All Cases (N=982,006) AEs (n=3,365,224)
	n (AERP,[h] %)	n (AERP, %)	n (AERP, %)
Blood and lymphatic system disorders			
Lymphadenopathy [b]	29,431 (4.5)	4187 (2.4)	48,081 (4.9)
Gastrointestinal disorders			
Nausea [b]	55,741 (8.5)	9083 (5.2)	93,727 (9.5)
Diarrhoea [b]	20,881 (3.2)	3562 (2.1)	34,169 (3.5)
Vomiting [b]	15,923 (2.4)	4432 (2.6)	27,477 (2.8)
General disorders and administration site conditions			
Fatigue [b]	109,479 (16.7)	14,173 (8.2)	166,902 (17.0)
Pyrexia [b]	106,127 (16.1)	12,153 (7.0)	170,558 (17.4)
Vaccination site pain [b]	95,981 (14.6)	3422 (2.0)	139,567 (14.2)
Malaise [b]	81,598 (12.4)	6391 (3.7)	109,616 (11.2)

[20] Multiple episodes of the same event were reported with a different seriousness in some cases hence the sum of the events seriousness exceeds the total number of events.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

MedDRA SOC MedDRA PT	Reporting Period 19 Jun 2021 – 18 Dec 2021		Cumulatively through 18 Dec 2021
	All Cases (N=657,528) AEs (n=2,173,417)	**Serious Cases (N=173,179) Serious AEs[a] (n=542,562)**	**All Cases (N=982,006) AEs (n=3,365,224)**
	n (AERP,[h] %)	**n (AERP, %)**	**n (AERP, %)**
Chills[b]	53,523 (8.1)	5452 (3.1)	94,925 (9.7)
Pain[c]	37,943 (5.8)	6245 (3.6)	63,924 (6.5)
Vaccination site swelling[b]	22,115 (3.4)	670 (0.4)	29,275 (3.0)
Asthenia[b]	21,198 (3.2)	4773 (2.8)	45,807 (4.7)
Chest pain[c]	17,528 (2.7)	7437 (4.3)	22,706 (2.3)
Influenza like illness[c]	12,656 (1.9)	1831 (1.1)	21,409 (2.2)
Vaccination site erythema[b]	13,101 (2.0)	569 (0.3)	19,852 (2.0)
Infections and infestations			
COVID-19[d]	19,691 (3.0)	18,857 (10.9)	27,943 (2.8)
Injury, poisoning and procedural complications			
Off label use[e]	22,049 (3.4)	5764 (3.3)	25,873 (2.6)
Inappropriate schedule of product administration[e]	18,827 (2.9)	467 (0.3)	23.218 (2.4)
Musculoskeletal and connective tissue disorders			
Myalgia[b]	84,891 (12.9)	7203 (4.2)	134,432 (13.7)
Arthralgia[b]	56,611 (8.6)	7251 (4.2)	92,100 (9.4)
Pain in extremity[b]	39,010 (5.9)	8030 (4.6)	67,970 (6.9)
Nervous system disorders			
Headache[b]	135,039 (20.5)	16,738 (9.7)	219,030 (22.3)
Dizziness[c]	37,982 (5.8)	8760 (5.1)	62,240 (6.3)
Paraesthesia[f]	19,809 (3.0)	4766 (2.8)	29,497 (3.0)
Hypoaesthesia[f]	13,597 (2.1)	3980 (2.3)	19,995 (2.0)
Reproductive system and breast disorders			
Heavy menstrual bleeding[c]	16,613 (2.5)	4150 (2.4)	17,535 (1.8)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea[b]	23,757 (3.6)	9714 (5.6)	35,024 (3.6)
Skin and subcutaneous tissue disorders			
Rash[b]	17,591 (2.7)	3095 (1.8)	28,255 (2.9)
Pruritus[b]	16,653 (2.5)	2980 (1.7)	27,923 (2.8)
Surgical and medical procedures			
Immunisation[g]	21,712 (3.3)	8339 (4.8)	21,737 (2.21)

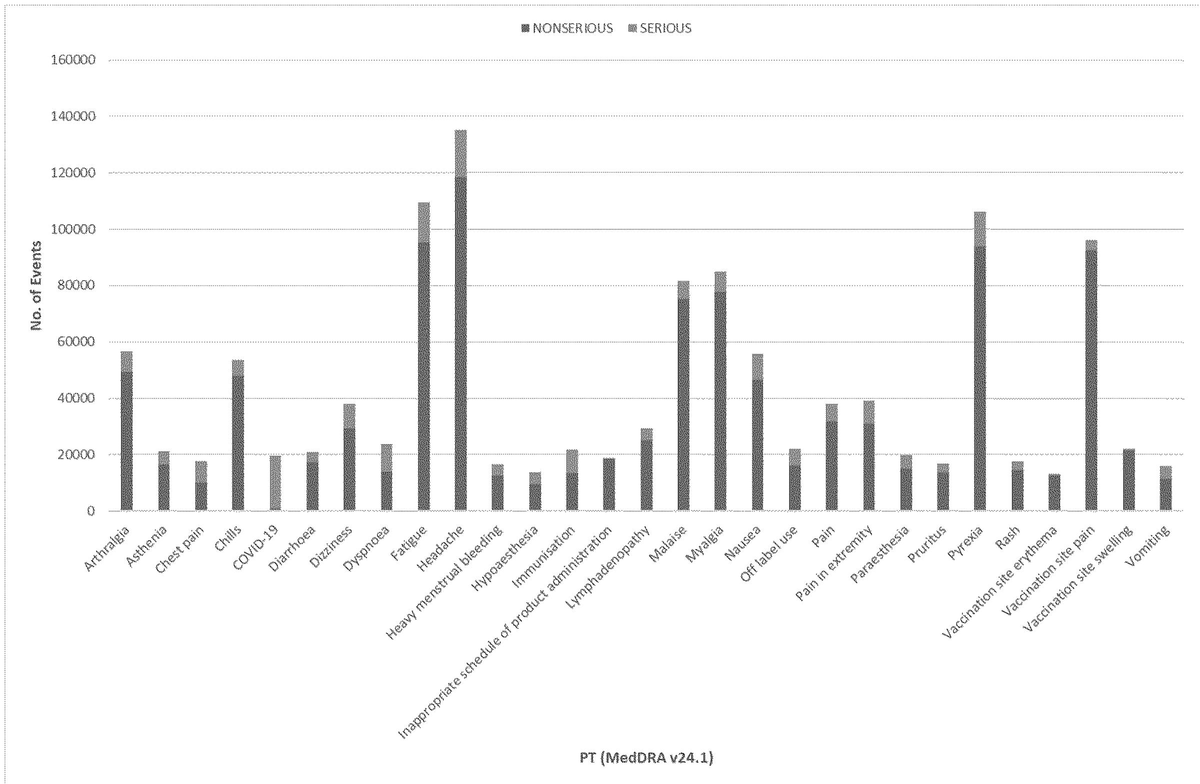
a. Non-serious events are not included.
b. Listed or consistent with listed AEs in current RSI.
c. Unlisted in the current RSI.
d. Listed per case processing conventions, except for fatal cases.
e. Listed per case processing conventions.
f. Paresthesia / Hypoesthesia are going to be included as ADRs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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Most of the frequently reported events are listed or consistent with listed events as per the current RSI.

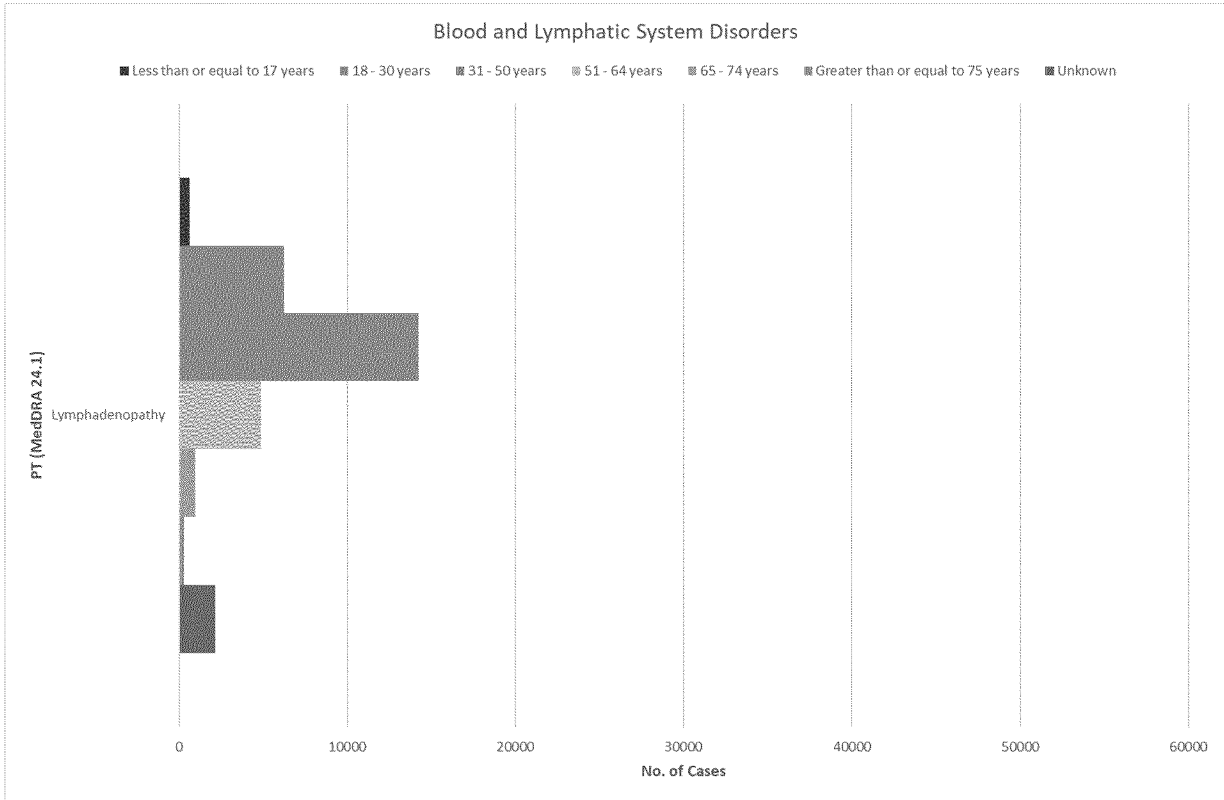
Out of the 2,173,417 AEs in the PM dataset, 75.0% of them were non-serious. Figure 11 shows the seriousness of the PTs reported in more than 2% of the cases where most of the occurrences were non-serious with the exception of COVID-19. Figure 12 provides information about the age breakdown in the clinical AEs reported in more than 2% of the cases; the age group 31-50 years is the one reporting more events and this is consistent being the largest group in terms of number of cases.

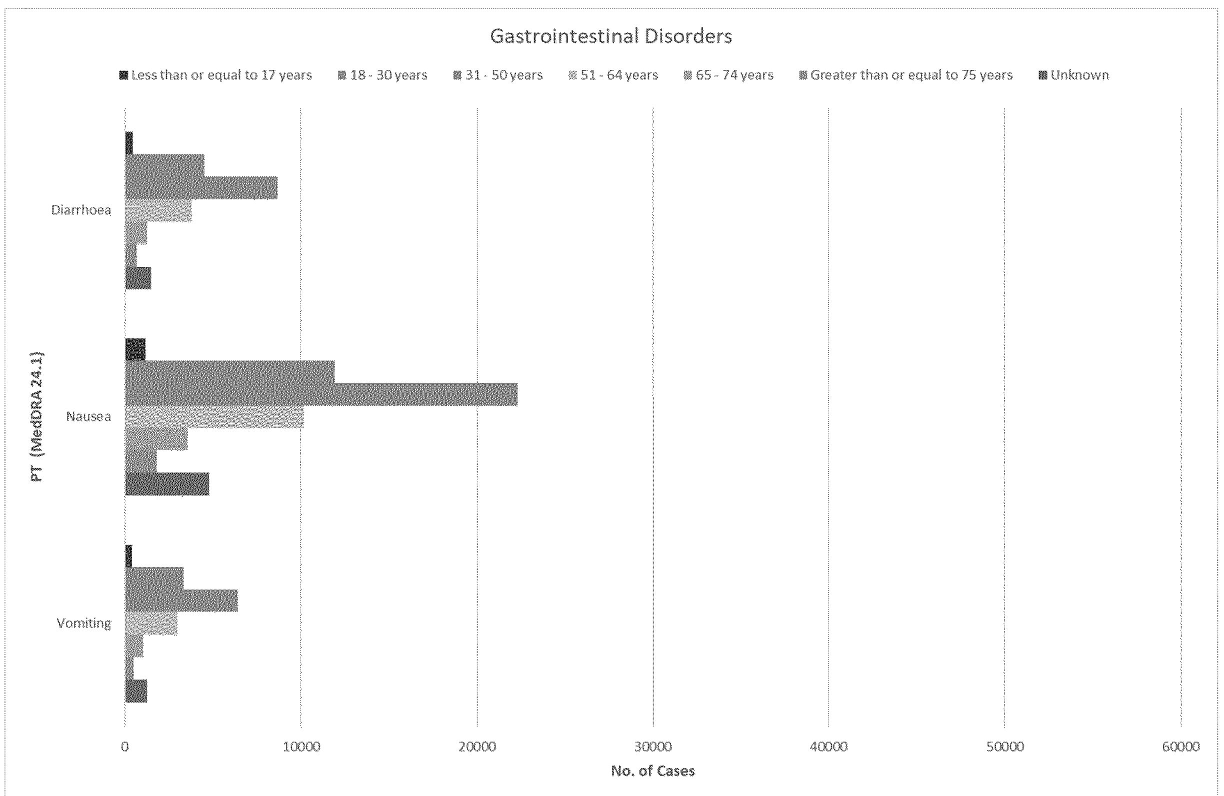
Figure 11. Post-Authorisation Data: Event Seriousness of the PTs ≥2% of Cases



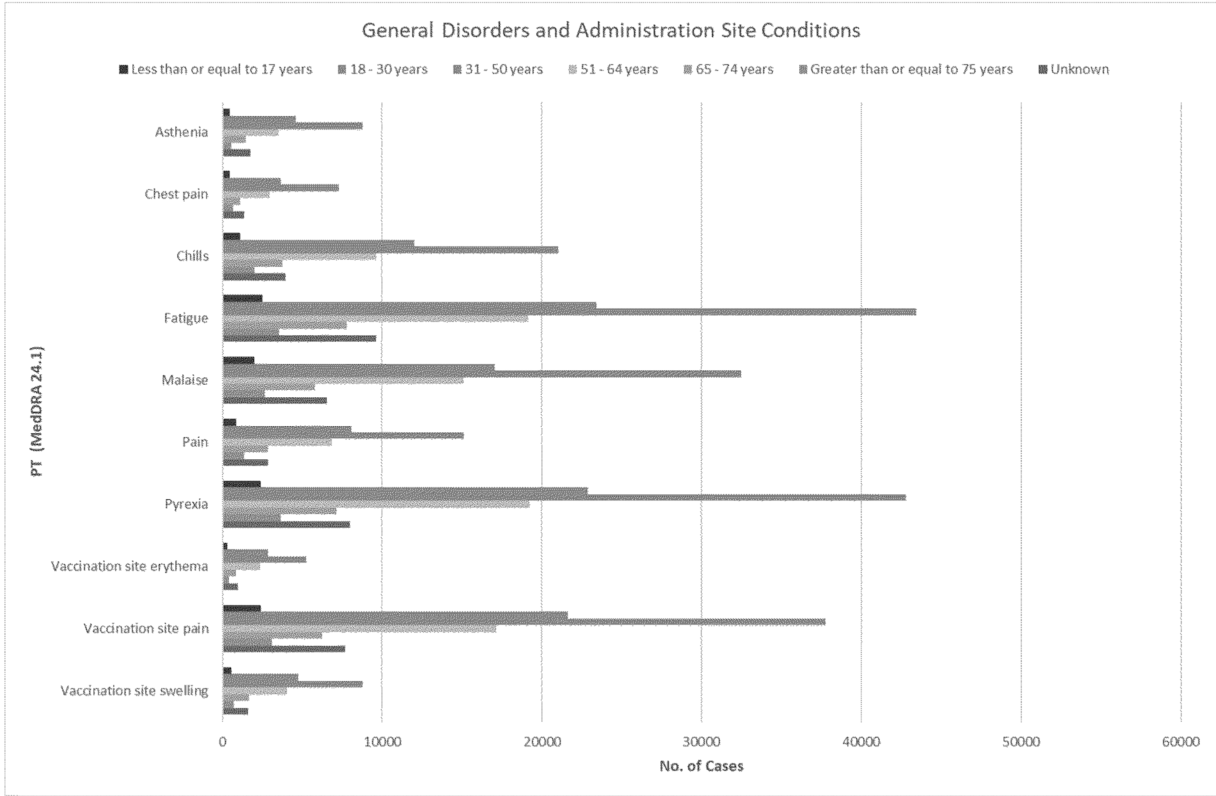
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

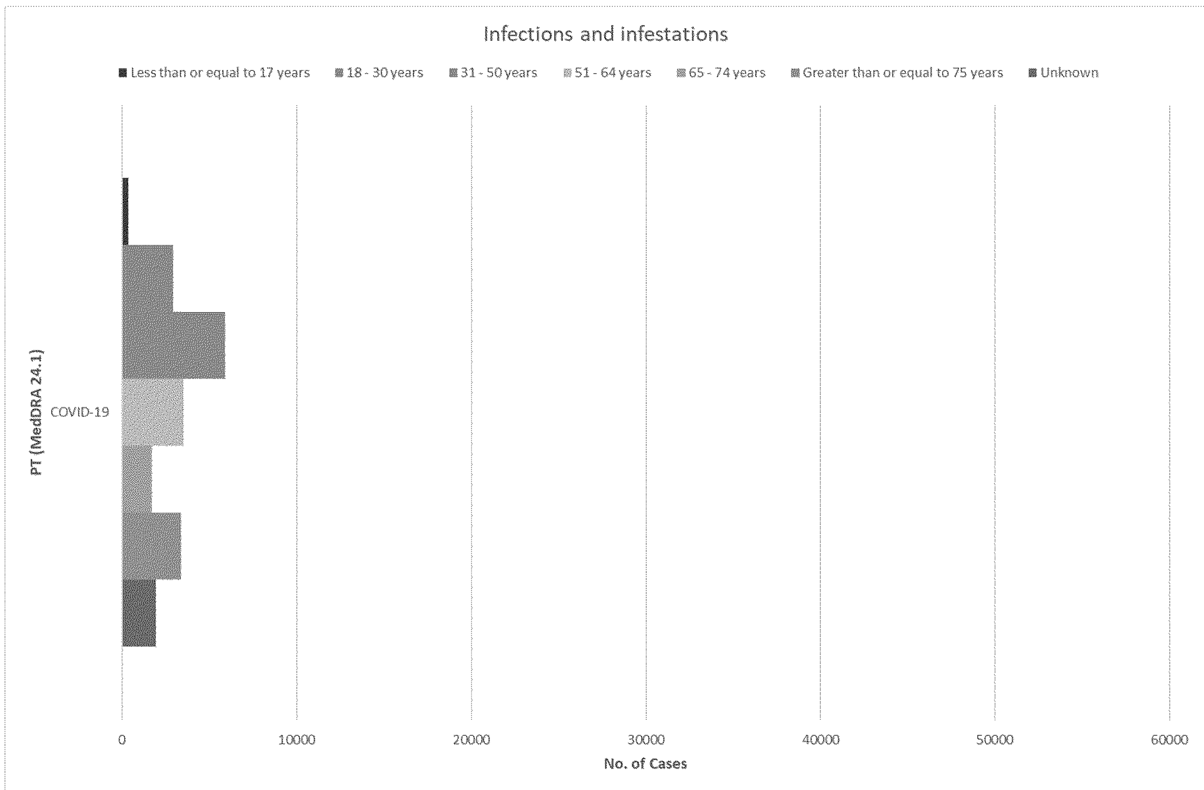
Figure 12. Post-Authorisation Data: Clinical AEs reported in ≥2 % of Cases by Age Group



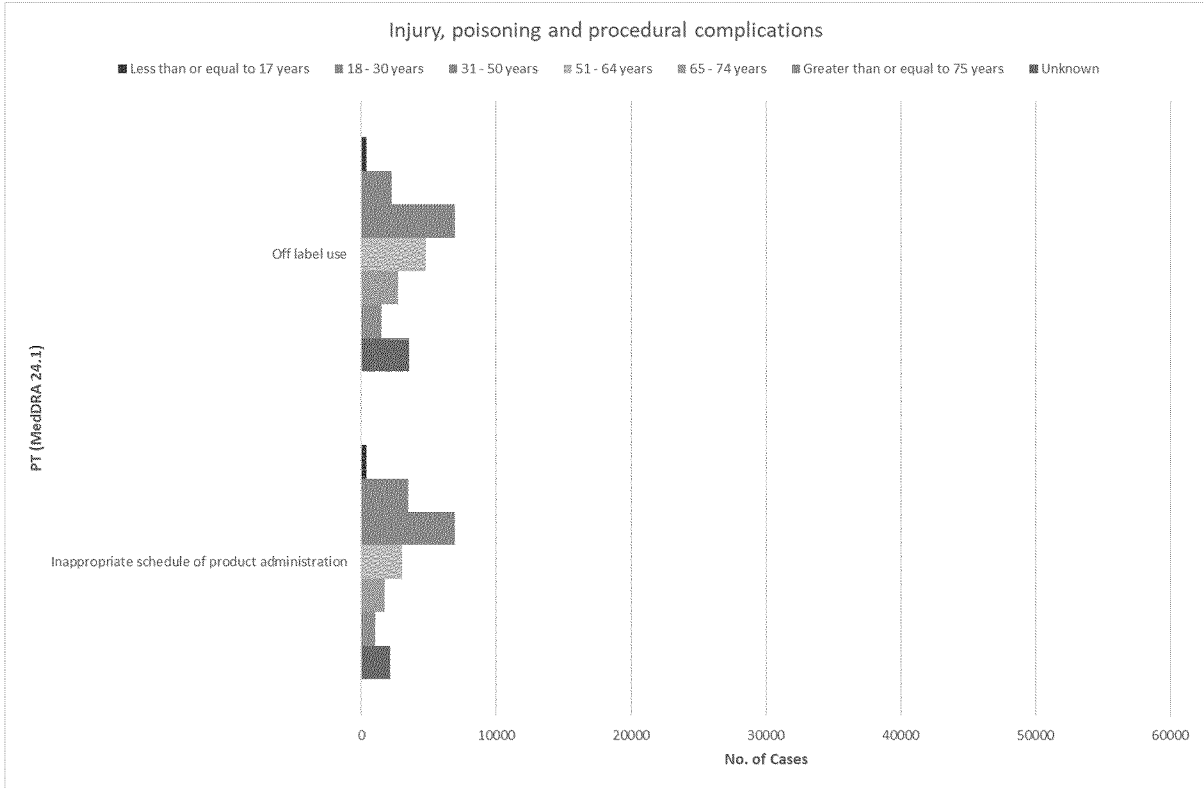


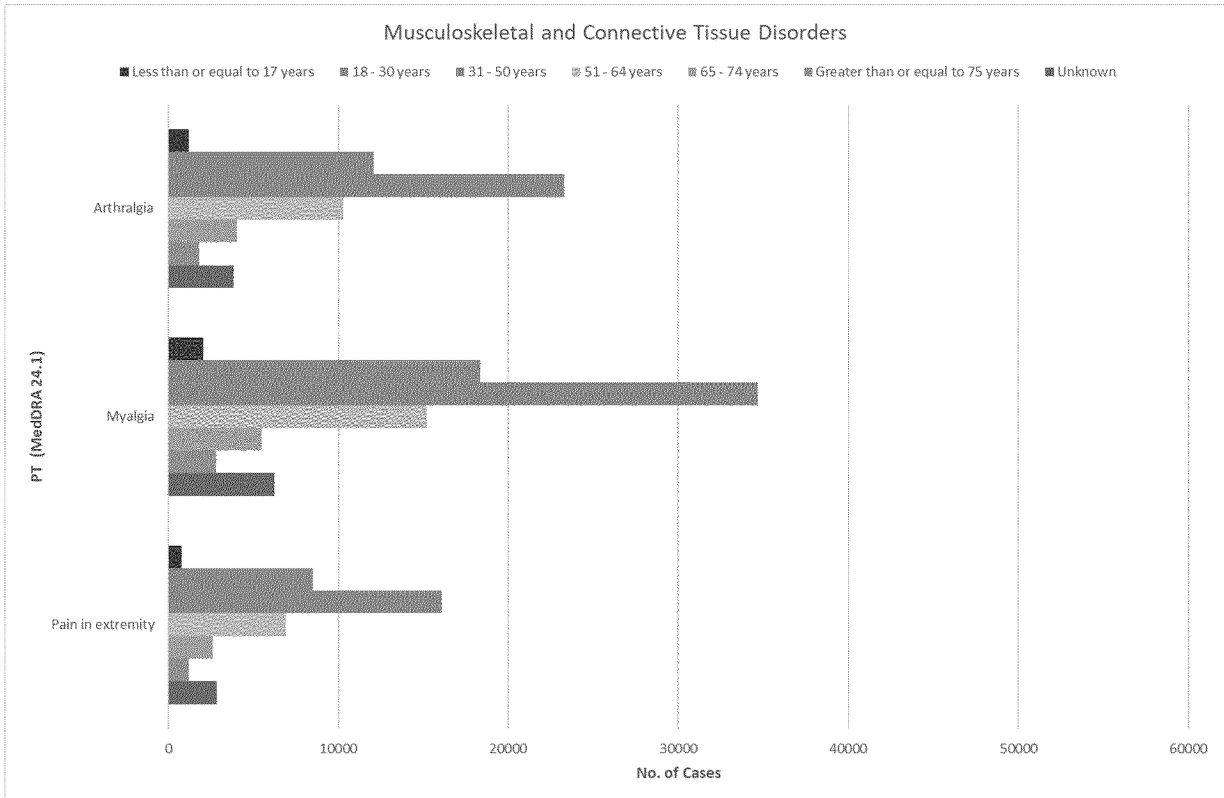
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)



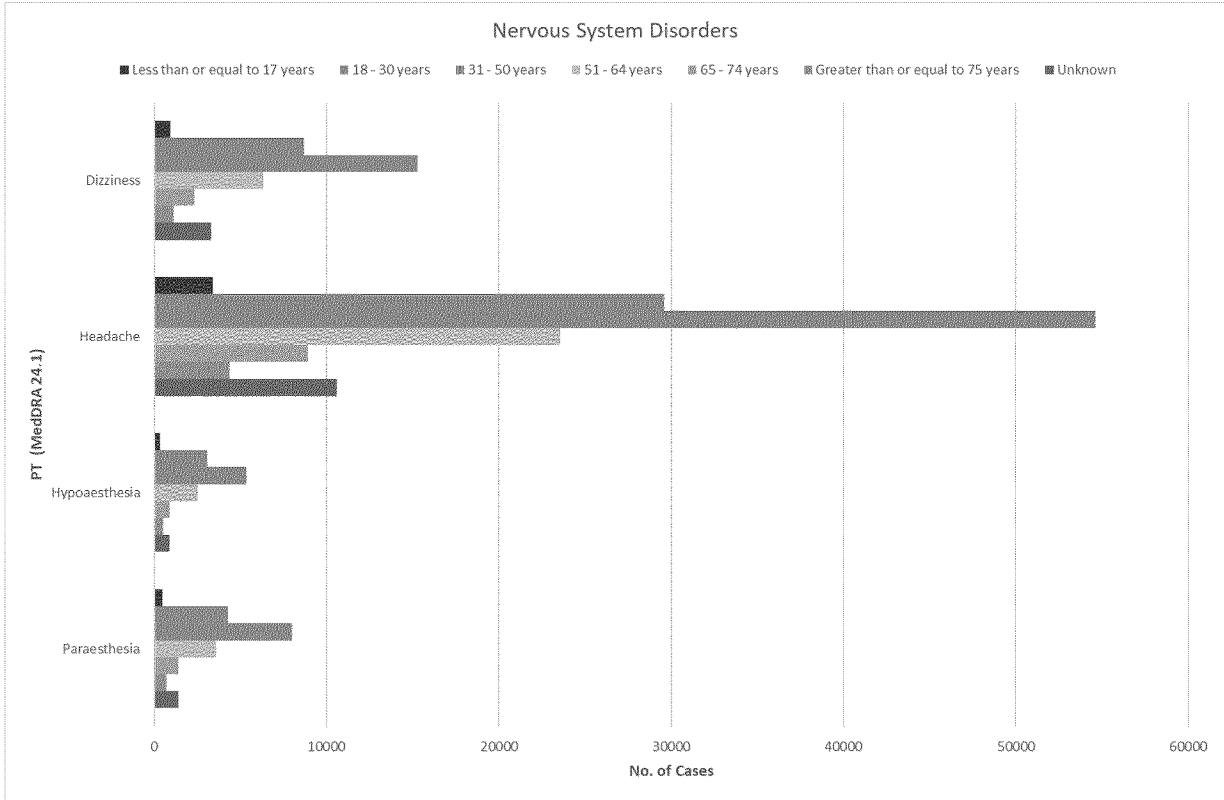


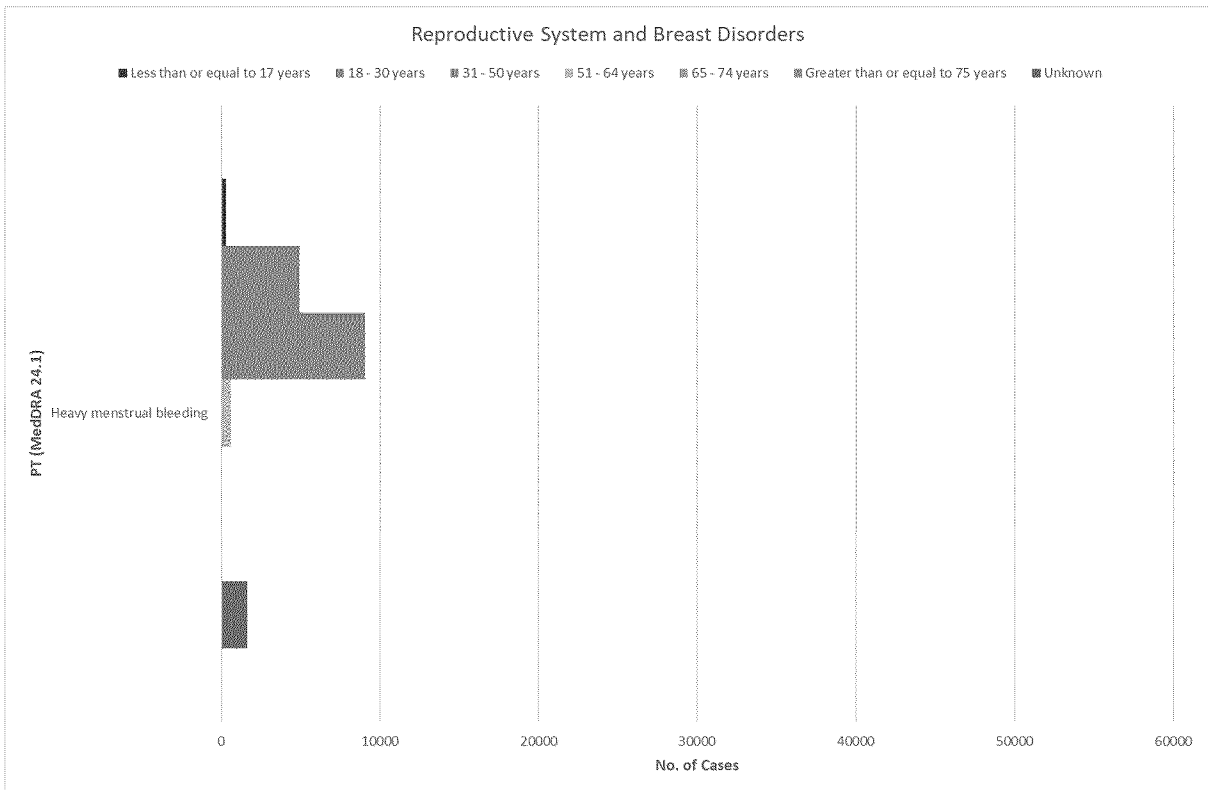
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)



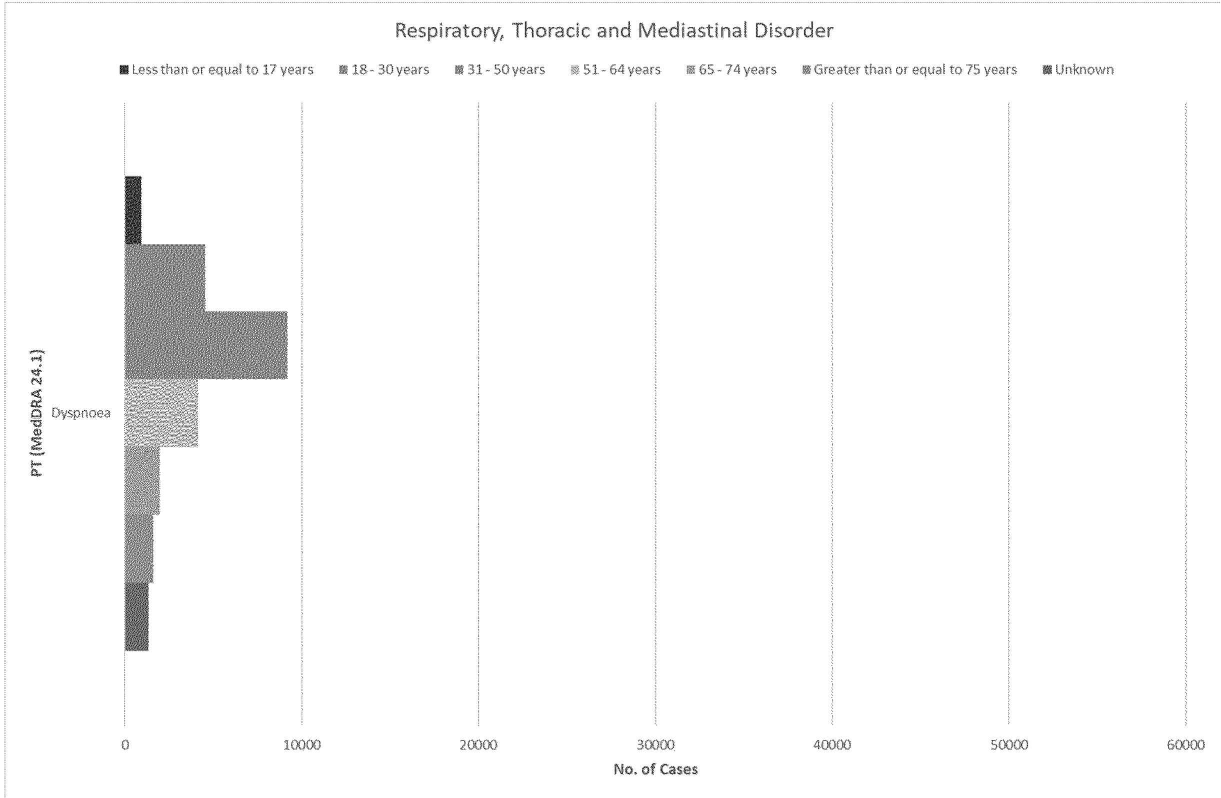


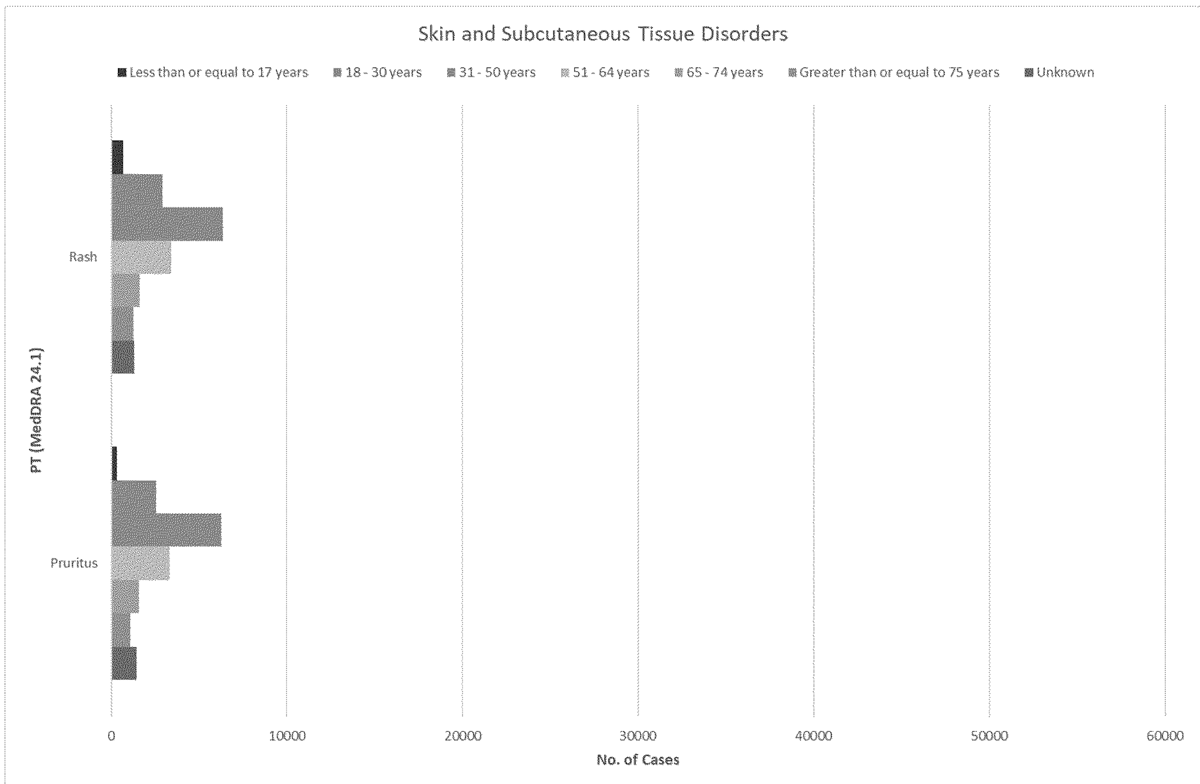
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)





090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)





090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Conclusion

Overall, during the reporting period, the serious cases represented 26.3% of the total PM; fatal outcomes occurred in less than 1% of the cases. More than two-thirds of the cases occurred in female subjects and the age group 31-50 years was the group most frequently reporting AEs. The most frequently reported (≥2%) AEs (listed in the current RSI) are in majority non-serious.

Based on the review of the PM cases, no new safety issues were identified.

6.3.1.1.2.1. Analysis by Dose

As per PSUR AR (Procedure No. EMEA/H/C/PSUSA/00010898/202106), the PRAC requested the MAH to address the following issues in the next PSUR:

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.*

Response

a. Administration of BNT162b2 with different time intervals between dose 1, 2, and 3 than the recommended posology

Cases were evaluated based on the time intervals specified in the RSI. Search criteria - Subjects who received dose 1, 2, and 3 of BNT162b2 with reported time interval between dose 1 and dose 2 different from 21 to 42 days and with reported time interval between dose 2 and dose 3 different from 181 to 183 days.

Please refer to Appendix 6A for details.

Conclusion

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

6.3.1.1.2.2. Tris/Sucrose Formulation

On 14 October 2021 a positive EMA's CHMP opinion was issued to add a new pharmaceutical form (dispersion for injection) with a new strength (0.1 mg/ml – Tris/Sucrose adult – grey cap) (Procedure No. EMEA/H/C/005735/X/0044/G, with referenced EU-RMP v2.4 and v2.5 [consolidating v2.3 and v2.4]). On 03 November 2021, a decision was adopted by the EC accordingly. On 25 November 2021, a positive EMA's CHMP opinion was received with regard to the line extension "5-11 years old" for a Tris/Sucrose paediatric formulation (0.1 mg/ml Concentrate for dispersion for injection – orange cap) (Procedure No. EMEA/H/C/005735/X/0077, with referenced EU-RMP v3.0 and v3.1 [consolidating v2.5 and v3.0]). The EC corrigendum decision was received on 03 December 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

A total of 963 PM case reports with Tris/Sucrose formulation[21] containing 2426 events (0.15% of the total PM dataset) fulfilled criteria for inclusion in this PSUR reporting period. Since the grey cap presentation was not administered during the reporting period, data presented in Table 17 through Table 19, refer to the paediatric 5-11 years old orange cap presentation. Demographic information of Tris/Sucrose cases received during the reporting interval are shown in Table 17. More than 80% of these cases (805) were reported in paediatric subjects (aged ≤ 17 years); a demographic and case comparison with paediatric PBS/Sucrose cases is provided in Table 18 and Table 19. There were no large differences in the demographic data between paediatric subjects receiving Tris/Sucrose formulation and those receiving PBS.

A higher percentage of medication error cases was reported in the Tris/Sucrose paediatric group and this may reflect initial difficulties in managing the new formulation (cross-referenced with Section 9.2 *Medication Errors* for errors related to Tris/Sucrose formulation). Routine pharmacovigilance activities to mitigate these medication errors, including label information (vial differentiation, instructions for reconstitution and administration, vaccination scheme, storage conditions for each formulation and available dosage), educational materials for healthcare providers, medical information call centers and traceability are listed in the approved version 4.0 of the EU-RMP adopted on 26 November 2021. The BLA US-PVP v 1.3 includes as routine pharmacovigilance activities label information on vial differentiation.

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

[21] Search criteria: "EUA TRIS" in the concentration field.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

PBS/Sucrose cases, Rash and Vomiting were assessed as serious events in 177 and 334 occurrences, with an AERP of 3.4% and 5.3, respectively.

Table 17. Demographic Information – Tris/Sucrose Cases – Orange Cap Received during the Reporting Interval

		Tris/Sucrose No. of Cases[a] (%)[b] / [Direct exposure][c] N=963
MC cases	Yes	627
	No	336
Country of occurrence	US	937 (97.3)
	Canada	21 (2.2)
	Israel, Puerto Rico	2 each (0.2)
	Germany	1 (0.1)
Gender	Female	304 (31.6)
	Male	309 (32.1)
	Unknown/No Data	350 (36.3)
Age (years)	N	760
	Min-Max	0.1 - 80
	Mean / Median	9.8 / 9.0
Age Range	≤ 17 years	807 (805)
	28 days to 23 months	2 (0.2) / [0]
	2-11 years	713 (74.0) / [713]
	12-17 years	92 (9.6) / [92]
	18-30 years	7 (0.7) / [7]
	31-50 years	7 (0.7) / [7]
	51-64 years	4 (0.4) / [4]
	65-74 years	3 (0.3) / [3]
	≥ 75 years	2 (0.2) / [2]
	Unknown	133 (13.8) / [133]
Case Seriousness	Serious	70
	Non-serious	893
Case Outcome	Fatal	3 (0.3)
	Not resolved	75 (7.8)
	Resolved/Resolving	148 (15.4)
	Resolved with sequelae	2 (0.2)
	Unknown/No data	735 (76.3)
Presence of comorbidities[17]	Yes	25 (2.6)
	No	938 (97.4)

a. Includes all subjects to whom BNT162b2 (Tris/Sucrose formulation) was administered.
b. Due to rounding, sum of percentages may not match 100%.
c. Includes only subjects to whom BNT162b2 (Tris/Sucrose formulation) was administered directly; does not include reports of foetus/neonates exposed before or during the mother' pregnancy or babies exposed through breastfeeding.
N: Number of cases.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 18. Demographic Information – Comparison of Paediatric Tris/Sucrose versus Paediatric PBS/Sucrose Cases

		Tris/Sucrose No. of Cases[a] (%)[b] N=805	PBS/Sucrose No. of Cases[a] (%)[b] N=18,972
MC cases	Yes	513	8559
	No	292	10413
Country of occurrence	US	781 (97.0)	2522 (13.3)
	Germany	1 (0.1)	1831 (9.7)
	Canada	19 (2.4)	366 (1.9)
	Israel	2 (0.2)	67 (0.4)
	Puerto Rico	2 (0.2)	49 (0.3)
	Other countries	0	14,137
Gender	Female	280 (34.8)	10,099 (53.2)
	Male	300 (37.3)	8265 (43.6)
	Unknown/No Data	225 (28.0)	608 (3.2)
Age (years)	N	736	18,422
	Min-Max	3-17	0-17
	Mean / Median	8.7 / 9.0	14.6 / 15.0
Age Range	0-27 days	0	13 (0.1)
	28 days to 23 months	0	45 (0.2)
	2-11 years	713 (88.6)	581 (3.1)
	12-17 years	92 (11.4)	18,333 (96.6)
Case Seriousness	Serious	66 (8.2)	7187 (37.9)
	Non-serious	739 (91.8)	11,785 (62.1)
Case Outcome	Fatal	3 (0.4)	75 (0.4)
	Not resolved	69 (8.6)	5765 (30.4)
	Resolved/Resolving	142 (17.7)	8660 (45.6)
	Resolved with sequelae	2 (0.2)	135 (0.7)
	Unknown/No data	589 (73.2)	4337 (22.9)
Presence of comorbidities[17]	Yes	22 (2.7)	1150 (6.1)
	No	783 (97.3)	17,822 (93.9)

a. Only paediatric subject received BNT162b2.
b. Due to rounding, sum of percentages may not match 100%.
N: Number of cases.

Table 19. Events Reported in ≥2%* Cases - Comparison of Paediatric Tris/Sucrose – Orange Cap versus PBS/Sucrose Cases – Purple Cap

	Tris/Sucrose	PBS/Sucrose
MedDRA SOC MedDRA PT	**N=805 n (AERP, %)**	**N=18,972 n (AERP, %)**
Blood and lymphatic system disorders		
Lymphadenopathy	4 (0.5)	658 (3.5)
Cardiac disorders		
Myocarditis	3 (0.4)	1009 (5.3)
Pericarditis	1 (0.1)	404 (2.1)
Gastrointestinal disorders		
Abdominal pain	4 (0.5)	446 (2.3)
Diarrhoea	15 (1.9)	455 (2.4)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 19. Events Reported in ≥2%* Cases - Comparison of Paediatric Tris/Sucrose – Orange Cap versus PBS/Sucrose Cases – Purple Cap

	Tris/Sucrose	**PBS/Sucrose**
MedDRA SOC MedDRA PT	**N=805** **n (AERP, %)**	**N=18,972** **n (AERP, %)**
Nausea	27 (3.3)	1943 (10.2)
Vomiting	***47 (5.8)***	1010 (5.3)
General disorders and administration site conditions		
Asthenia	9 (1.1)	517 (2.7)
Chest discomfort	1 (0.1)	474 (2.5)
Chest pain	12 (1.5)	1342 (7.1)
Chills	15 (1.9)	1079 (5.7)
Fatigue	35 (4.3)	2179 (11.5)
Malaise	10 (1.2)	1772 (9.3)
Pain	13 (1.6)	535 (2.8)
Pyrexia	61 (7.6)	3068 (16.2)
Vaccination site pain	18 (2.2)	1357 (7.1)
Injury, poisoning and procedural complications		
Expired product administered[a,c]	*180 (22.4)*	143 (0.8)
Inappropriate schedule of product administration	*23 (2.9)*	383 (2.0)
Incorrect dose administered	*61 (7.6)*	81 (0.4)
Off label use	*80 (9.9)*	322 (1.7)
Overdose	*66 (8.2)*	178 (0.9)
Poor product quality administered	*237 (29.4)*	580 (3.1)
Product administered to patient of inappropriate age[b]	*54 (6.7)*	286 (1.5)
Product preparation error	*34 (4.2)*	117 (0.6)
Product preparation issue	*175 (21.7)*	76 (0.4)
Product use issue	*46 (5.7)*	193 (1.0)
Underdose	*80 (9.9)*	94 (0.5)
Wrong product administered	*34 (4.2)*	56 (0.3)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (0.6)	580 (3.1)
Myalgia	8 (1.0)	1241 (6.5)
Pain in extremity	39 (4.8)	931 (4.9)
Nervous system disorders		
Dizziness	11 (1.4)	1418 (7.5)
Headache	44 (5.5)	3540 (18.7)
Presyncope	2 (0.2)	423 (2.2)
Syncope	1 (0.1)	915 (4.8)
Product issues		
Product temperature excursion issue	*40 (5.0)*	389 (2.0)
Reproductive system and breast disorders		
Menstrual disorder	2 (0.2)	424 (2.2)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	9 (1.1)	902 (4.8)
Skin and subcutaneous tissue disorders		
Rash	***28 (3.5)***	642 (3.4)
Urticaria	19 (2.4)	518 (2.7)
Total number of events	**2081**	**57,966**

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 19. Events Reported in ≥2%* Cases - Comparison of Paediatric Tris/Sucrose – Orange Cap versus PBS/Sucrose Cases – Purple Cap

	Tris/Sucrose	**PBS/Sucrose**
MedDRA SOC MedDRA PT	**N=805** **n (AERP, %)**	**N=18,972** **n (AERP, %)**

a. Upon review, 1 event of Expired product administered was excluded as not relevant for the Tris/Sucrose presentation.
b. Upon review, 14 events of Product administered to patient of inappropriate age were excluded as either occurred before the approval date or no error for the Tris/Sucrose presentation.
c. Majority of the cases reported uncertain expiry dates.
* Reporting proportion (% of total PM cases) in one or both paediatric populations.

Conclusion

Overall, more than 80% of the Tris/Sucrose cases was reported in paediatric subjects; the most frequently reported AEs in this population do not differ from the paediatric PBS/Sucrose formulation. A higher percentage of medication error cases was reported in the Tris/Sucrose paediatric group and this may reflect initial difficulties in managing the new formulation (Section 9.2 *Medication Errors*). Routine pharmacovigilance activities to mitigate these medication errors are listed in the approved version 4.0 of the EU-RMP adopted on 26 November 2021.

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

6.3.1.1.2.3. Third Dose / Booster Dose

As per PSUR AR (Procedure No. EMEA/H/C/PSUSA/00010898/202106), the PRAC requested the MAH to address the following issues in the next PSUR:

4. *In the PSUR under off-label use and in other relevant sections, the MAH should assess:*

    b. *the safety profile of Comirnaty when used in heterologous vaccination schedules with other vaccines.*

Response

Please refer to subsections "*Heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2)*" and "*Third/Booster doses of BNT162b2 administered after an unspecified primary COVID-19 vaccination series*".

<u>Analysis of Third Dose / Booster Dose</u>

On 12 August 2021 an EUA was granted in the US for a third dose of BNT162b2 administered at least 28 days following dose 2 in individuals 12 years of age or older who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

On 22 September 2021, EUA was also granted in the US for a single booster dose of the BNT162b2 vaccine administered at least 6 months after completing the primary series in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at -high risk of serious complications of COVID-19 including severe COVID-19.

On 19 November 2021, the US FDA issues an EUA to approve the use of BNT162b2 as a single booster dose in individuals 18 years of age or older, at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), or following completion of primary vaccination with another authorised COVID-19 vaccine (i.e., as a heterologous booster dose). On 09 December 2021, the US FDA issued an EUA expanding the eligible population for the homologous booster doses to individuals 16 years of age and older.

On 05 October 2021, the EC issued a decision implementing the SmPC update submitted under Type II variation 62 (Procedure No. EMEA/H/C/005735/II/0062) and covering the introduction of a third dose of the vaccine at least 28 days after the second dose to individuals 12 years of age and older who are severely immunocompromised.

On the same date, on 05 October 2021, the European Commission decision was also issued for variation 67 (Procedure No. EMEA/H/C/005735/II/0067) covering the introduction of a booster dose of BNT162b2 to be administered at least 6 months after the second dose in individuals 18 years of age and older, based on interim safety and immunogenicity data from the interventional study C4591001.

Search criteria - Dose number = 3 OR Dose Description containing the word "BOOSTER" OR LLT = BOOSTER.

Upon review,

- 22 cases (2 CT and 20 PM) involving babies were excluded due to indirect exposure to BNT162b2.
- 17 PM cases were determined to be non-contributory and were not included in the discussion since in these cases the booster dose administered was not BNT162b2.

Overall

- Number of cases: 25,852 (3.9% of 658,249, the total dataset).
- MC cases (6992), NMC cases (18,860).
- Country of incidence (≥2%): UK[22] (15,115), US (4627), Netherlands (1162), France (702), Italy (593), Germany (571).

[22] Booster dose approved on 29 October 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Case seriousness: serious (11,597), non-serious (14,255).
- Case outcome: fatal (422), resolved/resolving (8208), resolved with sequelae (346), not resolved (12,729), unknown (4147).
- Most frequently reported PTs (≥2% of third dose/booster dataset): Immunisation[23] (21,658), Off label use[23] (14,764), Interchange of vaccine products (9468), Headache (5371), Fatigue (4657), Pyrexia (4009), Chills (3050), Lymphadenopathy (3023), Pain in extremity (3022), Nausea (2584), Pain (2555), Myalgia (2471), Arthralgia (2382), Malaise (2165), Vaccination site pain (2094), Dizziness (1465), Diarrhoea (1156), Axillary pain (1135), Dyspnoea (1091), Pruritus (1068), Vomiting (997), Rash (983), Asthenia (977), Swelling (975), Chest pain (968), Peripheral swelling (962), Palpitations (803), Vaccination site swelling (771), Vaccination site erythema (693), Erythema (673), Influenza like illness (653), Lymph node pain (632), Feeling abnormal (580), Paraesthesia (556), Hyperhidrosis (546), Back pain (542), Insomnia (537), Cough (536), Illness (521) and Product use issue[23] (518).

Homologous doses schedule (primary series and booster with BNT162b2)

Clinical Trial Data

- Number of cases: 102 (BNT162b2/BNT162b2S01 [52], blinded therapy [44] and placebo [7]) (14.1% of 721 cases, the total CT dataset; 0.4 % of the third dose/booster dataset).
- Country of incidence: US (91), Argentina and Brazil (5 each), (1).
- Subjects' gender: female (49), and male (53).
- Subjects' age in years (n = 101), range: 10-83, mean: 56.9, median: 59.0.
- Case outcome: fatal (3), resolved/resolving (75), resolved with sequelae (4), not resolved (18), unknown (2).
- Medical history (n = 90): the medical conditions (≥5 occurrences) included Hypertension (39), Type 2 diabetes mellitus (22), Gastrooesophageal reflux disease (15), Obesity (14), Hyperlipidaemia and Osteoarthritis (12 each), Depression (11), Hypothyroidism (10), Anxiety, Blood cholesterol increased and Seasonal allergy (9 each), Asthma, Back pain, Hypercholesterolaemia, Insomnia (8 each), Irritable bowel syndrome (6), Atrial fibrillation, Benign prostatic hyperplasia, Coronary artery disease, Female sterilization, Intervertebral disc protrusion, Migraine, Myocardial infarction and Sleep apnoea syndrome (5 each).
- COVID-19 medical history: None.
- Number of SAEs: 124.
- The most reported (≥ 2% of homologous doses schedule CT cases) PTs were Acute kidney injury, Appendicitis, Diverticulitis, Nephrolithiasis, Prostate cancer, Small intestinal obstruction (3 each), Acute myocardial infarction, Back pain, Cellulitis,

[23] PT selected per case processing conventions to indicate cases reporting third/booster doses.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Cerebral haemorrhage, Cholecystitis acute, Condition aggravated, Coronary artery disease, Intervertebral disc protrusion, Myocardial infarction, Myocarditis, Non-cardiac chest pain, Osteoarthritis, Osteomyelitis, Pulmonary embolism, Road traffic accident and Suicidal ideation (2 each).

- BNT162b2 related (per investigator or sponsor) events coded to the PT: Myocarditis (2), Appendicitis, Hepatic enzyme increased (1 each). Time to onset of event ranged from 0 days (Myocarditis) to 16 days (Hepatic enzyme increased). None of the events were related to blinded therapy.

Post-Authorisation Data

- Number of cases: 13,569 (2.1% of 657,528 cases, the total PM dataset; 52.5% of the third dose/booster dataset).
- MC cases (4483), NMC cases (9086).
- Country of incidence (≥2%): UK (6226), US (3920), Netherlands (538), France (479), Italy (400), Germany (321).
- Subjects' gender: female (9545), male (3208) and unknown (816).
- Subjects' age in years (n = 11,501), range: 12 – 104, mean: 54.6, median: 54.0.
- Case outcome: fatal (257), resolved/resolving (4456), resolved with sequelae (194), not resolved (6065), unknown (2597).
- Medical history (n = 6263): the most frequently (≥2% of homologous doses schedule PM cases) reported medical conditions included Hypertension (1022), Asthma (594), Immunodeficiency (427), Drug hypersensitivity (404), Disease risk factor (380), Diabetes mellitus (309) and Hypothyroidism (307).
- COVID-19 Medical history (n = 914): Suspected COVID-19 (558), COVID-19 (359), Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (8 each), Asymptomatic COVID-19 and COVID-19 pneumonia (6 each), Exposure to SARS-CoV-2 (5), Coronavirus infection, Coronavirus test positive and Occupational exposure to SARS-CoV-2 (1 each).
- Number of events: 66,295.
- Event seriousness[20]: serious (24,542), non-serious (41,776).
- The most reported (≥ 2% of homologous doses schedule PM cases) PTs were Immunisation[23] (10,302), Off label use (4832), Headache (2611), Fatigue (2371), Pyrexia (2154), Chills (1519), Pain in extremity (1512), Lymphadenopathy (1500), Pain (1413), Nausea (1277), Myalgia (1268), Arthralgia (1187), Vaccination site pain (1092), Malaise (1031), Dizziness (753), Dyspnoea (582), Diarrhoea (573), Axillary pain (529), Asthenia (516), Vomiting (508), Swelling (500), Pruritus (498), Chest pain (495), Rash (494), Peripheral swelling (444), Vaccination site swelling (384), Palpitations (369), Extra dose administered[23] (367), Feeling abnormal (352), Vaccination site erythema (343), Product use issue (329), Erythema (326), Lymph node pain (324), COVID-19 (317), Back pain (298), Cough (296), Influenza like illness (293) and Paraesthesia (273).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2)[24]

Post-Authorisation Data

- Number of cases: 9609 (1.5% of 657,528 cases, the total PM dataset; 37.2% of the third dose/booster dataset).
- MC cases (1299), NMC cases (8310).
- Country of incidence (≥2%): UK (7934), Netherlands (616), US (237), Brazil (208).
- Subjects' gender: female (6796), male (2392) and unknown (421).
- Subjects' age in years (n = 8278), range: 0.5 – 103, mean: 55.0, median: 56.0.
- Case outcome: fatal (54), resolved/resolving (2923), resolved with sequelae (101), not resolved (5840), unknown (691).
- Medical history (n = 4594): the most frequently (≥2%) reported medical conditions included Hypertension (526), Immunodeficiency (523), Asthma (456), Clinical trial participant and Disease risk factor (417 each), Steroid therapy (288) and Hypothyroidism (199).
- COVID-19 Medical history (n = 1080): Suspected COVID-19 (826), COVID-19 (294), Post-acute COVID-19 syndrome (20), SARS-CoV-2 test positive (5), COVID-19 pneumonia (4), Asymptomatic COVID-19 (3) and Exposure to SARS-CoV-2 (1).
- Among the 9609 cases reporting administration of heterologous third/booster doses of BNT162b2 vaccine, the previous vaccine series consisted of:
  - 5187 subjects immunised with unknown non-Pfizer-BioNTech COVID-19 Vaccine[25];
  - 3257 subjects immunised with AstraZeneca vaccine[26];
  - 595 subjects immunised with Moderna vaccine;
  - 269 subjects immunised with Coronavac vaccine;
  - 184 subjects immunised with Johnson and Johnson vaccine;
  - 49 subjects immunised with Sinopharm vaccine;
  - 42 subjects immunised with Novavax vaccine;

---

[24] Per case processing convention the PT Interchange of vaccine products was co-reported.

[25] In mixed schedule including BNT162b2 + generic non-BNT162b2 vaccine, BNT162b2 + generic non-BNT162b2 vaccine + COVID-19 AstraZeneca vaccine or COVID-19 Moderna vaccine or COVID-19 J&J vaccine or Coronavac.

[26] In mixed schedule including BNT162b2 + COVID-19 AstraZeneca vaccine, BNT162b2 + COVID-19 AstraZeneca vaccine + COVID-19 Moderna vaccine or COVID-19 J&J vaccine or Coronavac or Covidshield or Zycovid.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 17 subjects immunised with Sputnik vaccine;
  - 3 subjects each immunised with Curevac or Covidshield vaccine;
  - 1 subject each immunised with Convidecia or Covilo, other vaccine.
- Number of events: 66,290.
- Event seriousness[20]: serious (36,044), non-serious (30,268).
- The most reported (≥ 2%) PTs were Interchange of vaccine products[24] (9468), Off label use (9143), Immunisation[23] (8969), Headache (2389), Fatigue (1991), Pyrexia (1452), Lymphadenopathy (1332), Chills (1321), Pain in extremity (1280), Nausea (1142), Arthralgia (1032), Myalgia (1029), Malaise (979), Pain (969), Vaccination site pain (841), Dizziness (604), Axillary pain (538), Diarrhoea (505), Pruritus (495), Peripheral swelling (444), Swelling (430), Rash (422), Vomiting (416), Chest pain (400), Dyspnoea (391), Palpitations (378), Asthenia and Vaccination site swelling (335 each), Vaccination site erythema (307), Influenza like illness (297), Erythema (296), Lymph node pain (263), Decreased appetite (253), Hyperhidrosis and Insomnia (248 each), Feeling cold (234), Paraesthesia (231), Tremor (223), Illness (218), Back pain (213), Vaccination site warmth (197) and Cough (194).

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

Post-Authorisation Data

- Number of cases: 2572 (0.4% of 657,528 cases, the total PM dataset).
- MC cases (1108), NMC cases (1464).
- Country of incidence (≥2%): UK (955), US (379), Italy (173), Germany (171), France (162), Austria (74), Lithuania (63), Spain (61), Sweden (60), Israel (51).
- Subjects' gender: female (1604), male (739) and unknown (229).
- Subjects' age in years (n = 2006), range: 6 – 108, mean: 58.4, median: 59.0.
- Case outcome: fatal (108), resolved/resolving (754), resolved with sequelae (47), not resolved (806), unknown (857).
- Medical history (n = 909): the most frequently (≥2%) reported medical conditions included Hypertension (185), Asthma (59), Atrial fibrillation (54) and Type 2 diabetes mellitus (52).
- COVID-19 Medical history (n = 73): Suspected COVID-19 (47), COVID-19 (24), SARS-CoV-2 antibody test positive and SARS-CoV-2 test positive (1 each).
- Number of events: 11,318.
- Event seriousness[20]: serious (4449), non-serious (6872).
- The most reported (≥ 2%) PTs were Immunisation[23] (2387), Off label use (789), Pyrexia (403), Headache (371), Fatigue (295), Pain in extremity (230), Chills (210), Lymphadenopathy (191), Myalgia (174), Pain (173), Nausea (165), Arthralgia (163),

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Vaccination site pain (161), Malaise (155), Asthenia (126), Dyspnoea (117), Dizziness (108), Poor quality product administered (99), Diarrhoea (78), Pruritus (75), Peripheral swelling (74), Vomiting (73), Chest pain (72), Axillary pain (68), Product temperature excursion issue and Rash (66 each), Influenza like illness (63), Expired product administered (62), Palpitations (56), Hyperhidrosis, Paraesthesia and Vaccination site swelling (52 each).

Analysis booster doses versus primary vaccination series

The most frequently reported clinical adverse events[27] in PM cases of subjects who received the third/booster doses of BNT162b2 were consistent with those reported in subjects receiving primary vaccination series, as shown in Table 20. A higher reporting frequency of 5 PTs (Chills, Lymphadenopathy, Pain in extremity, Axillary pain and Peripheral swelling) was noted in subjects who received the third / booster doses of BNT162b2 (11.8%, 11.7%, 11.7%, 4.4% and 3.7%, respectively) compared to subjects receiving the primary vaccination series (8.0%, 4.2%, 5.7%, 0.8% and 0.9%, respectively); of note, this is consistent, in the context of lymphadenopathy reactions, with the RSI data for participants receiving a booster dose as seen in interventional clinical studies.

Table 20. Comparison of clinical AEs reported in ≥2% Booster Dose or Third Dose Cases vs Primary Series Cases

PT Decode (Event)	Booster-3rd Dose Cases N = 25,852		Primary Series Cases N =632,358	
	n	AERP[a] (%)	n	AERP[a] (%)
Off label use	14764	(57.1)	7273	(1.2)
Headache	5371	(20.8)	129668	(20.5)
Fatigue	4657	(18.0)	104822	(16.6)
Pyrexia	4009	(15.5)	102118	(16.1)
Chills	3050	(11.8)	50473	(8.0)
Lymphadenopathy	3023	(11.7)	26408	(4.2)
Pain in extremity	3022	(11.7)	35989	(5.7)
Nausea	2584	(10.0)	53158	(8.4)
Pain	2555	(9.9)	35389	(5.6)
Myalgia	2471	(9.6)	82419	(13.0)
Arthralgia	2382	(9.2)	54231	(8.6)
Malaise	2165	(8.4)	79433	(12.6)
Vaccination site pain	2094	(8.1)	93887	(14.8)
Dizziness	1465	(5.7)	36517	(5.8)
Diarrhoea	1156	(4.5)	19725	(3.1)
Axillary pain	1135	(4.4)	4965	(0.8)
Dyspnoea	1091	(4.2)	22667	(3.6)
Pruritus	1068	(4.1)	15585	(2.5)
Vomiting	997	(3.9)	14927	(2.4)
Rash	983	(3.8)	16609	(2.6)
Asthenia	977	(3.8)	20220	(3.2)
Swelling	975	(3.8)	8329	(1.3)

[27] The PT Immunisation and Interchange of vaccine products are not included in the Table 20.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 20. Comparison of clinical AEs reported in ≥2% Booster Dose or Third Dose Cases vs Primary Series Cases

PT Decode (Event)	Booster-3rd Dose Cases N = 25,852		Primary Series Cases N =632,358	
	n	AERP[a] (%)	n	AERP[a] (%)
Chest pain	968	(3.7)	16565	(2.6)
Peripheral swelling	962	(3.7)	5951	(0.9)
Palpitations	803	(3.1)	12020	(1.9)
Vaccination site swelling	771	(3.0)	21344	(3.4)
Vaccination site erythema	693	(2.7)	12408	(2.0)
Erythema	673	(2.6)	9294	(1.5)
Influenza like illness	653	(2.5)	12003	(1.9)
Lymph node pain	632	(2.4)	3103	(0.5)
Feeling abnormal	580	(2.2)	7438	(1.2)
Paraesthesia	556	(2.2)	19252	(3.0)
Hyperhidrosis	546	(2.1)	6690	(1.1)
Back pain	542	(2.1)	7925	(1.3)
Insomnia	537	(2.1)	6832	(1.1)
Cough	536	(2.1)	10262	(1.6)
Illness	521	(2.0)	2229	(0.4)
Product use issue	518	(2.0)	3494	(0.6)

a. Calculated as n/N.

Conclusion

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

6.3.1.1.2.4. Batch-Related issues

The most frequently reported lot numbers in PM case reports (≥3000 cases) are listed in Table 21 below.

Table 21. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
FC5089	6054
FE1573	5755
FC3098	5621
FC3143	5104
FE7010	5028
FF4213	3821
FF0688	3582
EK9788	3419
EY5420	3402
ER7449	3330

The AEs most frequently reported (≥5%) with these lot numbers do not differ from those reported in the overall interval dataset.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Overall, there were no related quality issues identified during product complaint 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.

Conclusion

Based on the review of the cases with the most frequently reported lot numbers, no new safety issues were identified.

6.3.1.2. General Overview of the Safety Database - Unlocked Cases

A total of 139,698 unlocked[28] case reports (69 from CT and 139,629 from PM) containing 398,500 events fulfilled criteria for inclusion in this PSUR, compared to 145,825 (44.5%) case reports retrieved in the PSUR #1. Table 22 displays demographic information of the unlocked cases at the end of the reporting interval.

Table 22. Demographic Information - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=139,698	CT No. of Cases (%[a]) N=69	PM No. of Cases (%[a]) N=139,629
No. of Cases		139,698	69	139,629
MC	Yes	102,160 (73.1)	69 (100)	102,091 (73.1)
	No	37,538 (26.9)	0	37,538 (26.9)
Country of occurrence (≥2% of all cases)	Japan	81,092 (58.0)	0	81,092 (58.1)
	US	20,078 (14.4)	46 (66.7)	20,032 (14.3)
	Australia	9118 (6.5)	0	9118 (6.5)
	Canada	4151 (3.0)	0	4151 (3.0)
	Netherlands	3324 (2.4)	0	3324 (2.4)
	Other countries	21,935 (15.7)	23 (33.3)	21,912 (15.7)
Gender	Female	90,983 (65.1)	29 (42)	90,954 (65.1)
	Male	36,448 (26.1)	39 (56.5)	36,409 (26.1)
	Unknown/No Data	12,267 (8.8)	1 (1.4)	12, 266 (8.8)
Age (years)	N	111,630	61	111,569
	Min-Max	0.25 – 117	0.83 – 84	0.25 – 117
	Mean[b]	43.4	44.6	43.4
	Median[b]	42.0	53.0	42.0

[28] Unlocked cases are those cases either in the Drug Safety Unit, 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 22. Demographic Information - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=139,698	CT No. of Cases (%[a]) N=69	PM No. of Cases (%[a]) N=139,629
Age Range	≤ 17	4430 (3.2)	17 (24.6)	4413 (3.2)
	18-30	24,707 (17.7)	2 (2.9)	24,705 (17.7)
	31-50	47,236 (33.8)	11 (15.9)	47,225 (33.8)
	51-64	21,993 (15.7)	21 (30.4)	21,972 (15.7)
	65-74	9130 (6.5)	9 (13.0)	9121 (6.5)
	≥ 75	5563 (4.0)	6 (8.7)	5557 (4.0)
	Unknown	26,620 (19.1)	2 (2.9)	26,618 (19.1)
	Not applicable	19 (0.0)	1 (1.4)	18 (0.0)
Case Seriousness	Serious	7799 (5.6)	69 (100)	7730 (5.5)
	Non-serious	131,899 (94.4)	0	131,899 (94.5)
Case Outcome	Fatal	300 (0.2)	6 (8.7)	294 (0.2)
	Not resolved	18,514 (13.2)	11 (15.9)	18,503 813.39
	Resolved/Resolving	66,140 (47.3)	48 (69.6)	66,092 (47.3)
	Resolved with sequelae	636 (0.5)	3 (4.3)	633 (0.5)
	Unknown	54,108 (38.7)	1 (1.4)	54,107 (38.8)
Presence of comorbidities	Yes	9635 (6.9)	26 (37.7)	9609 (6.9)
	No	130,063 (93.1)	43 (62.3)	130,020 (93.1)

a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Values referred to all cases with an age in years not null; including 206 cases with indirect exposure.

6.3.1.2.1. General Overview of the Safety Database Unlocked Cases - Clinical Trials Data

The events reported more than once in clinical trial cases that were unlocked at the end of the reporting interval were coded to the PTs Maternal exposure during pregnancy (8), Urinary tract infection (4), Appendicitis and Coronary artery disease (3 each), Acute myocardial infarction, Cellulitis, Epilepsy, Pneumonia respiratory syncytial viral, Respiratory syncytial virus bronchiolitis and Syncope (2 each).

6.3.1.2.2. General Overview of the Safety Database Unlocked Cases - Post-Authorisation 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 23. Post-Authorisation Data: Events Reported in ≥2% of Unlocked Cases

MedDRA SOC MedDRA PTs	N=139,629 n (AERP,[d] %)
Blood and lymphatic system disorders	
Lymphadenopathy[a]	3157 (2.26)
Gastrointestinal disorders	
Nausea[a]	7332 (5.25)
Diarrhoea[a]	4072 (2.92)

Table 23. Post-Authorisation Data: Events Reported in ≥2% of Unlocked Cases

MedDRA SOC MedDRA PTs	N=139,629 n (AERP,[d] %)
General disorders and administration site conditions	
Vaccination site pain[a]	34,834 (24.95)
Pyrexia[a]	32,045 (22.95)
Malaise[a]	26,459 (18.95)
Fatigue[a]	17,780 (12.73)
Pain[b]	16,166 (11.58)
Chills[a]	9650 (6.91)
Vaccination site swelling[a]	8107 (5.81)
Swelling[b]	3982 (2.85)
Vaccination site erythema[a]	3472 (2.49)
Feeling cold[a]	3082 (2.21)
Injury, poisoning and procedural complications	
Inappropriate schedule of product administration[c]	5035 (3.61)
Poor quality product administered[c]	3085 (2.21)
Musculoskeletal and connective tissue disorders	
Myalgia[a]	21,647 (15.5)
Arthralgia[a]	13,310 (9.53)
Pain in extremity[a]	8160 (5.84)
Nervous system disorders	
Headache[a]	30,963 (22.18)
Dizziness[b]	5205 (3.73)
Hypoaesthesia[a]	2846 (2.04)
Skin and subcutaneous tissue disorders	
Pruritus [a]	3423 (2.45)
Total number of events	**398,401**

a. Listed or consistent with listed AEs in current RSI.
b. Unlisted in the current RSI.
c. Listed per case processing convention.
d. Reporting proportion (% of total cases) calculated as n/N at the end of the current reporting period.
N: Number of Cases; n: Number of events.

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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

7.2. Ongoing Clinical Trials

During the reporting period, there were 14 ongoing[29] 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 and older*] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.
  - C4591024 [*A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age*] is an ongoing PASS. No clinically important information has emerged from this ongoing PASS.
- Other trials where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.

Other Trials that reported new significant efficacy information

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.*
- *C4591007, A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children <12 years of age.*
- *C4591017, A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple production lots and dose levels of the vaccine candidate BNT162b2 against COVID-19 in healthy participants 12 through 50 years of age and the safety, tolerability, and immunogenicity of BNT162b2 RNA-based COVID-19 vaccine candidates as a booster dose in healthy participants 18 through 50 years of age.*
- *C4591031, A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.*

---

[29] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- *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,*[30] *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,*[30] *Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy subjects: A phase II, randomized, placebo-controlled, observer-blind study.*
- *BNT162-14, A Phase II, open-label rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.*

No clinically important information has emerged from ongoing clinical trials.

Remaining Trials

There were 3 ongoing clinical trials:

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

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

7.3. Long-term Follow-up

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

[30] This study is conducted by Shanghai Fosun Pharmaceutical Development, Inc. and sponsored by BioNTech SE.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

7.4. Other Therapeutic Use of Medicinal Product

BNT162b2 was also utilised in another Pfizer-sponsored clinical development program (B747). The study B7471026 is ongoing. There was no new clinically important safety information identified for this reporting period.

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 9 ongoing[29] 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[31], C4591010, C4591012[32], C4591021[32] and C4591022[32] are PASS. No clinically important information has emerged from PASS.
- Other studies where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product: None.

Other Studies

There were 4 ongoing non-interventional studies:

- *C4591006, General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).*
- *C4591014,[33] Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- *C4591019, Special investigation in the population with underlying diseases considered to increase the risk of severe illness of COVID-19.*
- *C4591035, Coronavirus Disease 2019 (COVID-19) Vaccination and Breakthrough Infections Among Persons with Immunocompromising Conditions in the United States.*

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

---

[31] 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.

[32] Studies C4591012, C4591021 and C4591022 are commitments to the US FDA and are Category 3 commitments in the EU-RMP.

[33] PAM-MEA-013.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

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

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

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

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

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

9.2. Medication Errors

As per the commitment included in the procedure EMEA/H/C/005735/MEA/002.10 (11th SMSR), "*The MAH should report on handling and dosing errors as a result of the different Comirnaty formulations on the market.*"

Response

Please refer to Appendix 6A for details.

Analysis of the Medication Errors

Cases potentially indicative of medication errors[34] that occurred in the reporting period are summarised below.

[34] Search criteria: MedDRA (version 24.1): *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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

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

Post-Authorisation Data

From the global safety database, 35,224 cases (5.4% of 657,528 cases, the total PM dataset) potentially indicative of medication errors were retrieved during the reporting period.

Of the 35,224 retrieved cases, 1390 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Off-label use or misuse rather than medication error was reported in 650 cases;
- Reporting information was no longer consistent to meet medication error criteria in 240 cases;
- Cases consisted of questions or requests for information about the scheduling of the 2 doses of BNT162b2 or the second dose (not administered yet at the time of reporting) or scheduling outside the prescribed dosing window were reported in 228 cases;
- Medical inquiries only were reported in 50 cases;
- The subject intentionally refused to be vaccinated or was not able to receive the scheduled BNT162b2 in 184 cases;
- In 15 cases subjects were exposed to the vaccine during the mother' pregnancy or through breastfeeding.
- An unspecified number of subjects were described in 23 cases.

The potentially relevant medication error cases during the reporting period were 33,834 (5.1%) reporting 42,992 events, compared to 10,776 relevant cases (3.3%) analysed in the PSUR #1.

---

errors and communication issues, OR *PTs*: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Contraindication to vaccination; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

The 33,834 relevant medication error cases originated mostly (≥2% of cases) from the following countries: the US (9748), the UK (5817), Germany (3292), Austria (2323), Netherlands (2270), Japan (2051), Canada (1784), Sweden (1510), and France (918).

Of the 33,834 medication error cases reporting 42,992 medication error events, the most frequently reported (≥2% of cases) medication error PTs were: Inappropriate schedule of product administration (18,537), Poor quality product administered (7503), Product temperature excursion issue (5509), Incorrect route of product administration (1873), Expired product administered (1689), Underdose (1058), Product preparation error (1048), Product storage error (1040), Product preparation issue (846), and Incorrect dose administered (811).

During the reporting interval, 6 different types of medication error cases (>175 occurrences) were identified coding the PTs Product temperature excursion issue and Poor quality product administered. All cases demonstrated no-harm and had no co-reported events:

From the US:

- in 590 cases BNT162b2 was stored in the standard freezer for a duration of more than 14 days prior to use.
- in 361 cases the undiluted BNT162b2 was moved from ultra-cold storage to standard freezer and stored in the standard freezer for more than 2 weeks prior to use.
- in 312 cases BNT162b2 was stored in standard freezer for 25 days and the vaccine was administered to subjects 7 days past excursion time.
- in 311 cases various temperature excursions for BNT162b2 vials stored in the standard freezer and refrigerator were reported (number of days of storage unspecified).
- in 191 cases, subjects were administered BNT162b2 that was stored in the standard freezer for more than 14 days.

From Canada:

- In 180 cases, subjects received BNT162b2 that was kept between 17 and 33 days in the freezer.

Medication Errors Analysis

Among the relevant medication error cases (33,834 cases[35]), the following scenarios, were described:

- Medication errors associated with harm [ie, resulting in adverse reaction(s)] according to EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014) were reported in 879 cases (2.6% of relevant

[35] Relevant medication error cases 33,834 (879 harm + 32582 no-harm + 373 potential + no intercepted errors).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

medication error cases) compared to 291 cases (2.9% of relevant medication error cases) analysed in the PSUR #1.

Of note, some cases involved more than one medication error.

Medication errors associated with harm (955 medication error events in 879 cases)

Of the 879 cases, 250 were medically confirmed and 629 were non-medically confirmed. Cases were mostly (>10 occurrences) reported from Germany (384), the US (139), Italy (63), Canada (47), France (44), Japan (34), the UK (32), Spain (26), and Netherlands (12).

There were 611 females and 216 male subjects, whereas the gender was not specified for 52 subjects. When provided (n = 802), the age ranged from 1 month to 97 years with a mean age of 44.5 years and a median of 44 years.

Of the 955 medication error events, 69 were serious and 886 were non-serious. The relevant event outcome was reported as fatal (3), resolved/resolving (37), resolved with sequelae (2), not resolved (25), and unknown (888).

There were 3 fatal medication error events reported in 2 cases and they were coded to the PTs Poor quality product administered, Product temperature excursion issue, Incomplete course of vaccination (Section 16.3.4.1 *Death*).

- First case (PTs Poor quality product administered, Product temperature excursion issue): A ████ subject of unknown age experienced COVID-19 at an unspecified interval post vaccine administration (unspecified dose and route). The subject's physician reported that the inadequate storage of the vaccine decreased its effectiveness. On an unspecified date, the subject died due to COVID-19. It was not reported if an autopsy was performed. This case had limited information and did not provide lot number, storage details, dose number, treatment details, medical history and concomitant medications.
- Second case from EudraVigilance (PT Incomplete course of vaccination): A ██████ ████ subject received a dose of BNT162b2 (batch/lot number: unknown) after having received AstraZeneca vaccine as ███ first COVID-19 vaccine dose. According to the reporter (consumer/other non-health care professional), the subject died from the event of myocardial infarction, interchange of vaccine products, and incomplete vaccination course on an unspecified date. It was unknown if an autopsy was performed. This case had limited information on the date of vaccine administration, concurrent disease, risk factors, event onset date, circumstances leading to fatal events, and laboratory details.

Serious medication errors

In 59 cases (involving 69 medication error events; 6.7% of 879 cases), serious medication errors potentially contributed to the occurrence of SAEs when compared to 60 serious cases (involving 64 medication error events; 20.6% of 291 cases) analysed in the PSUR #1.

Cases originated from the UK (14), the US (12), Ireland (6), Portugal, Canada, Sweden, Italy (4 each), Brazil (2), France, South Africa, Denmark, Mexico, Finland, Netherlands, Belgium, Germany, and Norway (1 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

The serious events indicative of medication error were Product administered at inappropriate site (20), Incorrect route of product administration (9), Product administration error (8), Product preparation error (7), Wrong technique in product usage process (6), Expired product administered (3), Extra dose administered, Incorrect dose administered, Product temperature excursion issue, Wrong product administered, Product administered to patient of inappropriate age (2 each), Vaccination error, Accidental overdose, Accidental exposure to product by child, Incomplete course of vaccination, Medication error, and Poor quality product administered (1 each).

The most frequently (>3 occurrences) co-reported clinical events were Pain in extremity (18), Headache (12), Vaccination site pain (9), Arthralgia, Fatigue (8 each), Myalgia, Pain (7 each), Pyrexia (6), Asthenia, Chills, Dizziness, Hypoaesthesia, Joint range of motion decreased, Peripheral swelling, Shoulder injury related to vaccine administration, and Vaccination site movement impairment (4 each).

Upon review of medication error serious events:

Vaccine administration errors (59 events, 49 cases)

Events described in these cases were: errors of vaccination at the wrong anatomical site, errors in administration technique, errors in route of administration, errors in vaccine dosage, administration of wrong vaccine, accidental exposure to vaccine, and other administration errors.

- *Errors of vaccination at the wrong anatomical site (26 events)*
  - The vaccine was administered in the shoulder (12 events), arm site other than deltoid (8 events), leg (2 events), bursa, brachial (1 event each), and unspecified site of administration (2 events).
- *Administration technique errors (10 events)*
  - Errors included injury to nerve or blood vessel (5 events), incorrect handling of syringe, administered too quickly, blue spot at the vaccination site (1 event each), and other unspecified administration technique errors (2 events).
- *Errors in the route of administration (8 events)*
  - The route of administration for the vaccine was intravenous (3 events), intradermal (2 events), intra-articular, subcutaneous and unspecified route other than intramuscular (1 event each).
- *Errors in vaccine dosage administered (5 events)*
  - Errors included administration of larger doses (2 events), received additional dose (1 event), and incorrect unspecified dose administered (2 events).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- *Wrong vaccine administered (3 events)*
  - Errors included administration of fourth dose of BNT162b2 instead of flu shot (1 event) and errors in mixed vaccination (first dose of Moderna vaccine and second dose of BNT162b2, first dose of BNT162b2 vaccine and second dose of AstraZeneca vaccine [1 event each]).
- *Use in unauthorised population (2 events)*
  - The event reported unintentional administrations of vaccine to paediatric subjects below 5 years of age.
- *Accidental exposure to vaccine (1 event)*
  - Error involved exposure to the skin.
- *Administration of inadequately prepared vaccine (1 event)*
  - Error included administration after temperature excursion.
- *Other vaccine administration errors (3 events)*
  - These events reported administration of expired vaccines.

Vaccine preparation errors (7 events, 7 cases)

- Errors included dilution not performed.
  - Other errors (3 events, 3 cases).
- Errors included temperature excursion (2 events) or error reported with unspecified details (1 event).

Non-serious medication errors

In 820 cases (involving 886 medication error events), non-serious medication errors potentially contributed to the occurrence of non-serious AEs. Most of the cases (>10 occurrences) originated from Germany (383),[36] the US (127), Italy (59), Canada, France (43 each), Japan (34), Spain (26), the UK (18), and Netherlands (11).

The most frequently (>30 occurrences) co-reported clinical events were Vaccination site pain (170), Headache (157), Fatigue (139), Pain in extremity (113), Pyrexia (110), Nausea (60), Myalgia (56), Dizziness, Influenza like illness (54 each), Pain (51), Limb discomfort (48),

[36] Among the 383 cases, majority of the cases (93.7%) originated from German Federal Agency (Paul Ehrlich Institute - an Agency of the German Federal Ministry of Health). Most of these cases were received in batches and reported event onset time prior to the reporting period of the current PSUR.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Arthralgia (46), Malaise (39), Asthenia (36), Paraesthesia (33), Lymphadenopathy and Rash (32 each).

- *Vaccine administration errors*[37] *(823 events):* Events mainly described errors in route of administration, errors in the volume or dosage of the vaccine administered, errors in administration of vaccine dose not adequately prepared, errors of vaccination at the wrong anatomical site, errors in the administration of incorrect product, and other administration errors.
- *Vaccine preparation errors*[38] *(29 events)*: Events mainly described errors during dilution and other preparation errors.
- *Other medication errors*[39] *(34 events)*: Events mainly described temperature excursion, vaccine administration technique, lot number, vaccination error, and other errors.

The summary of analysis of medication errors pertaining to the new BNT162b2 formulations (Tris/Sucrose presentation) is presented below.

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

Search criteria used for selecting the below cases for discussion: Paediatric subjects 5 to <12 years of age received Tris/Sucrose Orange cap (10 mcg/dose) presentation; Paediatric subjects (5 to <12 years) received adult/adolescent formulation (PBS/Sucrose Purple cap presentation) instead of Tris/Sucrose Orange cap presentation; Tris/Sucrose Orange cap formulation was used or administered to age groups other than 5 to < 12 years instead of PBS/Sucrose presentation.

There were 755 cases reporting 1411 events indicative of medication errors related to Tris/Sucrose presentation (paediatric formulation). Of which,

- In 638 cases, the reporter described the errors due to the use/administration of Tris/Sucrose presentation.

[37] PTs Incorrect route of product administration, Incorrect dose administered, Product administered at inappropriate site, Poor quality product administered, Product administered to patient of inappropriate age, Expired product administered, Underdose, Wrong technique in product usage process, Wrong product administered, Product administration error, Accidental overdose, Accidental exposure to product, Extra dose administered, Incomplete course of vaccination, Exposure via skin contact, Incorrect product formulation administered.

[38] PTs Product preparation error, Product preparation issue, Underdose, Accidental overdose (if associated to other PT indicative of erroneous preparation).

[39] PTs Product temperature excursion issue, Vaccination error, Medication error, Product storage error, Wrong technique in product usage process, Product lot number issue.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- In 112 cases,[40] involving paediatric subjects 5 to <12 years, they received PBS/Sucrose Purple cap presentation, either by mistake (39 cases) or for unknown reasons (73 cases).
- In 5 cases reporting errors in paediatric subjects of 5 to <12 years, there were no details about the use of Tris/Sucrose Orange cap paediatric presentation, but these cases are conservatively included based on the time of reporting post EUA for Tris/Sucrose Orange cap presentation.

All these cases describing medication errors were from non-EU/EEA countries [US (746) and Canada (9)].

The events (≥2% of cases) indicative of medication error were coded to the PTs Poor quality product administered (302), Expired product administered (206),[41] Product preparation issue (197), Incorrect dose administered (112), Underdose (109), Product administered to patient of inappropriate age (94), Product temperature excursion issue (70), Wrong product administered (63), Product preparation error (47), Circumstance or information capable of leading to medication error (46), Product storage error (31), Inappropriate schedule of product administration (27), Product administration error (21), and Accidental overdose (19).

Medication Errors Harm Analysis

Among the medication error cases, the following scenarios, categorised according to the EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014) were described:

- Medication errors associated with harm [i.e., resulting in adverse reaction(s)] were reported in 11 cases (1.5 % of medication error cases relevant to Tris/Sucrose Orange cap presentation).
- Medication errors without harm [i.e. not resulting in adverse reaction(s)][42] were reported in 704 cases (93.2 % of medication error cases relevant to Tris/Sucrose Orange cap presentation).
- Potential errors were reported in 40 cases (5.3% of medication error cases relevant to Tris/Sucrose Orange cap presentation).
- There were no cases reporting intercepted medication errors during the reporting interval.

Of note, some cases involved more than one medication error.

[40] These cases are not included in Section 6.3.1.1.2.2. *Tris/Sucrose Formulation.*

[41] Majority of the cases reported uncertain expiry dates.

[42] AEs may be co-reported in a case, but they are not considered to be a result of the medication error.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Medication errors with harm (17 medication errors in 11 cases)

In 11 cases (involving 17 medication error events), non-serious medication errors potentially contributed to the occurrence of non-serious AEs. These 11 cases originated from the US (10) and Canada (1). The relevant events mainly described errors in vaccine dosage or volume administered (of correct dosage), errors of vaccination at the wrong anatomical site, administration of incorrect formulation, administration of inadequately prepared vaccine, and other errors.

The co-reported clinical events (≥2 events) were Pain in extremity (5), Myalgia and Pyrexia (2 each).

- *Errors in vaccine dosage administered (7 events)*
  - Errors included administration of larger doses as the paediatric subject receiving adult/adolescent formulation (PBS/Sucrose presentation) or administration adult/adolescent formulation that led to error in vaccine dosage (4 events), smaller doses due to syringe leakage/other issues (3 events).
- *Errors of vaccination at the wrong anatomical site (2 events)*
  - The vaccine was administered at the site of arm other than deltoid or leg.
- *Errors in the administration of incorrect formulation (2 events)*
  - Errors in the choice of formulation included paediatric subject receiving adult/adolescent formulation (PBS/Sucrose presentation), or adolescent subject receiving paediatric formulation (Tris/Sucrose orange cap presentation).
- *Errors in administration of inadequately prepared vaccine (2 events)*
  - Errors included administration after temperature excursion.
- *Error in volume administered (of correct dosage) (1 event)*
  - Lower volume.
- *Other errors (3 events)*
  - These events described as issue in temperature excursion or administration of expired vaccines.

Medication errors without harm (1340 medication errors in 704 cases)

In 704 cases (involving 1340 medication error events), medication errors were reported during 1 or more steps of the vaccination process: preparation, administration, scheduling of second dose or other. These 704 cases originated from the US (697 cases) and Canada (7 cases).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Vaccine administration errors (925 events, 335 cases)

Events mainly described were accidental exposure to vaccine, errors in the administration of incorrect formulation, errors in vaccine dosage, errors in administration of inadequately prepared vaccine, errors of vaccination at the wrong anatomical site, administration of wrong vaccine, and other administration errors.

- *Errors in administration of inadequately prepared vaccine (288 events)*
  - Errors included administration after improper dilution (177 events), temperature excursion (49 events), inadequate storage (31 events), defective material (22 events), insufficient doses in the vial noted after administration (7 events), inappropriate diluent used, or diluent used after expiry (1 event each).
- *Errors in vaccine dosage administered (210 events)*
  - Errors included administration of smaller doses due to needle/other issues (91 events), errors in vaccine dosage or administration of larger doses as the paediatric subject received adult/adolescent formulation (PBS/Sucrose presentation) (62 events), errors in vaccine dosage or receiving smaller doses as a consequence of giving paediatric formulation (Tris/Sucrose presentation) to adolescent (39)/adult (4) subjects (43 events), larger doses (10 events), received third dose or additional doses by mistake (3 events), administered after splitting the recommended doses (1 event).
- *Errors in the administration of incorrect formulation (170 events)*
  - Errors in the choice of formulation included adolescent (77)/adult subjects (19) receiving paediatric formulation (Tris/Sucrose presentation) (96 events), paediatric subjects received adult/adolescent formulation (PBS/Sucrose presentation) (72 events), and elderly subject received paediatric formulation (Tris/Sucrose presentation) (2 events).
- *Errors of vaccination at the wrong anatomical site (9 events)*
  - The vaccine was administered in the leg/thigh (7 events), arm/site instead of deltoid (2 events).
- *Use in unauthorised population (7 events)*
  - The event reported unintentional administrations of vaccine to paediatric subjects below 5 years of age.
- *Wrong vaccine/product administered (7 events)*
  - Errors included administration of BNT162b2 instead of flu shot (4 events), administered Moderna vaccine instead of BNT162b2 (2 events), administration of saline instead of BNT162b2 (1 event).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- *Administration technique errors (3 events)*
  - Errors included partial administration of vaccine, vaccine was dripping from the needle or squired out of the syringe (1 event each).
- *Accidental exposure to vaccine (3 events)*
  - Errors involved accidental exposure to vaccine by child (2 events) and exposure to the skin (1 event).
- *Errors in route of administration (2 events)*
  - The route of administration of the vaccine was subcutaneous (2 events).
- *Other vaccine administration errors (226 events)*
  - These events reported administration of expired vaccines[43] (225 events) and other unspecified administration error (1 event).
- *Vaccine preparation errors (265 events, 239 cases):*
- *Incorrect dilution (241 events)*
  - Errors included diluent from the same vial was used for diluting several vaccine vials (162 events), dilution before use not performed (39 events), dilution before use with a larger volume of diluent or normal saline (11 events), dilution before use with a smaller volume of diluent, improper dilution (8 events each), dilution before use with a different solvent (7 events), diluent used for irrigation (4 events), vial of adult formulation was mixed with diluent of paediatric formulation, dilution before use with expired diluent (1 event each).
- *Errors in vaccine dosage (19 events)*
  - Errors included smaller doses or errors in vaccine dosage due to improper dilution.
- *Other vaccine preparation errors (5 events)*
  - Error described as vaccine left out for longer than the recommended hours after dilution.

[43] Majority of the cases reported uncertain expiry dates.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Scheduling errors (27 events, 20 cases):

- Errors included administration of second dose of the vaccine earlier than the 3-week schedule (23 events), second dose of the vaccine administered later than the 3-week schedule or 2 doses on the same day (2 events each).

Other errors (123 events, 110 cases):

- Errors included temperature excursion (69 events), storage of vaccine (38 events), dispensed expired product (11 events), vaccine with no expiry date (2 events), subject noncompliance, confusion between prepared syringes that led to the administration of incorrect formulation, and vial dispensed with insufficient dose (1 event each).

Potential medication errors (54 medication errors in 40 cases)

There were 40 cases from the US (39 cases) or Canada (1 case).

- The potential errors were described as the reporter requesting clarification regarding expiration date/not able to find expiration date (16 events), vial with no label/expiry date (4 events), confusion between manufacturing and expiration date, vaccine received without diluent/quality report, unsure if the subject received complete dose as the subject moved during injection (3 events each), potential error/dispensing error related to temperature excursion, potential dispensing error/clarification regarding storage conditions, different amount of doses in the vial each time after dilution, clarifying if the product can be administered to paediatric subject after temperature excursion (2 events each);

- The single occurrence of the remaining potential errors were described as the reporter requesting clarification regarding the storage instructions for pre-drawn syringes, clarification regarding expiration date as there were black particles in the vial, confusion about the printed expiration date on the vial, expiration date on the vial and in the handwritten form was different, no expiration date and lot number were seen on the vial, lot number in the vaccination card did not match with the state registry, concomitant treatment with prednisone, pharmacist pooled 13 doses after dilution, subject went for the second dose before the 3-week schedule, confusion in the instructions provided on the storage after dilution, incorrect volume of diluent used for reconstitution, diluent was sprayed out and did not have enough diluent, reporter requesting clarification if there are any side effects due to double doses of vaccine administration, clarification regarding recommended vaccine dose, discrepancy in the information showing 0.2 mL in some instances and 0.3 mL in other, instruction on the vial for storage condition after dilution was different from the prescribing information, reported received a communication that the vaccine was released but also stated that do not use, put in quarantine and wait for further instruction.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Tris/Sucrose Formulation - Adult/Adolescent 30 µg/dose:

There were no cases reporting events indicative of medication errors related to Tris/Sucrose presentation (adult/adolescent formulation).

Conclusion

Overall, among the 33,834 relevant medication error PM cases, 879 cases (0.1% of the total interval cases), 2.6% of total relevant medication error cases were considered harmful, 59 of which (0.01% of total relevant cases) were serious and most of them originated from vaccine administration issues (49 cases of 59 serious cases with harm). Some medication errors are expected to occur despite written instructions for handling the vaccine (thawing, dilution, preparation) and educational activities for HCPs administering the vaccine. The number and seriousness of the reported medication errors events do not indicate any trend and potential needs for any additional mitigation activity.

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 no studies that presented important new safety findings for BNT162b2. A literature review including 58 studies is available in Appendix 5.

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 (SMSR), 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

The list of periodic reports prepared and submitted by the MAH during the reporting period is provided below.

Periodic Report Type	No.	Reporting Period
SMSR	7	01 June 2021 through 30 June 2021
	8	01 July 2021 through 31 July 2021
	9	01 August 2021 through 31 August 2021
	10	01 September 2021 through 30 September 2021
	11	01 October 2021 through 28 October 2021
Summary Bimonthly Safety Report (SBSR)	1	29 October 2021 through 15 December 2021
Abbreviated SMRS[a]	1	29 October 2021 through 30 November 2021

a. Submitted to non-EEA countries.

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

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

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

14. LATE-BREAKING INFORMATION

After the DLP, an updated COVID-19 mRNA Vaccine CDS that was made effective on 21 December 2021 for the addition of the Booster Dose Study C4591031 information. The overall safety profile for the booster dose was similar to that seen after 2 doses. A higher frequency of lymphadenopathy was observed in participants receiving a booster dose in C4591031 (2.8%) compared to participants receiving 2 doses (0.4%).

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

<u>Signal Overview</u>

New signals detected for BNT162b2 during the reporting interval are presented below in Table 24 along with the ongoing signals and signals closed during the reporting interval. Appendix 3 provides a summary of the safety signals that were new, 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 previously known risks not considered to constitute a newly identified signal.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 24. Overview of Signals

Signal	Signal Type	Source	Category*	Regulatory Procedure
Liver Injury/ Autoimmune Hepatitis**	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/632042/2021 EMA/720589/2021 EPITT no: 19749
Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C)	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/473788/2021 EPITT no: 19732 Procedure no: SDA 038
Uveitis	Closed	Scientific literature	No risk	EMEA/H/C/005735/MEA/002.9
Rhabdomyolysis	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.7 EMEA/H/C/005735/MEA/002.8 EMEA/H/C/005735/MEA/002.9 EMEA/H/C/005735/MEA/002.10 EMEA/H/C/005735/MEA/002.11
Hypoaesthesia/ Paraesthesia	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/II/0080
Glomerulonephritis and Nephrotic Syndrome	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/416198/2021 EPITT no: 19722 Procedure no: SDA 035
Erythema Multiforme	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/398391/2021 EPITT no: 19721 Procedure no: SDA 034
Thrombocytopenia Thrombosis Syndrome (TTS)	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.6
Myasthenia gravis	Closed	Epidemiology O/E Analysis Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.8
Myocarditis and Pericarditis	Closed	Inquiry from a competent authority	Important identified risk (EU-RMP, US-PVP)	EMA/PRAC/575791/2021 EPITT no: 19712 SDA 032.2
Immune Thrombocytopenia	Closed	Inquiry from a competent authority. Evaluation for PSUR.	No risk	EMEA/H/C/PSUSA/00010898/202106
Herpes Zoster including Ophthalmic herpes zoster	Closed	Spontaneous report: non-statistical line listing	No risk	EMEA/H/C/005735/MEA/002.7

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 24. Overview of Signals

Signal	Signal Type	Source	Category*	Regulatory Procedure
Appendicitis	Closed	Clinical Trial Data Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.9
Vasculitis	Ongoing	Inquiry from a competent authority	Not yet determined	-
Cerebral venous sinus thrombosis	Ongoing	Inquiry from a competent authority	Not yet determined	-

* Reflects MAH position and entry into signal log following signal evaluation. This may not be the same as the position of the competent authority.
** On 09 November 2021, TGA (Australia) requested an analysis of Comirnaty and 'acute liver injury adverse events of special interest' and 'autoimmune hepatitis;' MAH provided a response on 14 December 2021. On 03 December 2021, EMA PRAC requested supplemental information from the MAH on the signal Autoimmune hepatitis; MAH provided a response on 31 January 2022.

Post-approval regulatory requests (worldwide)

According to the corePSUR19 guidance[44], safety reviews requested by the FAR and by PRAC's signal assessment reports to be addressed in the PSUR are in Appendix 6A.1 through Appendix 6A.5.

The HA requests, the search criteria and the conclusions are noted below for convenience of review.

15.1. Exacerbation (flare-up) of pre-existing AI/Inflammatory Disorders

PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), Question no.:

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.

[44] https://www.ema.europa.eu/en/documents/scientific-guideline/consideration-core-requirements-psurs-covid-19-vaccines_en.pdf

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Response

- Search Criteria:
  - SMQ Immune-mediated/autoimmune disorders (narrow scope);
  - HLGT Autoimmune disorders;
  - HLGT Immune disorders NEC (Primary Path);
  - HLT Neuromuscular junction dysfunction (Primary Path).

See Appendix 6A.1 for details.

Conclusion

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

15.2. Pregnancy and Lactation

PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), Question no.:

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.*

Response

For requests a) and c), please refer to the response to PRAC commitment No. 1 in Appendix 6A.

For request b) please refer to the Literature paragraph in Section 16.3.5.3 *Use in Pregnant/Lactating Women* including conclusion of the literature review sent to EMA in January 2022 as response to the email received on 17 December 2021.

For request d) please refer to the Section 16.3.5.3 *Use in Pregnant/Lactating Women* for summary on lactation cases. Breastfeeding was not a signal in the reporting interval.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

15.3. Chronic Urticaria/Worsening of Pre-Existing Chronic Urticaria

PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), Question no.:

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.*

Response

- Search Criteria: all cases reporting the PTs Urticaria chronic in the medical history and reporting Urticaria chronic as AE.

See Appendix 6A.2 for details.

Conclusion

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

15.4. Polymyalgia Rheumatica and Exacerbation or Flare-up

PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), Question no.:

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.*

Response

- Search Criteria: all cases reporting the PTs Polymyalgia rheumatica in the medical history and reporting Polymyalgia rheumatica as AE.

See Appendix 6A.3 for details.

Conclusion

A total of 628 reports were identified via the search strategy. Of these reports, 424 were excluded from further analysis because included confounders such as co-reported events in

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

SOC Infections or Neoplasm that can mimic PMR and a relevant medical history of previous auto-immune disorders, endocrine and musculoskeletal diseases and neoplasms. Out of the remaining 204 cases, only 16 co-reported elevated CRP and ESR levels, while 26 cases report only elevated CRP and 6 reported only elevated ESR. Most of the reports (30 cases) did not report sufficient information to confirm the PMR diagnosis or reported it in the context of alternative diseases that could cause elevation of CRP or ESR (11 cases). Seven reports described possible PMR cases after vaccination. The number of cases reporting flare of PMR after vaccination are low also taking in consideration that we know only the number of cases with a history of PMR that report an AE after vaccination, but we are not aware of how many patients with underlying PMR were vaccinated. The number of cases reported versus an expected rate in an unvaccinated population (O/E ratio) is below 1 suggesting the number of reports observed is not unexpected. Furthermore, clinical study data has not produced a signal and the literature is not sufficient to deduce a causal association. Overall, considering that more than 2 billion doses of COVID-19 vaccine has been administered worldwide, the totality of the data does not suggest a causal association between COMIRNATY and PMR; therefore, the signal is refuted. Safety updates to the product information and/or the risk management plan are not warranted at this time. The benefit risk profile of the vaccine remains favourable. The topic will continue to be closely monitored with routine pharmacovigilance.

15.5. Subacute Thyroiditis

PSUR Assessment Report (AR) (Procedure No. EMEA/H/C/PSUSA/00010898/202106), Question no.:

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.*

Response

The MAH will provide a cumulative review on the association between Comirnaty and subacute thyroiditis as a separate response.

15.6. Glomerulonephritis and Nephrotic Syndrome

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

"Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of the COVID-19 mRNA vaccine (nucleoside-modified) COMIRNATY (BioNTech Manufacturing GmbH) should closely monitor the issue of 'glomerulonephritis/nephrotic syndrome', including

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

exacerbations, and present a cumulative review of cases from all sources and relevant literature in the upcoming PSUR submissions. However, if new relevant information becomes available earlier that would support an association with the vaccine, the MAH should propose updates of the product information accordingly and without delay".

Response

- Search Criteria: HLT Glomerulonephritis and nephrotic syndrome.

See Appendix 6A.4 for details.

Conclusion

The MAH does not consider that the currently available information supports a causal association between these renal disorders and the vaccine. Pfizer/BioNTech will continue to monitor. No updates to current labelling are warranted at this time. Please refer to Appendix 6A.4 for a cumulative review of this topic as requested by PRAC.

15.7. Multisystem Inflammatory Syndrome in Children and Adult

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

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

Response

- Search Criteria: All cases reporting the PTs Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome, Multiple organ dysfunction syndrome, Kawasaki's disease, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Cytokine release syndrome, Cytokine storm, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, Autoinflammatory disease, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome.

See Appendix 6A.5 for details.

Conclusion

Considering the totality of the data, including the number of reports received (n=440) in the context of the hundreds of millions of doses of vaccine administered, the MAH does not

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

consider that the currently available information supports a causal association between MIS-C/A and Comirnaty. No updates to current labelling or the RMP are warranted at this time. Surveillance on this topic will continue.

15.8. Erythema Multiforme

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

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

Conclusion

Following PRAC assessment of the signal, the MAH was requested to add Erythema multiforme as an adverse reaction (frequency "Not known") to section 4.8 of the European SmPC. This topic will continue to be monitored via routine pharmacovigilance (see also Appendix 6A).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 25 summarises the important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU-RMP ver. 2.0 adopted on 31 May 2021.

Table 25. Ongoing Safety Concerns

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

During the reporting period, on 05 August 2021, the MAH submitted the 2.3 version of the EU-RMP including myocarditis/pericarditis[45] as important identified risk; this version received a positive CHMP opinion on 30 September 2021. In the PSUR #1, the MAH had proposed to include myocarditis/pericarditis in the list of safety concerns for the next

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

reporting period, subject to the PRAC approval of the EU-RMP version 2.3, therefore interval data for this risk are presented in Section 16.3.1.2.

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

16.2. Signal Evaluation

Please refer to Table 24 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**

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

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in PSUR #1.

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

The signal was re-opened on 14 October 2021 due to a PRAC notification of signal assessment procedure following the results of the Nordic registries study. The MAH conducted an updated evaluation of myocarditis and pericarditis from clinical studies, post-marketing data, literature and O/E analyses. In the large, controlled, pivotal study C4591001 myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis or pericarditis events. Efforts are ongoing to evaluate the background rate of troponin abnormalities in healthy study participants prior to vaccination, to inform whether or not troponin may represent a useful biomarker for presence of subclinical myocarditis or pericarditis (if such conditions exist). The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. Further, animal models of myocarditis or pericarditis are not well established and therefore do not serve as a viable model to perform additional nonclinical assessments. In the interpretation of the epidemiology data, it is important to note that data described above reflect rates from different regions, different data sources (eg spontaneous reports, registries, administrative), and using different methodologies. This could explain, at least partially, the variability in the reported rates between studies. Therefore, an integrated or side-by-side analysis is not appropriate, and it is not possible to use the available data to provide a single estimate of risk. Overall, in

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

aggregate, the studies reported higher risk after Dose 2 compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination. The review of the post-marketing cases of myocarditis found that although the number of cases reported has increased with vaccine exposure increases, the profile of cases remains largely unchanged. Within this profile, a minority of cases (10%) qualify for BC level 1 classification, and thus provide a high degree of diagnostic accuracy. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration. Overall, no new or significant information regarding myocarditis or pericarditis became available. The reported data continues to align with the information presented in the EU SmPC. Therefore, no changes to the product information or risk management strategy are warranted. Myocarditis and pericarditis are important identified risks in the EU RMP and subject to close monitoring and extensive pharmacovigilance activities, routine and additional. This signal was closed on 10 November 2021 and the complete evaluation provided to PRAC in procedure EPITT: 19712. After the signal closure date, the PRAC requested the MAH to revise the EU SmPC to update the frequency of myocarditis and pericarditis to 'Very rare'. No new or significant safety information became available after the closure of the PRAC signal assessment procedure.

- **Signals Determined to be Identified Risks (Not Categorized as Important)**

None.

- **Signals Determined Not to be Risks**

Liver Injury/Autoimmune Hepatitis (EMA/PRAC/632042/2021, EMA/720589/2021 EPITT no: 19749)

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

Autoimmune hepatitis has been infrequently reported following vaccination. However, most cases do not report sufficient relevant information (medical history, laboratory and other diagnostic data) to allow a proper evaluation. Among the cases that provided a medical history, the majority do report underlying hepatic disorders or concomitant autoimmune diseases that are known to have an increased incidence of developing autoimmune hepatitis independently of the trigger; in other cases, the diagnosis was a hypothesis or as part of a differential diagnosis. Even taking a conservative approach and including all 63 cases (irrespective of diagnostic certainty or causality), O/E ratios and the upper limit of the 95% CIs were well below 1 overall and for all ages assuming both 21- and 42-day risk windows,

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. In a large double-blind placebo-controlled study of the vaccine there were zero (0) cases of autoimmune hepatitis in the Pfizer-BioNTech COVID-19 vaccine arm. Thus, the study results do not support an increased risk of autoimmune hepatitis between placebo and vaccine. The literature analysis did not reveal an increased risk of developing autoimmune hepatitis after Pfizer BioNTech COVID-19 vaccine administration. In addition, the pandemic has been associated with increased alcohol consumption, unhealthy eating habits, and interruptions to hepatology services, which might lead to an upward trend in liver disease incidence and severity that has been that has not been realised until after hospitals resumed more normal operations following the initial months of the COVID-19 pandemic. Regarding liver injury AESIs, almost half of the cases (732/1680 received until 31 October 2021) were confounded by pre-existing hepatic medical history, concurrent illnesses and/or co-suspect/concomitant medications which could predispose patients to a hepatic event. Thirty-one (31) cases reported liver injury, acute hepatic failure and/or hepatic failure. Most of these 31 cases reported a relevant event without any supporting clinical, diagnostic procedures, and/or laboratory values confirming the diagnosis. The remaining cases in the overall dataset reported PTs that in themselves were not reflective of a clinically significant hepatic impairment as they presented only isolated LFT laboratory abnormalities, or signs and symptoms that may be related to the liver. For liver injury, O/E ratios and the upper limit of the 95% CIs were well below 1 overall and for all ages assuming 21- and 42-day risk windows, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. In a large double-blind placebo-controlled study of the vaccine (21926 participants in the BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and 21921 participants in the placebo group) there were zero (0) cases of autoimmune hepatitis or liver injury in the Pfizer-BioNTech COVID-19 vaccine arm. Thus, the study results do not support an increased risk of autoimmune hepatitis or liver injury between placebo and vaccine. The MAH does not consider that the currently available information supports a causal association between the relevant conditions and the vaccine. The signal was closed on 15 December 2021.

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

Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C) (EMA/PRAC/473788/2021 EPITT no: 19732 Procedure no: SDA 038)

Please refer to the PRAC request for this signal in Section 15.7 and in Appendix 6A.5.

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

The signal was identified from the review of scientific literature (Renisi et al., Anterior uveitis onset after BNT162b2 vaccination: is this just a coincidence?). The MAH conducted an analysis of the signal using post-marketing database and O/E analyses. The safety database search was conducted for all cases reporting MedDRA v24.0 PTs: Autoimmune uveitis, Diabetic uveitis, Immune recovery uveitis, Immune-mediated uveitis, Tubulointerstitial nephritis and uveitis syndrome, Uveitis, Viral uveitis until 09 September 2021 retrieving a total of 142 reports amid 1,359,989,180 doses administered globally as of

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

22 September 2021. Given the complexity of diagnosing uveitis, the majority (53.5%) were not medically confirmed, with only 46.5% of cases categorized as medically confirmed. Almost half of the medically confirmed cases had either history of uveitis and/or no time of onset reported and thus excluded from analysis. Only 35 cases (almost 25% of the total reported cases) were medically confirmed without a medical history of an ocular pathology and had a time to onset of 30 days or less post-vaccination. A review of these cases showed that while the majority did not resolve at the time of reporting, there were no dose-dependent sequence of occurrence. None of these cases resulted in hospitalisation or was fatal. Nevertheless, 20 of these cases did not have a medical history reported, some did not have concomitant medications reported, clinical or laboratory investigations conducted to exclude causes for differential diagnosis, nor intensity assessment. This missing information further confounds a proper assessment of causality to the vaccine. The O/E ratios for both 21-day and no risk windows were <1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons. In conclusion, the aggregate review of cases reporting Uveitis, the detailed review of those cases categorised as medically confirmed, and the calculated O/E ratios did not identify a safety concern or sufficient evidence to confirm a causal association that would necessitate an update to product labeling at this time. Based on this review, the MAH considers the safety signal not causing a potential risk and closed. The signal was closed on 30 September 2021 and the complete assessment was provided in SMSR #10.

Rhabdomyolysis (EMEA/H/C/005735/MEA/002.7, EMEA/H/C/005735/MEA/002.8, EMEA/H/C/005735/MEA/002.9, EMEA/H/C/005735/MEA/002.10, EMEA/H/C/005735/MEA/002.11)

The signal was opened following the PRAC request in the Assessment Report of SMSR #8 as the upper limit of the 95% CI exceeded 1 for the 21-day risk window in the cumulative period, and for both the 21-day and no risk windows in the interval periods. The MAH conducted an analysis of the signal using clinical, post-marketing, literature and O/E analyses. Phase 2/3 Study C4591001 placebo-controlled unblinded data (data cutoff date 13 March 2021) was reviewed for the PT Rhabdomyolysis. In the Phase 2/3 safety population, the event rhabdomyolysis was reported in 1 participant out of 21,921 in the placebo group and none in the BNT vaccine group from dose 1 to 1 month after dose 2 in subjects ≥16 years of age. The Pfizer safety database was searched for all BNT162b2 vaccine reports received through 12 August 2021 using MedDRA version 24.0 search criteria: PT: Rhabdomyolysis and a total of 112 cases were retrieved for further analysis. Of the total 112 cases, 2/3 of the cases were eliminated from further analysis due to insufficient clinical details and implausible latency. Subsequently, the remaining 1/3 of the cases either provided a clear alternate aetiology for rhabdomyolysis or were confounded by concurrent conditions and/or concomitant medications. O/E signal detection analyses for rhabdomyolysis showed some O/E ratios > 1, however the conservative approach and multiple limitations of these analyses lead this data to be weighed less heavily than the clinical study and spontaneous case series review. Based on the totality of the data, rhabdomyolysis is not determined to be a causally associated adverse effect of the vaccine. This signal was closed on 01 September 2021 and the complete signal evaluation provided in SMSR #9 (and as a safety topic in subsequent reports).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

Hypoaesthesia/Paraesthesia (EMEA/H/C/005735/II/0080)

Glomerulonephritis and Nephrotic Syndrome (EMA/PRAC/416198/2021 EPITT no: 19722 Procedure no: SDA 035)

Please refer to the PRAC request for this signal in Section 15.6 and in Appendix 6A.4.

Erythema Multiforme (EMA/PRAC/398391/2021 EPITT no: 19721 Procedure SDA 034)

Please refer to the PRAC request for this signal in Appendix 6A.

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

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

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

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

During the reporting interval, the signal was re-opened and validated at the request of Health Canada following review of SMSR #7 considering that the upper level of the 95% CI exceeded 1 for both the 21-day and no risk windows in the interval period in the overall O/E analysis. The MAH conducted an analysis of the signal using clinical, post-marketing, literature and O/E analyses. Phase 2/3 Study C4591001 placebo-controlled unblinded adverse events in participants 16 years and older from dose 1 to 1 month after dose 2 (data cutoff date 13 March 2021) found that MG was reported in 0 of 21926 participants in the BNT162b2 group compared with 0 of 21921 participants in the placebo group. The safety database search for PT myasthenia gravis cases reported up to 15 August 2021 using MedDRA 24.0 revealed a total of 56 cases which were reviewed in detail. Most spontaneous cases are confounded by a medical history reporting a pre-existing MG or other significant clinical risk factors (ongoing autoimmune disease and or cancer). Overall, 10 subjects reported the diagnosis confirmed by EMG and/or autoantibodies of which 5 had underlying autoimmune condition and 3 had an ongoing neoplasm. In the literature a worsening of MG symptoms after vaccination has not been identified as a risk while it is clearly reported that infections account for 40-70% of the exacerbations. In addition, if the patient is not medically optimised, s/he could develop a cytokine storm, despite being on steroids. Moreover, up to 15% of patients may experience worsening MG symptoms and/or exacerbations upon initiation of oral prednisolone therapy.

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

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

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

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

Phase 2/3 data from Study C4591001 placebo-controlled period (Dose 1 to 1 month after dose 2) for participants 16 years of age and older (data-lock date 13 March 2021) had 1 report of thrombocytopenia in the BNT162b2 group (N=21,926) and 1 in the placebo group (N=21,921). The Pfizer safety database was searched for BNT162b2 adverse event reports

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

using MedDRA v 24.0 search strategy HLT Thrombocytopenias, received cumulatively to 18 June 2021. A total of 760 cases were retrieved from the safety database which were reviewed in further detail and according to BC criteria. The O/E were <1 for all analyses. Overall, the review of thrombocytopenia from clinical study data, post-authorisation spontaneous reports, medical literature and O/E analyses. While there are spontaneous post-vaccination reports of de-novo and worsening thrombocytopenia in patients with and without known thrombocytopenia, respectively, it is not outside of the range that would be expected without BNT162b2 vaccination. While it is acknowledged that patients with a diagnostic history of immune thrombocytopenia may be the most vulnerable to thrombocytopenia if precipitated by the vaccine, the undulating nature of the disorder calls into question the vaccine as the clear cause. A hypothesis can be made about an immune response and molecular mimicry as a mechanism for thrombocytopenia, but this would be speculative in nature. Based on the totality of the data, thrombocytopenia is not determined to be a causally associated adverse effect of the vaccine. This signal was closed on 04 August 2021 and the complete evaluation provided in PSUR #1

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

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

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in PSUR #1.

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

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

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

The signal was initially opened and closed prior to the reporting interval and evaluations reported accordingly in PSUR #1.

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

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

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

None.

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 26. Signal Evaluation Plan for Ongoing Signals

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

16.3. Evaluation of Risks and New Information

Evaluation of new information for previously recognised important identified and important potential risks, other risks (not categorised as important), special situations, and special patient populations for BNT162b2 is provided below in Section 16.3.1, Section 16.3.2, Section 16.3.3, Section 16.3.4 and Section 16.3.5, respectively.

As per PRAC commitment (procedure EMEA/H/C/PSUSA/00010898/202106),

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).*

Response

Please refer to Appendix 6A.

16.3.1. Evaluation of Important Identified Risks

Evaluation of incremental data for the important identified risks Anaphylaxis, Myocarditis and Pericarditis is provided below.

16.3.1.1. Important Identified Risks – Anaphylaxis

Search criteria - PTs: Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock. [46]

[46] According to the criteria specified for Anaphylaxis in the EU-RMP v 4.0.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 2 (0.28% of 721 cases of the total CT dataset), compared to 1 case (0.14%) retrieved in the PSUR #1.

The investigator and the Sponsor reported that there was not a reasonable possibility that the events anaphylactic reactions in both cases were related to the blinded study vaccine/BNT162b2, or clinical trial procedure. In 1 case the participant had an anaphylaxis secondary to insect bite and the other case reported acute anaphylaxis reaction to walnuts.

Post-Authorisation Data

- Number of cases: 3508. Upon review, 1 case was determined to be non-contributory and was not included in the discussion since this subject was exposed to the vaccine through breastfeeding.
- Number of relevant cases: 3507 (0.53% of 657,528 cases, the total PM dataset), compared to 3827 cases (1.2%) retrieved in the PSUR #1.
- MC cases (2705), NMC cases (802).
- Country of incidence (top 10): Japan (1460), Germany (361), Australia (232), UK (217), US (152), France (146), New Zealand (119), Sweden (76), Italy (66), and Norway (55).
- Subjects' gender: female (2655), male (714) and unknown (138).
- Subjects' age in years: n = 3250, range: 8 - 98, mean: 43.5, median: 43.0.
- Medical history (n = 1828): the most frequently (≥ 45 occurrences) reported medical conditions Food allergy (388), Asthma (365), Drug hypersensitivity (269), Hypertension (201), Hypersensitivity (183), Anaphylactic reaction (155), Seasonal allergy (153), Dermatitis contact (84), Urticaria (73), Diabetes mellitus (71), Contrast media allergy (63), Rhinitis allergic (50), Mite allergy (49), Anaphylactic shock (45), and Hypothyroidism (45).
- COVID-19 Medical history (n = 69): COVID-19 (46), Suspected COVID-19 (20), Asymptomatic COVID-19 (1), Coronavirus infection (1), and Post-acute COVID-19 syndrome (1).
- Co-suspects (n = 74): Relevant co-suspect vaccines/medications included macrogol (31), COVID-19 AstraZeneca vaccine (5), influenza vaccine (3), ibuprofen, iopamidol (2 each), acetylsalicylic acid, magnesium oxide, adalimumab, allopurinol, amlodipine, amoxicillin, amoxicillin trihydrate, clavulanic acid, ascorbic acid, biotin, calcium carbonate, calcium pantothenate, carbohydrates NOS, copper sulfate, cyanocobalamin, ergocalciferol, fats NOS, ferrous sulfate, folic acid, linoleic acid, magnesium chloride, manganese chloride, nicotinamide, phytomenadione, potassium chloride, potassium citrate, potassium iodide, protein, pyridoxine hydrochloride, retinol palmitate, riboflavin, sodium polymetaphosphate, thiamine hydrochloride, tocopheryl acetate, zinc sulfate, beclometasone, cefalexin, cefcapene pivoxil hydrochloride hydrate, cetirizine, COVID-19 vaccine, COVID-19 Moderna vaccine, dexamethasone, diclofenac sodium, epinephrine bitartrate, febuxostat, fluoxetine, hydrocortisone, hydrocortisone hydrogen

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

succinate, hydrocortisone sodium succinate, immunoglobulin human normal, infliximab, influenza vaccine inact SAG 3V, influenza vaccine inact SPLIT 4V, iomeprol, lemborexant, leuprorelin acetate, loxoprofen sodium, macrogol 3350, magnesium aspartate hydrochloride, mepolizumab, mirabegron, mirtazapine, montelukast sodium, morphine, phenoxymethylpenicillin potassium, rebamipide, rosuvastatin calcium, sulfasalazine, teicoplanin (1 each).

- Number of relevant events: 3657.
- Relevant event seriousness: serious (3654), non-serious (3).
- Reported relevant PTs: Anaphylactic reaction (3015), Anaphylactic shock (552), Anaphylactoid reaction (87), Anaphylactoid shock (3).
- Time to event onset (n = 3008), range: <24 hours to 151 days, median: 0 days.
  - <24 hours: 2723 events;
  - 1 day: 114 events;
  - 2 - 7 days: 86 events;
  - 8 - 14 days: 33 events;
  - 15 - 31 days: 28 events;
  - 32 - 181 days: 20 events.
- Duration of relevant events (n = 1195 out of 1929 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 102 days, median: 0 days.
  - <24 hours: 762 events;
  - 1 day: 274 events;
  - 2 - 7 days: 127 events;
  - 8-14 days: 15 events;
  - 15-31 days: 12 events;
  - 32-181 days: 5 events.
- Relevant event outcome[47]: fatal (19), resolved/resolving (2573), resolved with sequelae (64), not resolved (273), unknown (734).

Of the 19 cases reporting a fatal outcome, 5 cases reported limited information regarding one or more of the following: medical history, concomitant medication, and clinical course of events, precluding a meaningful medical assessment.

[47] Multiple episodes of the same event were reported with a different outcome in some cases hence the sum of the events outcome exceeds the total number of events.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

In 4 cases, the subjects had history of anaphylactic shock, hypersensitivity, allergy to vaccine and/or food allergy. Of these 4 cases, 2 cases reported reaction after second dose, 1 case reported reaction after first dose and in 1 case the dose number was unknown.

Three (3) cases from Vietnam reported on 3 adolescent male subjects who experienced anaphylactic shock/anaphylactic reaction after receiving BNT162b2 first dose (2 cases) and unknown dose number (1 case). Medical history or concomitant medications were unknown. Latency was reported as <24 hours in 2 cases and 3 days in 1 case.

A subject previously received two doses of Sinopharm vaccine on an unspecified date as dose 1 and 2. The subject received the third dose of BNT162b2 on The same day the was found as unconscious, pulse not palpable on blood vessels, pupils dilated, not responding when addressed. The subject died on The cause of death was unknown; however, anaphylaxis was suspected. The outcome of the events was fatal.

An subject received the first dose of BNT162b2 on the left thigh. Five minutes later, the subject experienced anaphylaxis. The subject became cold and clammy, blood pressure and oxygen saturations dropped, had tachycardia and peripheral cyanosis. The subject was treated with adrenaline via epinephrine, oxygen, and fluids subcutaneously. The subject died approximately 10.5 hours later. It was reported that the subject was in a nursing home for end of life care with a do-not-resuscitate order.

A subject received the second dose of BNT162B2 intramuscular on Relevant medical history included cardiogenic shock. Historical vaccine included first dose of BNT162B2 in nd experienced felt something like a burning and recovered. Ten minutes after she was vaccinated, the subject complained of a 'burning' pain in chest and back and collapsed. The subject deteriorated very quickly, despite the efforts of the physicians to revive and died on . The reporting physician reported it was not a pulmonary embolism and anaphylaxis was not verified yet.

In the remaining 4 cases, the healthcare professional reported unassessable causal relationship (2 cases) or possibility related to BNT162B2 however, underlying conditions may have contributed to the fatal events (2 cases). In these 4 cases, the subjects had relevant medical history (Cardiac failure chronic, respiratory arrest, aortic dissection, emphysema, myocardial infarction or malignant brain neoplasm) that may have contributed to the co-reported fatal events of Cardio-respiratory arrest, Aortic dissection, respiratory disorder in addition to anaphylactic reaction.

Analysis by age group

PM: Paediatric (179), Adults (2694), Elderly (401) and Unknown (233).

- No significant difference observed in the reporting proportion of anaphylaxis relevant PTs between paediatric, adult and elderly populations (0.91.% in paediatric vs 0.55% in adults vs 0.46% in elderly).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by presence of comorbidities[17,48]

Number of subjects with comorbidities: 733 (21% of the cases reporting anaphylaxis).

- The reporting proportion of anaphylaxis related events with fatal outcome (0.8%) is comparable in individuals with comorbid conditions when compared to the reporting proportion (0.5%) observed in the individuals without comorbidities.

Literature 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.

16.3.1.2. Important Identified Risks – Myocarditis and Pericarditis

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

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

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

For the incremental evaluation of Myocarditis and Pericarditis cases, please refer to Section 16.3.1.2.1 and Section 16.3.1.2.2, respectively.

[48] CT and PM pooled data.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 myocarditis and pericarditis 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: "Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients".[49]

This risk will continue to be monitored through routine pharmacovigilance.

16.3.1.2.1. Important Identified Risks – Myocarditis

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

Overall - All Ages

Clinical Trial Data

- Number of cases: 2 cases of BNT162b2 (0.3% of 721 cases of the total CT dataset); no cases were retrieved in the PSUR #1.
- Country of incidence: (1 each).
- Subjects' gender: (2).
- Subjects' age in years: n = 2,
- Co-suspects: None.
- Number of relevant serious events: 2
- Reported relevant PTs: Myocarditis (2), both related to BNT162b2.
- Relevant event outcome: Resolved/resolving (2).
- Time to onset of relevant events: 64 days and 3 days.

[49] Myocarditis and pericarditis are listed in Section 4.8 of the EU-SmPC.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Duration of myocarditis was reported as 6 days in one case. Duration of myocarditis was not reported in the second case.

Post-Authorisation Data

- Number of cases: 6347 (1.0% of 657,528 cases of the total PM dataset), compared to 503 cases (0.15%) retrieved in the PSUR #1.[50]
- Country of incidence: Germany (1338), UK (994), Australia (826), France (537), Japan (320), Canada (317), US (215), Italy (211), Sweden (170), and Spain (146). The remaining 1273 cases were distributed among 50 countries.
- MC (3797), NMC (2550).
- Subjects' gender: female (2032), male (4022) and unknown (293).
- Subjects' age in years: n = 5615, range: 6-102, mean: 34.3, median: 30.0.
- Medical history (n = 2122): the most frequently (≥50 occurrences) reported medical conditions included Hypertension (236), Asthma (205), Tobacco user (156), Seasonal allergy (125), Myocarditis (103), Drug hypersensitivity (92), Obesity (82), Hypothyroidism (65), Non-tobacco user (64), Food allergy (63), Migraine (59), Alcohol use, Chest pain (54 each), Diabetes mellitus (50).
- COVID-19 Medical history (n = 331): COVID-19 (168), Suspected COVID-19 (148), SARS-CoV-2 test positive (7), Asymptomatic COVID-19 (4), Coronavirus infection, COVID-19 pneumonia, Post-acute COVID-19 syndrome (3 each), and Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (1 each).
- Co-suspect vaccines/medications (>1 occurrence): COVID-19 AstraZeneca vaccine (9), COVID-19 Moderna vaccine, influenza vaccine (5 each), acetylsalicylic acid, azathioprine, cannabis sativa, clozapine, colchicine, hepatitis a vaccine, ibuprofen, nivolumab, sulfamethoxazole/trimethoprim (2 each).
- Number of relevant events: 6349.
- Relevant event seriousness: serious (6345), non-serious (4).
- Reported relevant PTs: Myocarditis (6338), Eosinophilic myocarditis (4), Autoimmune myocarditis, Hypersensitivity myocarditis (3 each), Immune-mediated myocarditis (1).
- Relevant event outcome[47]: fatal (74), resolved/resolving (2618), resolved with sequelae (119), not resolved (1950), unknown (1599).

[50] During the reporting period of PSUR #1 there were 503 events of myocarditis [Autoimmune myocarditis (1), Myocarditis (502)].

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Age-stratified data[51]

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

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

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

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 10 cases (0.002% of 657,528 cases of the total PM dataset; 0.95% of the 1049 subjects aged 5-11 years); 1 case (0.0003%) was retrieved in the PSUR #1.
- Country of incidence: Canada (6), US (2), [redacted] (1 each).
- Subjects' age in years: n = 10, range: 6-9, mean: 8.2, median: 9.0.
- Medical history (n = 4): the reported medical conditions included Alopecia universalis, Anxiety, Attention deficit hyperactivity disorder, Drug hypersensitivity, Dyspnoea Paroxysmal nocturnal, Food allergy, Mitral valve prolapse, Orthopnoea, and Renal artery stent placement (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Most co-reported PTs (>1 occurrence): Chest pain, Product administered to patient of inappropriate age (6 each), Dyspnoea, Fatigue, Pyrexia (3 each), Headache, Off label use, Palpitations, Pericarditis, and Product use issue (2 each).

Myocarditis relevant data in this subgroup of subjects are summarised Table 27.

[51] Cases where the age was reported as Child (5 cases), Adolescent (39 cases), Adult (122 cases) and Elderly (8 cases) are included in the subgroup of Age Unknown age and in the overall.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 27. Myocarditis in Subjects aged 5 – 11 Years (N=10)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	2	7	0
	No	0	1	0
Relevant PT[a]	Myocarditis	2	8	0
Hospitalization required/prolonged	Yes	0	4	0
	No	2	4	0
Relevant suspect dose	Dose 1	1	2	0
	Dose 2	0	6	0
	Unknown	1	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=6	≤ 24 hours	0	1	0
	1-5 days	0	3	0
	6-13 days	1	1	0
	14-21 days	0	0	0
	22-31 days	0	0	0
	Unknown	1	3	0
Event Outcome	Fatal	0	0	0
	Not resolved	0	2	0
	Resolved	1	1	0
	Resolved with sequelae	0	0	0
	Resolving	0	0	0
	Unknown	1	5	0
Duration of event[b] n=0	Up to 3 days	0	0	0
	4-6 days	0	0	0
	7-25 days	0	0	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 12 - 15 years

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 488 (0.07% of 657,528 cases of the total PM dataset; 4.7% of the 10,377 subjects aged 12-15 years), compared to 13 cases (0.004%) retrieved in the PSUR #1.
- Country of incidence: Australia (78), Japan (65), Germany (53), Hong Kong (47), Canada (31), UK (30), France (29), Taiwan Province of China (27), US (16), and Israel (13). The remaining 99 cases were distributed among 25 countries.
- Subjects' age in years: n = 488, range: 12-15, mean: 13.8, median: 14.0.
- Medical history (n = 88): the most frequently (>1 occurrence) reported medical conditions included Asthma (15), Attention deficit hyperactivity disorder (9), Food allergy (6), Autism spectrum disorder, Cardiac murmur, Myocarditis (4 each), Allergy to animal, Hypersensitivity, Mite allergy, Pneumonia, Rhinitis allergic, Seasonal allergy, Wheezing (3 each), Allergy to arthropod sting, Arrhythmia, Body height above normal, Cardiac murmur functional, Chest pain, Dermatitis atopic, Infectious mononucleosis, Intellectual disability, Laboratory test abnormal, Migraine, Nasopharyngitis, scoliosis, Vaccination complication, Varicella, Ventricular tachycardia (2 each).
- COVID-19 Medical history (n = 15): COVID-19 (9), SARS-CoV-2 test positive, Suspected COVID-19 (2 each), Asymptomatic COVID-19, and Exposure to SARS-CoV-2 (1 each).
- Co-suspect vaccine/medication: Guanfacine, influenza vaccine live reassort 4V (1 each)
- Most frequently co-reported PTs (>5 occurrence): Chest pain (197), Pyrexia (94), Pericarditis (68), Troponin increased (57), Dyspnoea (56), Palpitations (39), Headache (36), Chest discomfort (31), Tachycardia (29), Fatigue (28), Electrocardiogram ST segment elevation (24), Vomiting (22), Dizziness (20), Blood creatine phosphokinase increased, Malaise (18 each), Troponin T increased (16), Nausea (15), Blood creatine phosphokinase MB increased, Troponin I increased (14 each), Myalgia (12), C-reactive protein increased (10), Electrocardiogram abnormal, Oropharyngeal pain, Pain in extremity (9 each), Cough, Pallor, Pericardial effusion, Troponin abnormal (8 each), Chills, Diarrhoea, Influenza like illness, Pain, Vaccination site pain (7 each), Decreased appetite, Hypotension, and Syncope (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 28.

Table 28. Myocarditis in Subjects aged 12 – 15 Years (N=488)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	72	302	4
	No	24	84	2
Relevant PT[a]	Myocarditis	96	386	6
	Hypersensitivity myocarditis	0	1	0
Hospitalization required/prolonged	Yes	44	256	4
	No	52	130	2
Relevant suspect dose	Dose 1	33	93	2
	Dose 2	36	219	2
	Dose 3	1	0	0
	Unknown	26	74	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=325	≤ 24 hours	6	15	0
	1-5 days	27	210	3
	6-13 days	11	16	0
	14-21 days	8	11	0
	22-31 days	0	8	0
	>31 days	2	8	0
	Unknown	42	119	3
Event Outcome	Fatal	0	3	1
	Not resolved	24	71	1
	Resolved	18	100	0
	Resolved with sequelae	0	3	0
	Resolving	27	114	0
	Unknown	27	96	4
Duration of event[b] n=42, median=5 days	Up to 3 days	0	13	0
	4-6 days	3	12	0
	7-25 days	3	11	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 16 - 17 years

Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.14% of 721 cases of the total CT dataset); no case was retrieved in the PSUR #1.
- Country of incidence: ██ (1).
- Subjects' age in years: █ years.
- Medical history: Anxiety, Joint dislocation, Nephrolithiasis, Seasonal allergy.
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of relevant serious events: 1.
- Reported relevant PTs: Myocarditis (1).
- Relevant event outcome: Resolving (1).
- Time to onset of relevant events: 3 days.
- Duration of myocarditis was not reported.
- Co-reported PTs: None.

Post-Authorisation Data

- Number of cases: 470 (0.07% of 657,528 cases of the total PM dataset; 6.1% of the 7647 subjects aged 16-17 years), compared to 34 cases (0.01%) retrieved in the PSUR #1.
- Country of incidence: Germany (97), Australia (74), France (40), UK (32), Japan (29), Italy (27), Spain (22), Taiwan Province of China (18), US (15), and Austria (13). The remaining 103 cases were distributed among 29 countries.
- Subjects' age in years: n = 470, range: 16-17, mean: 16.5, median: 17.0.
- Medical history (n = 133): the most frequently (>2 occurrence) reported medical conditions included Asthma (20), Attention deficit hyperactivity disorder, Seasonal allergy (8 each), Tobacco user (7), Chest pain, Rhinitis allergic (6 each), Drug hypersensitivity, Food allergy, Myocarditis, Obesity (5 each), Acne, Dermatitis atopic, Hypersensitivity, Migraine, Non-tobacco user, Substance use (4 each), Alcohol use, Mite allergy (3 each).
- COVID-19 Medical history (n = 17): COVID-19 (9), Suspected COVID-19 (6), Asymptomatic COVID-19, SARS-CoV-2 antibody test positive, SARS-CoV-2 test positive (1 each).
- Co-suspect vaccine/medications: Diazepam, lorazepam, meningococcal group ACWY-TT conjugate vaccine, venlafaxine, zopiclone (1 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Most frequently co-reported PTs (>5 occurrences): Chest pain (171), Pyrexia (90), Troponin increased (59), Dyspnoea, Headache (46 each), Pericarditis (34), Fatigue (31), Chest discomfort (27), Myalgia (25), Vomiting (22), Tachycardia (21), Nausea (19), Malaise (17), Inappropriate schedule of product administration, Palpitations (16 each), Electrocardiogram ST segment elevation, Pain in extremity (13 each), Asthenia, Blood creatine phosphokinase increased, Troponin I increased (12 each), Angina pectoris, C-reactive protein increased, Diarrhoea, Pain, Pericardial effusion (11 each), Arthralgia, Chills, Cough, Paraesthesia (10 each), Oropharyngeal pain (9), Influenza like illness, Troponin T increased (7 each), Decreased appetite, Hypotension, Lethargy, Myocardial necrosis marker increased, and Syncope (6 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 29.

Table 29. Myocarditis in Subjects aged 16 – 17 Years (N=470)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	50	291	2
	No	19	106	2
Relevant PT[a]	Myocarditis	69	397	4
Hospitalization required/prolonged	Yes	38	294	0
	No	31	104	4
Relevant suspect dose	Dose 1	26	86	0
	Dose 2	20	219	3
	Dose 3	0	1	0
	Unknown	23	91	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=349	≤24 hours	4	19	0
	1-5 days	29	185	0
	6-13 days	4	48	1
	14-21 days	3	15	1
	22-31 days	1	16	0
	32-90 days	6	17	0
	Unknown	23	97	2
Event Outcome	Fatal	0	2	0
	Not resolved	21	113	1
	Resolved	14	103	0
	Resolved with sequelae	0	5	0
	Resolving	20	107	1
	Unknown	15	67	2
Duration of event[b] n=54, median=5 days	Up to 3 days	3	13	0
	4-6 days	2	12	0
	7-25 days	3	19	0
	26-31 days	1	1	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 18 - 24 years

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 1187 (0.18% of 657,528 cases of the total PM dataset, 2.3% of the 50,779 subjects aged 18-24 years), compared to 120 cases (0.04%) retrieved in the PSUR #1.
- Country of incidence: Germany (256), Australia (180), France (165), UK (117), Italy (54), Japan (49), Sweden (43), Spain (34), US (30), Canada and Denmark (20 each). The remaining 219 cases were distributed among 36 countries.
- Subjects' age in years: n = 1187, range: 18-24, mean: 20.6, median: 20.0.
- Medical history (n = 330): the most frequently (>2 occurrence) reported medical conditions included Asthma (44), Tobacco user (40), Myocarditis (27), Seasonal allergy (26), Non-tobacco user (16), Alcohol use (15), Chest pain, Drug hypersensitivity (13 each), Suppressed lactation[19](12), Attention deficit hyperactivity disorder, Depression, Migraine, Mite allergy, Obesity, Pericarditis, Substance use (9 each), Appendicectomy, Contraception, Nicotine dependence (8 each), Food allergy (7), Allergy to animal, Tonsillectomy, Tonsillitis (6 each), Anxiety, Childhood asthma, Dust allergy, Dyspnoea, Epilepsy (5 each), Acne, Autism spectrum disorder, Crohn's disease, Gilbert's syndrome, Irritable bowel syndrome, Rhinitis allergic, Type 1 diabetes mellitus (4 each), Adenotonsillectomy, Circulatory collapse, Cough, Diarrhoea, Familial risk factor, Glucose-6-phosphate dehydrogenase deficiency, Nasopharyngitis, and Tobacco abuse (3 each).
- COVID-19 Medical history (n = 55): COVID-19 (37), Suspected COVID-19 (15), SARS-CoV-2 test positive (2), Asymptomatic COVID-19, Coronavirus infection (1 each).
- Co-suspect vaccines/medications: clozapine, colchicine, COVID-19 AstraZeneca vaccine (2 each), cannabis sativa, COVID-19 Moderna vaccine, hepatitis A vaccine, ibuprofen, influenza vaccine (1 each).
- Most frequently co-reported PTs (>10 occurrences): Chest pain (412), Pyrexia (192), Dyspnoea (157), Troponin increased (152), Chest discomfort (122), Pericarditis (96), Palpitations (89), Fatigue (88), Headache (80), Tachycardia (54), Pain (48), Chills (45), Electrocardiogram ST segment elevation (42), Inappropriate schedule of product administration, Myalgia (41 each), Malaise (40), Nausea (37), Off label use (36), Dizziness, Pain in extremity (33 each), Influenza like illness (32), C-reactive protein increased (31), Arthralgia (28), Asthenia, Interchange of vaccine products (27 each), Pericardial effusion (26), Diarrhoea (24), Blood creatine phosphokinase increased, Cough (23 each), Vomiting (22), Arrhythmia (21), Electrocardiogram abnormal, Immunisation[23] (20 each), Troponin T increased (19), Heart rate increased (18), Angina pectoris,

Hyperhidrosis, Oropharyngeal pain (16 each), Lethargy (15), Disease recurrence, Myocardial necrosis marker increased (14 each), Dyspnoea exertional, Paraesthesia, Syncope, Troponin I increased (13 each), Cardiac failure, Vaccination site pain (12 each), COVID-19, Lymphadenopathy, Pleuritic pain (11 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 30.

Table 30. Myocarditis in Subjects aged 18 – 24 Years (N=1187)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	158	642	3
	No	82	295	7
Relevant PT[a]	Myocarditis	239	934	10
	Autoimmune myocarditis	1	1	0
	Hypersensitivity myocarditis	0	2	0
Hospitalization required/prolonged	Yes	111	658	6
	No	129	281	4
Relevant suspect dose	Dose 1	75	211	4
	Dose 2	76	524	3
	Dose 3	7	18	0
	Unknown	82	184	3
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=875	≤24 hours	17	38	1
	1-5 days	76	469	5
	6-13 days	21	96	2
	14-21 days	13	40	0
	22-31 days	9	30	0
	32-60 days	11	28	0
	61-232 days	3	16	0
	Unknown	90	227	2
Event Outcome	Fatal	1	1	0
	Not resolved	81	255	3
	Resolved	47	187	1
	Resolved with sequelae	4	13	0
	Resolving	65	328	3
	Unknown	42	159	3
Duration of event[b] n=95, median=5 days	Up to 3 days	9	17	0
	4-6 days	4	28	1
	7-25 days	4	25	0
	26-86 days	2	5	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 25 - 29 years

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 589 (0.09% of 657,528 cases of the total PM dataset, 1.0% of the 58,731 subjects aged 25-29 years), compared to 55 cases (0.02%) retrieved in the PSUR #1.
- Country of incidence: Germany (137), Australia (96), UK (95), France (56), Italy (24), Finland (20), Japan (18), Sweden (15), Canada (13), Austria, Belgium, and Spain (12 each). The remaining 79 cases were distributed among 29 countries.
- Subjects' age in years: n = 589, range: 25-29, mean: 26.9, median: 27.0.
- Medical history (n = 193): the most frequently (>2 occurrences) reported medical conditions included Tobacco user (22), Asthma (15), Seasonal allergy (14), Myocarditis (13), Drug hypersensitivity (10), Alcohol use, Food allergy, Non-tobacco user, Suppressed lactation[19] (9 each), Obesity (7), Migraine (6), Pericarditis (5), Attention deficit hyperactivity disorder, Drug dependence, Dyspnoea, Nicotine dependence, Palpitations, Polycystic ovaries (4 each), Abstains from recreational drugs, Allergy to animal, Anxiety, Appendicectomy, Breast feeding, Cardiac disorder, Chest pain, Colitis ulcerative, Depression, Drug abuse, Endometriosis, Ex-tobacco user, Hypersensitivity, Immunodeficiency, Irritable bowel syndrome, Mite allergy, Oropharyngeal pain, Pyrexia, substance use, and Type 1 diabetes mellitus (3 each).
- COVID-19 Medical history (n = 33): COVID-19 (19), Suspected COVID-19 (14), Occupational exposure to SARS-CoV-2, and Post-acute COVID-19 syndrome (1).
- Co-suspect vaccines/medications: COVID-19 Moderna vaccine, diphtheria vaccine toxoid/ pertussis vaccine acellular/ tetanus vaccine toxoid, ibuprofen, and sumatriptan (1 each)
- Most frequently co-reported PTs (>10 occurrences): Chest pain (197), Dyspnoea (111), Pyrexia (89), Palpitations (80), Pericarditis (73), Fatigue (68), Chest discomfort (64), Troponin increased (56), Headache (47), Tachycardia (46), Asthenia, Dizziness, Malaise (28 each), Nausea, Pain (26 each), Inappropriate schedule of product administration, Myalgia, Pain in extremity, Pericardial effusion (25 each), Arrhythmia (23), Chills (22), Angina pectoris (21), Arthralgia (20), Heart rate increased (19), Syncope (17), Paraesthesia (15), Immunisation[23] (13), Vomiting (12), Cough, Hyperhidrosis, Off label use (11 each).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 31.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 31. Myocarditis in Subjects aged 25 – 29 Years (N=589)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	79	254	1
	No	83	167	5
Relevant PTs[a]	Myocarditis	0162	420	6
	Autoimmune myocarditis	0	1	0
Hospitalization required/prolonged	Yes	60	252	2
	No	102	169	4
Relevant suspect dose	Dose 1	54	104	3
	Dose 2	61	212	0
	Dose 3	7	5	1
	Unknown	40	100	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=392	≤ 24 hours	13	29	1
	1-5 days	45	155	1
	6-13 days	18	40	0
	14-21 days	2	29	0
	22-31 days	9	11	0
	32-60 days	9	17	0
	61-111 days	3	10	0
	Unknown	63	130	4
Event Outcome	Fatal	1	6	0
	Not resolved	69	130	3
	Resolved	17	77	0
	Resolved with sequelae	6	6	0
	Resolving	38	128	0
	Unknown	31	74	3
Duration of event[b] n=41, median=5 days	Up to 3 days	3	10	0
	4-6 days	1	8	0
	7-25 days	2	11	0
	26-165 days	1	5	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 30 - 39 years

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 995 (0.15% of 657,528 cases of the total PM dataset, 0.8% of the 129,478 subjects aged 30-39), compared to 91 cases (0.03%) retrieved in the PSUR #1.
- Country of incidence: UK (204), Germany (202), Australia (162), France (84), Sweden (34), Canada (31), Italy, Japan (29 each), US (27), Austria (24). The remaining 169 cases were distributed among 31 countries.
- Subjects' age in years: n = 995, range: 30-39, mean: 34.3, median: 34.0.
- Medical history (n = 342): the most frequently (>5 occurrences) reported medical conditions included Tobacco user (40), Seasonal allergy (28), Asthma (27), Obesity (24), Hypertension (18), Drug hypersensitivity (17), Chest pain (15), Alcohol use, Myocarditis (13 each), Non-tobacco user, Suppressed lactation[19] (12 each), Hypothyroidism (11), Depression, Food allergy, hypersensitivity, Pericarditis (10 each), Allergy to animal, Anxiety, Ex-tobacco user, Migraine (9 each), Mite allergy (8), Dyspnoea, Nicotine dependence (7 each), Abstains from alcohol, Immunodeficiency, Irritable bowel syndrome, Pregnancy (6 each).
- COVID-19 Medical history (n = 66): Suspected COVID-19 (33), COVID-19 (32), COVID-19 pneumonia (1).
- Co-suspect vaccines/medications: COVID-19 vaccine Moderna, influenza vaccine (3 each), COVID-19 vaccine AstraZeneca (2), brigatinib, cannabis sativa, cortisone, and influenza vaccine (surface antigen, inactivated, adjuvanted) (1 each).
- Most frequently co-reported PTs (>20 occurrence): Chest pain (292), Dyspnoea (210), Palpitations (161), Fatigue (156), Pericarditis (139), Pyrexia (114), Tachycardia (93), Chest discomfort (88), Headache (73), Inappropriate schedule of product administration (55), Dizziness, Troponin increased (51 each), Nausea (46), Myalgia (45), Angina pectoris (43), Immunisation[23] (38), Pain in extremity (37), Off label use (36), Arrhythmia, Asthenia, Malaise (32 each), Pain (31), Hyperhidrosis (29), Chills, Hypoaesthesia (28 each), Arthralgia, Interchange of vaccine products (27 each), Diarrhoea, Syncope (26 each), Heart rate increased, Vaccination site pain (25 each), Pericardial effusion (24), COVID-19 (23), Paraesthesia (22), Influenza like illness (21)

Myocarditis relevant data in this subgroup of subjects are summarised in Table 32.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 32. Myocarditis in Subjects aged 30 – 39 Years (N=995)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	188	338	1
	No	189	267	12
Relevant PT[a]	Myocarditis	376	605	13
Hospitalization required/prolonged	Yes	131	309	3
	No	246	296	10
Relevant suspect dose	Dose 1	122	177	3
	Dose 2	128	257	8
	Dose 3	27	11	1
	Unknown	100	160	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=625	≤24 hours	32	29	1
	1-5 days	79	176	1
	6-13 days	45	80	1
	14-21 days	17	48	2
	22-31 days	15	27	0
	32-60 days	18	24	0
	61-170 days	11	19	0
	Unknown	161	203	8
Event Outcome	Fatal	0	7	0
	Not resolved	152	222	5
	Resolved	51	102	1
	Resolved with sequelae	12	10	0
	Resolving	71	156	2
	Unknown	91	109	5
Duration of event[b] n=63, median=7 days	Up to 3 days	6	12	0
	4-6 days	2	8	0
	7-25 days	8	12	0
	26-181 days	4	11	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.14% of 721 cases of the total CT dataset); no cases were retrieved in the PSUR #1.
- Country of incidence: ██████ (1).
- Subjects' age in years: ██ years.
- Medical history: Not reported.
- COVID-19 Medical history: Not reported.
- Co-suspects: None.
- Number of relevant serious events: 1.
- Reported relevant PTs: Myocarditis (1).
- Relevant event outcome: Resolved (1).
- Time to onset of relevant events: 64 days.
- Duration of myocarditis was reported as 6 days.
- Co-reported PTs: None

Post-Authorisation Data

- Number of cases: 1876 (0.3% of 657,528 cases of the total PM dataset, 0.6% of the 323,358 subjects ≥ 40 years), compared to 164 cases (0.05%) retrieved in the PSUR #1.
- Country of incidence: Germany (428), UK (366), Australia (195), France (154), Japan (96), US (66), Italy (62), Sweden (56), Canada (52), and New Zealand (45). The remaining 356 cases were distributed among 36 countries.
- Subjects' age in years: n = 1876, range: 40-102, mean: 55.2, median: 53.0.
- Medical history (n = 886): the most frequently (>10 occurrences) reported medical conditions included Hypertension (199), Asthma (63), Hypothyroidism (44), Tobacco user (42), Atrial fibrillation (40), Diabetes mellitus, Drug hypersensitivity (39 each), Seasonal allergy (38), Myocarditis (37), Obesity, Type 2 diabetes mellitus (32 each), Dyslipidaemia (30), Hypercholesterolaemia (29), Migraine (26), Immunodeficiency (25), Non-tobacco user (21), Rheumatoid arthritis (20), Hyperlipidaemia (19), Coronary artery disease, Depression, Food allergy, Myocardial infarction (18 each), Autoimmune thyroiditis, Cardiac disorder, Gastrooesophageal reflux disease (17 each), Arrhythmia, Steroid therapy (16 each), Chronic obstructive pulmonary disease, Hypersensitivity, Osteoarthritis (15 each), Alcohol use, Colitis ulcerative, Ex-tobacco user, Pericarditis (14 each), Cerebrovascular accident, Mite allergy, Nicotine dependence, Osteoporosis (13 each), Anxiety, Benign prostatic hyperplasia, Chest pain, Menopause (12 each), Arteriosclerosis coronary artery, Gout, Tobacco abuse (11 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- COVID-19 Medical history (n = 105): COVID-19 (51), Suspected COVID-19 (50), Coronavirus infection, COVID-19 pneumonia, Post-acute COVID-19 syndrome (2 each), Asymptomatic COVID-19 (1).
- Co-suspect vaccine/medications (> 1 occurrence): COVID-19 AstraZeneca Vaccine (5), acetylsalicylic acid, azathioprine, nivolumab, sulfamethoxazole/trimethoprim (2 each).
- Most frequently co-reported PTs (>50 occurrence): Chest pain (484), Dyspnoea (447), Fatigue (349), Pericarditis (307), Palpitations (288), Pyrexia (264), Immunisation[23] (240), Off label use (202), Tachycardia (188), Chest discomfort (170), Interchange of vaccine products (160), Headache (156), Malaise (108), Asthenia (107), Inappropriate schedule of product administration (104), Dizziness (102), Troponin increased (99), Arrhythmia (87), Nausea (86), Pericardial effusion (84), Arthralgia (76), Pain, Pain in extremity (69 each), Chills (67), Cardiac failure (64), Myalgia (62), Angina pectoris (61), Syncope (59), Heart rate increased (57), and Atrial fibrillation (53).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 33.

Table 33. Myocarditis in Subjects aged ≥40 Years (N=1876)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	430	513	7
	No	474	436	16
Relevant PTs[a]	Myocarditis	902	944	23
	Eosinophilic myocarditis	2	2	0
	Immune-mediated myocarditis	0	1	0
Hospitalization required/prolonged	Yes	375	516	6
	No	529	435	17
Relevant suspect dose	Dose 1	237	239	4
	Dose 2	342	422	7
	Dose 3	145	96	3
	Unknown	180	192	9
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=1102	≤24 hours	56	25	2
	1-5 days	148	219	2
	6-13 days	92	124	2
	14-21 days	69	85	0
	22-31 days	30	48	1
	32-60 days	54	61	1
	61-220 days	41	41	1
	Unknown	416	347	14
Event Outcome	Fatal	13	29	1
	Not resolved	317	298	8
	Resolved	121	120	1
	Resolved with sequelae	31	23	0
	Resolving	195	242	1
	Unknown	227	238	12

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 33. Myocarditis in Subjects aged ≥40 Years (N=1876)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Duration of event[b] n=88, median=7 days	Up to 3 days	13	7	0
	4-6 days	11	8	0
	7-25 days	14	14	1
	26-169 days	9	11	0

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

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: No cases were retrieved during the current reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 732 (0.11% of 657,528 cases of the total PM dataset, 0.97% of the 74704 subjects with unknown age), compared to 26 cases (0.01%) retrieved in the PSUR #1.
- Country of incidence: Germany (165), Canada (154), UK (149), Hong Kong (53), US (48), Australia (41), Japan (34), Greece (17), Brazil (12), France (9). The remaining 50 cases were distributed among 26 countries.
- Subjects' age in years (n = 732[52]): Unknown.
- Medical history (n = 146): the most frequently (≥6 occurrences) reported medical conditions included Asthma (21), Hypertension (13), Anxiety (12), Depression, SARS-CoV-2 test negative (9 each), Immunodeficiency, Seasonal allergy (8 each), Attention deficit hyperactivity disorder, Drug hypersensitivity, Food allergy, Hypothyroidism (7 each), and Diabetes mellitus (6).
- COVID-19 Medical history (n = 40): Suspected COVID-19 (28), COVID-19 (11), SARS-CoV-2 test positive (2).
- Co-suspect medications: amoxicillin, emtricitabine/tenofovir disoproxil, propranolol, ramipril, and varenicline (1 each)
- Most frequently co-reported PTs (>10 occurrences): Chest pain (173), Pericarditis (119), Dyspnoea (109), Fatigue (91), Palpitations (82), Pyrexia (77), Tachycardia (49), Immunisation[23] (46), Chest discomfort (44), Off label use (34), Headache (31), Pain in extremity (29), Chills, Interchange of vaccine products, Nausea (25 each), Myalgia (21), Malaise, Pain (20 each), COVID-19, Dizziness (19 each), Asthenia, Back pain, Cough,

[52] Including 5 child, 39 Adolescents, 122 Adults and 8 elderly.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Inappropriate schedule of product administration (17 each), Drug ineffective, Vomiting (16 each), Diarrhoea (14), Arthralgia, Hyperhidrosis, Hypoaesthesia (13 each), Syncope (12), and Angina pectoris (11).

Myocarditis relevant data in this subgroup of subjects are summarised in Table 34.

Table 34. Myocarditis in Subjects of Unknown Age (N=732)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	83	199	171
	No	99	120	60
Relevant PT[a]	Myocarditis	182	319	231
Hospitalization required/prolonged	Yes	53	144	14
	No	129	175	217
Relevant suspect dose	Dose 1	59	102	17
	Dose 2	69	131	24
	Dose 3	22	17	10
	Unknown	32	69	180
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=157	≤24 hours	4	7	2
	1-5 days	19	60	3
	6-13 days	12	14	0
	14-21 days	5	9	1
	22-31 days	2	6	1
	32-72 days	3	9	0
	Unknown	138	216	224
Event Outcome	Fatal	1	5	3
	Not resolved	54	107	12
	Resolved	36	72	9
	Resolved with sequelae	3	3	0
	Resolving	18	19	4
	Unknown	70	115	203
Duration of event[b] n=6, median=4 days	Up to 3 days	1	0	1
	4-6 days	1	1	1
	7-27 days	0	1	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects with booster dose

Clinical Trial Data

- Number of cases: 2 cases (0.3% of 721 cases of the total CT dataset, 0.008% of the 25787 subjects who received a booster dose), compared to no cases in the PSUR #1.
- In both the (male) cases, aged [redacted] respectively, the patients received homologous booster dose. Please see above the "Overall- All Ages" subsection for complete details.

Post-Authorisation Data

- Number of cases: 381 (0.06% of 657,528 cases of the total PM dataset, 1.5% of the 25787 subjects who received a booster dose), compared to no cases in the PSUR #1.
- Country of incidence: UK (303), Israel (18), Germany (17), France (9), Italy (8), US (6), Sweden (4), Austria, Brazil, Denmark, Norway (2 each). The remaining 8 cases were distributed among 8 countries.
- MC (102), NMC (279).
- Subjects' gender: female (209), male (157), and unknown (15).
- Subjects' age in years: n = 332, range: 13-90, mean: 52.1, median: 53.0.
- Medical history (n = 94): the medical conditions reported (>4 occurrence) included Hypertension (15), Immunodeficiency (15), Type 2 diabetes mellitus (7), Depression (6), Anxiety, Asthma, Fibromyalgia, Influenza immunisation, Neoplasm, and Rheumatoid arthritis (5 each).
- COVID-19 Medical history (n = 27): Suspected COVID-19 (21). COVID-19 (6), Post-acute COVID-19 syndrome (1).
- Co-suspect vaccines (n=13) reported more than once: influenza vaccine (5), hepatitis A vaccine (2).
- Number of relevant events: 381.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Myocarditis (381).
- Relevant event outcome:[47] fatal (4), resolved/resolving (83); resolved with sequelae (2), not resolved (93), unknown (200).
- Most frequently co-reported PTs (>20 occurrence): Immunisation[23] (359), Off label use (243), Fatigue (194), Interchange of vaccine products, Pericarditis (173 each), Chest pain (168), Palpitations (157), Dyspnoea (147), Tachycardia (120), Pyrexia (104), Headache (59), Arthralgia (34), Chest discomfort, Chills, Dizziness, Pain in extremity (31 each), Nausea (29), Asthenia (27), Malaise, Pain (26 each), Myalgia (23), and Syncope (21).

The number of myocarditis cases occurred after a booster dose in each age group is reported in Table 35.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 35. Myocarditis in Subjects who Received a Booster dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases		
		F	M	U	F	M	U
Age group	0 to 17 years	0	0	0	1	1	0
	18 to 24 years	2	7	0	5	13	0
	25 to 29 years	2	3	0	5	3	1
	30 to 39 years	15	6	1	12	7	0
	40 years and older	84	64	2	61	36	1
	Unknown	9	9	3	13	8	7
	TOTAL	112	89	6	97	68	9

F=female; M=male; U=unknown

Cases Medically Confirmed and Having a TTO ≤ 21 Days: 2007 Cases

These 2007 cases were individually reviewed and assessed according to BC Myocarditis Case Definition and Level of Certainty Classification (version 1.5.0, 16 July 2021), as per table below:

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

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

Cases BC Level 1 (out of 2007 cases above reviewed): 275 cases

- Number of events: 1274 (of which 272 coding to the PT Myocarditis, 1 to PTs Autoimmune myocarditis, Eosinophilic myocarditis and Hypersensitivity myocarditis).
- Country of incidence (>5 occurrence): France (123), Spain (33), Japan (18), UK (11), Czech Republic, Germany, Sweden (10 each), Denmark, Italy (9 each), Netherlands (7), and Switzerland (6). The remaining 29 cases were distributed among 16 countries.
- Subjects' gender: female (47) and male (228);
- Subjects' age in years (n =274): range: 12 – 84, mean: 27.7, median 22.0.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Medical history (n=164): medical conditions (≥10 occurrences) included Tobacco user (34), Myocarditis (16), Asthma (13), Obesity (12), Hypertension and Alcohol use (10).
- Time to event onset:
  - <24 hours: 13 events;
  - 1-5 days: 180 events;
  - 6-13 days: 55 events;
  - 14-21 days: 27 events.
- Duration of relevant events (for those cases where the event resolved); n=39
  - Up to 3 days: 7 events;
  - 4-6 days: 15 events;
  - 7-31 days: 17 events.
- Most frequently co-reported PTs (≥20 occurrence): Chest pain (107), Pyrexia (69), Dyspnoea (31), Headache (26), Troponin increased (24), Nausea (22).
- Relevant event outcome: fatal (4), resolved/resolving (207), resolved with sequelae (7), not resolved (43) and unknown (14).

Out of 275 cases assessed as BC level 1 with a time to onset ≤21 days, there were 4 fatal cases.

18-24 years of age (1)

- One (1) subject, from [redacted] who developed myocarditis 5 days after vaccination (dose no. 1):
  - A [redacted] subject, suffering from blood pressure increased. Reported PTs: Myocarditis (outcome: fatal), no co-reported PTs.

25-29 years of age (1)

- One (1) subject, from [redacted] who developed myocarditis 4 days after vaccination (dose no. 2):
  - A [redacted] subject, suffering from autoimmune disorder and autoimmune thyroiditis. Reported PTs: Myocarditis (outcome: fatal), Cardiomyopathy, Pyrexia, Chills, Decreased appetite, Arthralgia, Headache, Cerebral venous sinus thrombosis, Pulmonary oedema, Thrombocytopenia, and Cerebral venous thrombosis.

40 years and older (2)

- A [redacted] subject, from [redacted] concurrently suffering from benign prostatic hyperplasia, diabetes mellitus, and hypertension. Reported PTs: Myocarditis (82 days

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

after dose 1; outcome: fatal), Multiple organ dysfunction syndrome, Cardiac failure, Altered state of consciousness, Bradycardia, Shock, Depressed level of consciousness, Loss of consciousness, Cardio-respiratory arrest, Atrioventricular block complete, Conduction disorder, Troponin T increased, Blood creatine phosphokinase increased, Fall, Left ventricular dysfunction, Multi-organ disorder, Hypotension, Small intestinal haemorrhage, and White blood cell count increased.

- An [redacted] subject, from [redacted] concurrently suffering from Cerebral infarction, and oesophageal carcinoma. Reported PTs: Myocarditis (22 days after first dose; outcome: fatal).

16.3.1.2.2. Important Identified Risks – Pericarditis

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

Overall - All Ages

Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.14% of 721 cases of the total CT dataset), compared to 1 case (0.14 %) retrieved in the PSUR #1.
- Country of incidence: [redacted].
- Subjects' gender: [redacted]
- Subject's age in year: [redacted]
- Co-suspects: none.
- Number of relevant serious events: 1.
- Reported relevant PT: Pericarditis.
- Time to onset: 66 days.
- Event's outcome: recovering.
- MAH's and Investigator's causality: unrelated.

Post-Authorisation Data

- Number of cases: 5311 (0.80% of 657,528 cases of the total PM dataset), compared to 375 cases[53] (0.11%) retrieved in the PSUR #1.
- Country of incidence: Australia (1925), the UK (661), France (623), Italy (357), Canada (223), Germany (199), Netherlands (139), Norway (135), Japan (133), New Zealand (100). The remaining 816 cases were distributed among 43 countries.

[53] During the reporting period of PSUR #1 there were 375 events of pericarditis [Pericarditis (363), Pleuropericarditis (12)].

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- MC (3747), NMC (1564).
- Subjects' gender: female (2354), male (2829) and unknown (128).
- Subjects' age in years: n = 4948, range: 2-98, mean: 38.4, median: 35.0.
- Medical history: (n= 1531) the most frequently (≥1%) reported relevant medical included: Hypertension (213), Pericarditis (200), Asthma (116), Tobacco user (74), Seasonal allergy (68), Drug hypersensitivity (61), Hypothyroidism (58).
- COVID-19 Medical history (n = 233): COVID-19 (128), Suspected COVID-19 (97), Post-acute COVID-19 syndrome (6), Asymptomatic COVID-19 syndrome (3), COVID-19 pneumonia (2), Coronavirus infection, Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibodies test positive, SARS-CoV-2 test positive (1 each).
- Co-suspects: 49 cases. Frequently (≥3 occurrences) reported relevant co suspect vaccines/medications were colchicine (5), COVID-19 AstraZeneca vaccine and influenza vaccine (4 each), COVID-19 Moderna Vaccine (3).
- Number of relevant events: 5320.
- Relevant event seriousness: serious (5314), non-serious (6).
- Reported relevant PTs: Pericarditis (5274), Pericarditis constrictive (11), Pleuropericarditis (34), Pericarditis adhesive (1).
- Relevant event outcome[47]: fatal (9), resolved/resolving (2071), resolved with sequelae (55), not resolved (1936), unknown (1253).

Age-stratified data[54]

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

Clinical Trial Data

- Number of cases: none. No cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 1; no cases were retrieved in the PSUR #1.
- Country of incidence: [redacted]
- Subject' age in year: [redacted]
- Gender: [redacted]
- Medical history: unknown.
- Co-suspects: none.

[54] Cases where the age was reported as Child (2 cases), Adolescent (15 cases), Adult (31 cases) and Elderly (3 cases) are included in the subgroup of unknown age and in the overall.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Relevant PT: Pericarditis.
- Medically confirmed: yes.
- Hospitalization required: no.
- Time to onset (pericarditis): 1 day after dose 1.
- Co-reported PTs: Chest pain, Off-label use, Palpitations, and Product use issue.

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

Clinical Trial Data

- Number of cases: none. No cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 4 (0.0006% of 657,528 cases of the total PM dataset, 0.4% of the 1049 subjects aged 5-11 years); no cases were retrieved in the PSUR #1.
- Country of incidence: Canada (2), [redacted] (1 each).
- Subjects' age in years: n = 4, range: 5-9, mean: 7.8, median: 8.5.
- Medical history: none.
- COVID-19 Medical history: none.
- Co-suspects: None.
- Most frequently co-reported PTs (≥2 occurrences): Chest pain (4), Fatigue and Pyrexia (3 each), Dyspnoea, Myocarditis, and Product administered to patient of inappropriate age (2 each).

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 36. Pericarditis in Subjects aged 5-11 years (N=4)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	1	2	0
	No	0	1	0
Relevant PT[a]	Pericarditis	1	3	0
Hospitalization required/prolonged	Yes	0	2	0
	No	1	1	0
Relevant suspect dose	Dose 1	0	1	0
	Dose 2	1	2	0
	Dose 3	0	0	0
	Unknown	0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=4	≤ 24 hours	1	0	0
	1-5 days	0	1	0
	Unknown	0	0	2
Event Outcome[b]	Fatal	0	0	0
	Not resolved	1	0	0
	Resolved	0	0	0
	Resolved with sequelae	0	0	0
	Resolving	0	1	0
	Unknown	0	2	0
Duration of event	Not applicable			

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

<u>**Subjects aged 12 - 15 years**</u>

Clinical Trial Data

- Number of cases: 215 (0.03% of 657,528 cases of the total PM dataset, 2.1% of the 10,377 subjects aged 12-15 years), compared to 4 cases (0.001%) retrieved in the PSUR #1.
- Country of incidence: Australia (76), Hong Kong (27), Japan (19), Canada (18), France, UK (15 each), Italy (14). The remaining 31 cases were distributed among 15 countries.
- Subjects' age in years: n = 215, range: 12-15, mean: 13.8, median: 14.0.
- Medical history (n = 27): the medical conditions reported more than once included Asthma (3), Allergy to plants, and Glucose-6-phosphate dehydrogenase deficiency (2 each).
- COVID-19 Medical history (n = 4): COVID-19 (3), Suspected COVID-19 (1).
- Co-suspects: None.
- Most frequently co-reported PTs (≥2%): Chest pain (100), Myocarditis (68), Dyspnoea (33), Pyrexia (31), Palpitations (18), Tachycardia (15), Chest discomfort, Troponin

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

increased (13 each), Malaise (12), Fatigue, Headache (11 each), Electrocardiogram ST segment elevation (10), Dizziness, Electrocardiogram abnormal (9 each), Nausea (8), Asthenia, Pain, Pericardial effusion (6 each), Chills (5).

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

Table 37. Pericarditis in Subjects aged 12-15 years (N=215)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	45	138	0
	No	9	22	1
Relevant PT[a]	Pericarditis	54	160	1
Hospitalization required/prolonged	Yes	12	55	0
	No	42	105	1
Relevant suspect dose	Dose 1	15	49	0
	Dose 2	17	68	0
	Dose 3	0	0	0
	Unknown	22	43	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=118	≤ 24 hours	4	6	0
	1-5 days	13	57	1
	6-13 days	1	14	0
	14-21 days	6	7	0
	22-31 days	1	5	0
	≥ 32 days	0	3	0
	Unknown	29	68	0
Event Outcome	Fatal	0	0	0
	Not resolved	22	40	1
	Resolved	6	31	0
	Resolved with sequelae	0	1	0
	Resolving	5	36	0
	Unknown	21	52	0
Duration of event[b] n=12, median: 7	Up to 3 days	1	1	0
	4-6 days	0	3	0
	7-10 days	0	2	0
	11-26 days	2	3	0

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

Subjects aged 16 - 17 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #1.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 174 (0.03% of 657,528 cases of the total PM dataset, 2.3% of the 7647 subjects aged 16-17 years), compared to 7 cases (0.002%) retrieved in the PSUR #1.
- Country of incidence: Australia (74), France (24), Italy (15), UK (13). The remaining 48 cases were distributed among 23 countries.
- Subjects' age in years: n = 174, range: 16-17, mean: 16.5, median: 16.0.
- Medical history (n = 32): the medical conditions reported more than once included Asthma (5), Attention deficit hyperactivity disorders, Chest pain, drug Hypersensitivity, Pericarditis, Seasonal allergy, Surgery, Urticaria (2 each).
- COVID-19 Medical history (n = 9): COVID-19 (5), Suspected COVID-19 (3), Asymptomatic COVID-19 (1).
- Co-suspect vaccine/medications (n=3): colchicine, cholecalciferol, ethinylestradiol/levonorgestrel, HPV vaccine VLP RL1 9V (Yeast), and mesalazine (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (67), Myocarditis (34), Dyspnoea (29), Pyrexia (28), Headache (16), Fatigue (15), Tachycardia (11), Nausea, Palpitations, Pericardial effusion (10 each), Chest discomfort (9), Electrocardiogram ST segment elevation, Troponin increased (7 each), Lethargy, Myalgia, Vomiting (6 each), Arthralgia, Back pain, Diarrhoea, Dizziness, Lymphadenopathy (5 each), C-reactive protein increased, Electrocardiogram abnormal, Pain, pain in extremity, Troponin I increased, and Vaccination site pain (4 each).

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

Table 38. Pericarditis in Subjects aged 16-17 years (N=174)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	43	103	0
	No	10	16	2
Relevant PT[a]	Pericarditis	53	119	2
Hospitalization required/prolonged	Yes	16	42	1
	No	37	77	1
Relevant suspect dose	Dose 1	23	34	0
	Dose 2	16	39	2
	Dose 3	0	0	0
	Unknown	14	46	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=100	≤ 24 hours	4	4	0
	1-5 days	15	36	1
	6-13 days	8	12	0
	14-21 days	3	6	0
	22-31 days	1	3	0

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 38. Pericarditis in Subjects aged 16-17 years (N=174)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
	≥ 32 days	2	5	0
	Unknown	20	53	1
Event Outcome	Fatal	0	0	0
	Not resolved	14	35	1
	Resolved	5	19	0
	Resolved with sequelae	1	0	0
	Resolving	20	33	0
	Unknown	13	32	1
Duration of event[b] n=9, median: 7	Up to 3 days	0	1	0
	4-6 days	1	0	0
	7-10 days	0	0	0
	11-26 days	1	3	0
	27-43 days	0	3	0

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

Subjects aged 18 - 24 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 659 (0.10% of 657,528 cases of the total PM dataset, 1.3% of the 50,779 subjects aged 18-24 years), compared to 34 cases (0.01%) retrieved in the PSUR #1.
- Country of incidence: Australia (290), France (79), UK (71), Italy (42), Germany (23), Japan, New Zealand (18 each), Norway, Sweden (14 each), Canada, US (12 each), Ireland, and Spain (11 each). The remaining 44 cases were distributed among 15 countries.
- Subjects' age in years: n = 659, range: 18-24, mean: 21.2, median: 21.0.
- Medical history (n = 133): the medical conditions reported more than twice included Pericarditis (24), Asthma (15), Chest pain, Seasonal allergy (8 each), Suppressed lactation[19] (7), Drug hypersensitivity, Tobacco user (6 each), Allergy to animal, Migraine, Mite allergy (5 each), Appendicectomy, Attention deficit hyperactivity disorder, Non-tobacco user (4 each), Cardiomyopathy, Childhood asthma, Food allergy, and Pericardial effusion (3 each).
- COVID-19 Medical history (n = 23): COVID-19 (15), Suspected COVID-19 (8).
- Co-suspect vaccines/medications (n=4 cases): ciprofloxacin, hepatitis A vaccine, ibuprofen, influenza vaccine, metronidazole, and naproxen (1 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Most frequently co-reported PTs (≥2%): Chest pain (231), Dyspnoea (116), Myocarditis (96), Pyrexia (72), Chest discomfort (56), Palpitations (54), Fatigue (49), Headache (45), Tachycardia (37), Malaise (30), Pericardial effusion (28), Myalgia (27), Dizziness and Pain (26 each), Inappropriate schedule of product administration (24), Nausea (23), Troponin increased (21), Arthralgia, Lethargy (20 each), Chills, Electrocardiogram ST segment elevation (18 each), C-reactive protein increased (16).

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

Table 39. Pericarditis in Subjects aged 18-24 years (N=659)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	167	335	4
	No	63	89	1
Relevant PT[a]	Pericarditis	230	424	5
Hospitalization required/prolonged	Yes	53	115	1
	No	177	309	4
Relevant suspect dose	Dose 1	164	279	5
	Dose 2	62	140	0
	Dose 3	4	5	0
	Unknown	0	0	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=303	≤ 24 hours	14	27	0
	1-5 days	55	109	0
	6-13 days	20	44	1
	14-21 days	14	24	0
	22-31 days	10	12	0
	≥ 32 days	9	17	0
	Unknown	108	191	4
Event Outcome	Fatal	0	0	0
	Not resolved	94	147	0
	Resolved	33	65	0
	Resolved with sequelae	3	2	0
	Resolving	64	119	1
	Unknown	36	91	4
Duration of event[b] n=29, median: 6	Up to 3 days	2	6	0
	4-6 days	1	6	0
	7-10 days	0	4	0
	11-26 days	1	4	0
	27-57 days	3	1	0
	516 days	0	1	0

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Subjects aged 25 - 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 614 (0.09% of 657,528 cases of the total PM dataset, 1.0% of the 58,731 subjects aged 25-29 years), compared to 22 cases (0.007%) retrieved in the PSUR #1.
- Country of incidence: Australia (293), France, UK (73 each), Italy (37), Germany (27), Netherlands (13), Belgium, and New Zealand (10 each). The remaining 78 cases were distributed among 21 different countries.
- Subjects' age in years: n = 614, range: 25-29, mean: 27, median: 27.0.
- Medical history (n = 141): the medical conditions reported more than twice included Pericarditis (19), Asthma (16), Seasonal allergy (12), Tobacco user (11), Drug hypersensitivity (8), Alcohol use, Colitis ulcerative, Depression, Obesity (5 each), Ex-tobacco user, migraine, Non-tobacco user, Suppressed lactation[19] (4 each), Appendicectomy, Chest pain, Endometriosis, Food allergy, Gastroesophageal reflux disease, Hypersensitivity, Lung disorder, Mite allergy, Nicotine dependence, Overweight, Rhinitis allergic (3 each).
- COVID-19 Medical history (n = 27): COVID-19 (15), Suspected COVID-19 (10), Post-acute COVID-19 syndrome (2), Asymptomatic COVID-19, Occupational exposure to SAR-CoV-2 test positive, SARS-CoV-2 test positive (1 each).
- Co-suspect vaccines/medications (n=1): Varicella zoster vaccine live.
- Most frequently co-reported PTs (≥2%): Chest pain (222), Dyspnoea (125), Palpitations (75), Myocarditis (73), Fatigue (66), Pyrexia (59), Headache (58), Chest discomfort (56), Tachycardia (42), Pericardial effusion (33), Myalgia (28), Nausea (23), Dizziness (22), Electrocardiogram abnormal (20), Lethargy (19), Inappropriate schedule of product (18), Pain in extremity, Paraesthesia (17 each), Arthralgia (16), Asthenia, Malaise, Pain (15 each), Cough (14), Hearth rate increased, Syncope (14 each), and Troponin increased (13).

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

Table 40. Pericarditis in Subjects aged 25-29 years (N=614)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	159	285	2
	No	79	85	4
Relevant PT[a]	Pericarditis	236	369	6
	Pericarditis constrictive	1	0	0
	Pleuropericarditis	1	1	0

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 40. Pericarditis in Subjects aged 25-29 years (N=614)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Hospitalization required/prolonged	Yes	36	90	2
	No	202	280	4
Relevant suspect dose	Dose 1	80	120	3
	Dose 2	56	96	1
	Dose 3 (homologous booster)	7	5	1
	Unknown	95	149	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=307	≤ 24 hours	11	23	0
	1-5 days	60	92	1
	6-13 days	17	33	0
	14-21 days	14	14	1
	22-31 days	5	11	0
	≥ 32 days	12	15	0
	Unknown	119	184	4
Event Outcome	Fatal	0	0	0
	Not resolved	109	161	1
	Resolved	20	44	0
	Resolved with sequelae	0	2	0
	Resolving	60	101	3
	Unknown	50	62	2
Duration of event[b] n=21, median: 8	Up to 3 days	2	2	0
	4-6 days	1	2	0
	7-10 days	1	4	0
	11-26 days	1	4	0
	27-84 days	0	4	0

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

<u>Subjects aged 30 - 39 years</u>

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 1222 (0.2% of 657,528 cases of the total PM dataset; 0.9% of the 129,478 subjects aged 30-39), compared to 50 cases (0.002%) retrieved in the PSUR #1.
- Country of incidence: Australia (587), UK (145), France (138), Italy (65), Germany (35), Netherlands (31), Canada 30), Norway (28), New Zealand (24), Sweden (23), Spain, US (17 each), Japan (15), Belgium (14). The remaining 53 cases were distributed among 20 different countries.
- Subjects' age in years: n = 1222, range: 30-39, mean: 34.2, median: 34.0.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Medical history (n = 261): the medical conditions reported more than 5 times included Pericarditis (44), Asthma (28), Seasonal allergy (18), Drug hypersensitivity (14), Hypothyroidism, Non-tobacco user (13 each), Hypertension, Tobacco user (12 each), Depression, Hypersensitivity (9 each), Gastroesophageal reflux disease, Immunodeficiency, Suppressed lactation[19] (8 each), Chest pain, Contraception, Migraine, Mite allergy (7 each), Anxiety, Autoimmune thyroiditis, Food allergy (6 each).
- COVID-19 Medical history (n = 52): COVID-19 (27), Suspected COVID-19 (25), Post-acute COVID-19 syndrome (2).
- Co-suspect vaccines/medications (n=9): colchicine (3), influenza vaccine, levothyroxine (2 each), acetylsalicylic acid, hepatitis A vaccine inactivated, ibuprofen, ocrelizumab (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (468), Dyspnoea (263), Fatigue (143), Myocarditis (140), Palpitations (139), Chest discomfort (121), Pyrexia (102), Tachycardia (83), Headache (81), Dizziness (56), Pericardial effusion (51), Paraesthesia (47), Myalgia (45), Pain in extremity (44), Electrocardiogram abnormal, Inappropriate schedule of product administration, Pain (37 each), Nausea (34), Lethargy (32), Malaise (31), Angina pectoris (28), Arthralgia (27), Immunisation[23] (27), and Hypoaesthesia (26).
- Pericarditis events with fatal outcome (1).

Pericarditis cases in adult (30-39 years of age) (1 case, non-medically confirmed)

A [redacted] subject from [redacted]

- Medical history: alcohol use, gastroenteritis, non-tobacco user, pertussis, seasonal allergy.
- Co-suspect medications: none.
- PTs with fatal outcome: Cardiac tamponade, Pericarditis, Pericardial haemorrhage.
- Time to onset (pericarditis): 30 days after dose 2.
- Causes of death: all the above.

Pericarditis relevant data in this subgroup of subjects are summarized in Table 41.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 41. Pericarditis in Subjects aged 30-39 years (N=1222)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	405	466	12
	No	171	161	8
Relevant PT[a]	Pericarditis	575	624	20
	Pericarditis constrictive	1	0	0
	Pleuropericarditis	0	3	0
Hospitalization required/prolonged	Yes	111	144	0
	No	465	482	20
Relevant suspect dose	Dose 1	174	201	4
	Dose 2	140	153	9
	Dose 3	18	8	1
	Unknown	244	264	6
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=609	≤ 24 hours	35	23	0
	1-5 days	118	127	3
	6-13 days	57	62	2
	14-21 days	34	31	2
	22-31 days	17	23	0
	≥ 32 days	30	45	0
	Unknown	285	316	13
Event Outcome	Fatal	0	1	0
	Not resolved	272	272	6
	Resolved	38	80	0
	Resolved with sequelae	4	2	0
	Resolving	141	152	2
	Unknown	121	120	12
Duration of event[b] n=37, median: 11	Up to 3 days	2	6	0
	4-6 days	3	1	0
	7-10 days	3	3	0
	11-26 days	4	8	0
	27-67 days	3	4	0

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

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.14% of 721 cases of the total CT dataset), compared to 1 case (0.14%) retrieved in the PSUR #1. Please see above the "Overall – All Ages" subsection.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 2059 (0.3% of 657,528 cases of the total PM dataset, 0.6% of the 323,358 subjects ≥ 40 years), compared to 204 cases (0.06%) retrieved in the PSUR #1.
- Country of incidence: Australia (537), France (287), UK (266), Italy (179), Germany (95), Netherlands (82), Norway (81), Canada (57), Japan (57 each), Sweden, US (49 each), Greece (48), Spain (43), Denmark (42), New Zealand (40, Belgium (33), Finland, Ireland (16 each), and Portugal (12). The remaining 70 cases were distributed among 24 countries.
- Subjects' age in years: n = 2059, range: 40-98, mean: 54.3, median: 51.0.
- Medical history (n = 844): the medical conditions reported more than 10 times included Hypertension (178), Pericarditis (103), Asthma (45), Hypothyroidism (41), Tobacco user (42), Dyslipidaemia (38), Atrial fibrillation (37), Type 2 diabetes mellitus, Diabetes mellitus (32 each), Obesity (31), Non-tobacco user (28), Ex-tobacco user (27), Seasonal allergy (25), Drug hypersensitivity, Hypercholesterolaemia, Migraine (2 each), Gastroesophageal reflux disease, Osteoporosis (21 each), Alcohol use, Immunodeficiency (19 each), Hypersensitivity (18), Depression (17), Appendicectomy, Chest pain, Chronic obstructive pulmonary disease (15 each), Myocardial infarction, Autoimmune thyroiditis, Pericardial effusion, Sleep apnoea syndrome (14 each), Cholecystectomy (13), Breast cancer, Chronic kidney disease, Overweight, Thyroidectomy, Suppressed lactation[19] (12 each), and Cardiac disorder (11).
- COVID-19 Medical history (n = 95): COVID-19 (55), Suspected COVID-19 (36), COVID-19 pneumonia, Post-acute COVID-19 syndrome (2 each), Asymptomatic COVID-19, Coronavirus infection (1 each).
- Co-suspect vaccines/medications (n=26), reported more than once: COVID-19 AstraZeneca (4), COVID-19 Moderna Vaccine (3).
- Most frequently co-reported PTs (≥2%): Chest pain (673), Dyspnoea (424), Myocarditis (308), Fatigue (293), Palpitations (240), Pericardial effusion (218), Pyrexia (207), Immunisation[23] (185), Chest discomfort (165), Tachycardia (158), Off label use (139), Headache (124), Interchange of vaccine products (114), Malaise (98), Arthralgia (92), Dizziness (80), Myalgia (75), Asthenia (72), Inappropriate schedule of product administration (68), Nausea (65), Pain in extremity (63), Pleural effusion (62), Atrial fibrillation (58), Chills, Pain (54), Hypertension (53), Back pain, Cough (48 each), Paraesthesia (46), and C-reactive protein increased (42).
- Pericarditis events with fatal outcome (8) occurred in subjects between 55 and 95 years of age (n=8, Mean =73.8, median=73.0).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Pericarditis cases in adult (51-64 years of age) (1 case, medically confirmed)

A [redacted] subject from [redacted]

- Medical history: chronic kidney disease, cystoscopy, gout, hypertension, panic disorder, renal failure.
- Co-suspect medications: none.
- PTs with fatal outcome: Cardiac failure acute, Pericarditis.
- Time to onset (pericarditis): 23 days after dose 2.
- Cause of death: Cardiac failure acute.

Pericarditis cases in elderly (65-74 years of age) (3 cases, medically confirmed)

A [redacted] subject from [redacted]

- Medical history: details not provided.
- Co-suspect medications: none.
- PTs with fatal outcome: Atrial fibrillation, Cardiac failure acute, Pericarditis.
- Time to onset (pericarditis): 13 days after an unknown dose.
- Causes of death: All the above.

A [redacted] subject, from [redacted]

- Medical history: cardiac disorder.
- Co-suspect medications: none.
- PTs with fatal outcome: Cardiomyopathy, Cardio-respiratory arrest, Myocarditis, Pericarditis.
- Time to onset (pericarditis and myocarditis): < 24 hours after dose 2.
- Causes of death: All the above.

A [redacted] subject from [redacted]

- Medical history: aortic aneurysm, chemotherapy, chronic leukaemia in remission, frontotemporal dementia, gastrectomy, gastric cancer.
- Co-suspect medications: azacytidine.
- PTs with fatal outcome: Cardiac failure, Endocarditis, Myocarditis, Pericarditis.
- Time to onset (pericarditis and myocarditis): 9 days after dose 1.
- Causes of death: Endocarditis, Myocarditis, Pericarditis.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Pericarditis cases in elderly (> 75 years of age – 4 cases)

- Two cases were medically confirmed:

An [redacted] subject from [redacted]

- Medical history: not provided.
- Co-suspect medications: none.
- PTs with fatal outcome: Cardiogenic shock, Pericardial effusion, Pericarditis.
- Time to onset (pericarditis and myocarditis): unknown (after dose 2).
- Causes of death: cardiogenic shock, pericardial effusion.

A [redacted] subject from [redacted]

- Medical history: constipation, decreased appetite, gastroesophageal reflux disease, hyperlipidemia, hypertension, insomnia, loss of personal independence in daily activities, neurogenic bladder, psychotic disorder, schizophrenia, tuberculosis, type 2 diabetes mellitus.
- Co-suspect medications: none.
- PTs with fatal outcome: Cardiac failure, Pericarditis.
- Time to onset (pericarditis): 6 days after dose 2.
- Causes of death: all the above.

- Two cases were not medically confirmed:

A [redacted] male subject, from [redacted]

- Medical history: chronic obstructive pulmonary disease.
- Co-suspect medications: none.
- PTs with fatal outcome: Branchial cyst, Chest pain, Lymphadenitis, Lymphadenopathy, Pericarditis.
- Time to onset (pericarditis): 33 days after dose 2.
- Causes of death: all the above.

A [redacted] subject from [redacted]

- Medical history: not provided.
- Co-suspect medications: none.
- PTs with fatal outcome: Acute coronary syndrome, Chest pain, Dyspnoea, Myocarditis, Pericarditis.
- Time to onset (pericarditis): unknown (after a booster dose of BNT162b2; previous COVID-19 vaccine unknown).
- Causes of death: acute coronary syndrome, chest pain, dyspnoea.

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 42. Pericarditis in Subjects aged ≥ 40 years (N=2059)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	704	630	9
	No	388	39	8
Relevant PT[a]	Pericarditis	1071	941	17
	Pericarditis adhesive	1	0	0
	Pericarditis constrictive	4	5	0
	Pleuropericarditis	16	13	0
Hospitalization required/prolonged	Yes	327	422	2
	No	764	533	15
Relevant suspect dose	Dose 1	299	274	3
	Dose 2	389	345	7
	Dose 3	110	81	4
	Unknown	291	255	3
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=1229	≤ 24 hours	58	32	1
	1-5 days	212	155	1
	6-13 days	123	126	2
	14-21 days	80	91	1
	22-31 days	52	58	9
	≥ 32 days	106	128	3
	Unknown	463	375	9
Event Outcome[b]	Fatal	3	5	0
	Not resolved	386	259	4
	Resolved	147	160	1
	Resolved with sequelae	19	20	1
	Resolving	293	308	2
	Unknown	245	209	9
Duration of event[c] n=145, median: 15	Up to 3 days	6	14	0
	4-6 days	10	9	1
	7-10 days	6	13	0
	11-26 days	18	16	1
	27-171 days	30	22	0

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

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #1.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 363 (0.06% of 657,528 cases of the total PM dataset, 0.5% of the 74,704 subjects with unknown age), compared to 36 (0.01%) cases retrieved in the PSUR #1.
- Country of incidence: Canada (95), UK (77), Australia (67), Hong Kong (46), US (15), Germany (14). The remaining 49 cases were distributed among 16 countries.
- Subjects' age in years: Unknown.[55]
- Medical history (n = 93): the medical conditions reported more than three times included Hypertension (20), Diabetes mellitus (8), Drug hypersensitivity, Immunodeficiency, Pericarditis (7 each), Anxiety, Depression (6 each), Gastroesophageal reflux (5), Asthma, Attention deficit hyperactivity disorder, Chronic obstructive pulmonary disease (4 each).
- COVID-19 Medical history (n = 23): Suspected COVID-19 (14), COVID-19 (8), SARS-CoV-2 antibody test positive (1).
- Co-suspect vaccines/medications (n=6): Colchicine, lenvatinib mesylate, ramipril, risankizumab, semaglutide, tafamidis (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (134), Myocarditis (119), Dyspnoea (81), Fatigue (63), Palpitations (46), Pyrexia (39), Chest discomfort (33), Immunisation[23] (28), Tachycardia (26), Dizziness (25), Headache (24), Off label use (21), Pericardial effusion (18), Pain in extremity (17), Interchange of vaccine products (15), Asthenia, Malaise, Pain (12 each), Chills, Myalgia, Nausea (11 each), Paresthesia, Pleuritic pain (10 each), Diarrhoea, Syncope (9 each) and Vomiting (8).

Pericarditis relevant data in this subgroup of subjects are summarised in Table 43.

Table 43. Pericarditis in Subjects with Unknown Age (N=363)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	70	116	59
	No	44	56	18
Relevant PT[a]	Pericarditis	114	172	77
Hospitalization required/prolonged	Yes	19	46	3
	No	95	126	74
Relevant suspect dose	Dose 1	30	55	10
	Dose 2	36	63	8
	Dose 3	12	13	5
	Unknown	36	41	54

[55] Including 11 Adolescents, 67 Adults and 9 Elderly.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 43. Pericarditis in Subjects with Unknown Age (N=363)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=109	≤ 24 hours	6	3	1
	1-5 days	13	34	1
	6-13 days	9	19	0
	14-21 days	3	6	0
	22-31 days	4	3	0
	≥ 32 days	3	4	0
	Unknown	76	103	75
Event Outcome	Fatal	0	0	0
	Not resolved	51	53	6
	Resolved	15	45	3
	Resolved with sequelae	0	0	0
	Resolving	7	11	1
	Unknown	41	63	67
Duration of event[b] n=4, median: 16.5	Up to 3 days	1	0	0
	4-6 days	0	0	0
	7-10 days	0	1	0
	11-26 days	1	0	0
	27-67 days	0	1	0

a. All serious occurrences but 1.
b. For those cases where the event resolved or resolved with sequelae.

Subjects with booster dose

Clinical Trial Data

- The single clinical trial case retrieved in the pericarditis dataset (Please see above the "Overall – All Ages" subsection) involved a [redacted] participant who developed pericarditis 2 months and 3 days after receiving the 3rd dose of the blinded vaccine (study C4591031). The SAE was assessed as unrelated to the study vaccine both by the Investigator and by the Sponsor.

Post-Authorisation Data

- Number of cases: 283 (0.04% of 657,528 cases of the total PM dataset, 1.1% of the 25787 subjects who received a booster dose), compared to no cases in the PSUR #1.
- Country of incidence: UK (219), Italy (22), US (1), France (10). The remaining 31 cases were distributed among 17 countries.
- MC (109), NMC (175).
- Subjects' gender: female (153), male (120), and unknown (11).
- Subjects' age in years: n = 254, range: 19-89, mean: 52.4, median: 52.50.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Medical history (n = 163): the medical conditions reported more than 4 times included Hypertension (29), Immunodeficiency (23), Pericarditis (15), Asthma (11), Type 2 diabetes mellitus (19), Depression (9), Anxiety, Atrial fibrillation, Diabetes mellitus, Hypothyroidism, Influenza immunization, Migraine (6 each), Arthralgia, Fibromyalgia, Gastroesophageal reflux disease, Neoplasm, Rheumatoid arthritis, Steroid therapy (5 each).
- COVID-19 Medical history (n = 38): Suspected COVID-19 (28), COVID-19 (9), Post-acute COVID-19 syndrome (4).
- Co-suspects (n=10): Influenza vaccine (4), colchicine (2), diphtheria vaccine toxoid, hib vaccine, pertussis vaccine, polio vaccine inact, tetanus vaccine toxoid, hepatitis A vaccine, influenza vaccine inact SPLIT 4V influenza vaccine (surface antigen, inactivated, adjuvanted), ramipril (1 each).
- Number of relevant events: 284.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Pericarditis (280), Pleuropericarditis (4).
- Relevant event outcome[47]: fatal (1), resolved/resolving (63), resolved with sequelae (1), not resolved (52), unknown (168).
- Most frequently co-reported PTs (>3%): Immunisation[23] (259), Myocarditis (173), Off-label use (166), Fatigue (162), Chest pain (157), Palpitations (131), Dyspnoea (129), Interchange of vaccine products (124), Tachycardia (98), Pyrexia (71), Headache (30), Chest discomfort (29), Chills, Pain in extremity (22 each), Arthralgia (21), Pericardial effusion (20), Dizziness, Myalgia, Syncope (19 each), Nausea (18), Malaise (16), Angina pectoris (15), Heart rate increased (14), Pain (13), and Insomnia (12).

The number of pericarditis cases occurred after a booster dose in each age group is reported in Table 44.

Table 44. Pericarditis in Subjects who Received a Booster dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases		
		F	M	U	F	M	U
Age group	0 to 17 years	0	0	0	0	0	0
	18 to 24 years	0	2	0	4	3	0
	25 to 29 years	3	4	0	4	3	1
	30 to 39 years	7	5	1	12	4	0
	40 years and older	55	52	3	57	34	1
	Unknown	4	9	3	8	4	2
	Total	*69*	*72*	*7*	*85*	*48*	*4*

F=female; M=male; U=unknown

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Cases Medically Confirmed with a TTO ≤ 21 days: 1461 cases

In 1461 cases out of 5311, pericarditis was medically confirmed and had a TTO ≤21 days. These cases were individual reviewed and assessed according to the Brighton Collaboration (BC) Pericarditis Case Definition and Level of Certainty Classification (version 1.0.0, 15 July 2021), as per table below:

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

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

Out of 1461 cases with a time to onset ≤21 days, there were 22 cases assessed as BC level 1.

12-15 years of age (3)

- Three (3) cases involved male subjects (medical history not provided) who developed pericarditis and myocarditis 2 or 3 days after BNT162b2 dose no. 2:
  - A [redacted] subject from [redacted] Reported PTs: Pericarditis (outcome: unknown), Myocarditis (outcome: resolving), Chest pain, Parvovirus B19 test positive, Troponin increased.
  - A [redacted] subject from [redacted] Reported PTs: Pericarditis (outcome: resolving), Myocarditis (outcome: resolving), Blood creatine phosphokinase increased, Blood creatine phosphokinase MB increased, Brain natriuretic peptide increased, and Troponin I increased.
  - A [redacted] subject from [redacted] reported PTs: Pericarditis (outcome: resolving), Myocarditis (outcome resolving), Cardiac disorder, Chest discomfort, Electrocardiogram ST segment elevation.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16-17 years of age (2)

- Two (2) cases from [redacted] involved subjects who developed pericarditis 5 and 9 days after dose 1, respectively:
  - A [redacted] subject, concurrently suffering from rectocolitis, treated with mesalazine, and from multiple allergies to mites, animals and pollen. Reported PTs Pericarditis (outcome: resolving), Breath sound abnormal, Hepatic pain, Pericardial effusion, Pleural effusion, Pyrexia, and Tachycardia. Mesalazine was discontinued due to a possible iatrogenic reaction.
  - A [redacted] subject, concurrently treated with ethinylestradiol/levonorgestrel, colecalciferol, and colchicine and with 2 previous episodes of pericarditis while [redacted] suffered from Bechet's disease. Reported PTs: Pericarditis (outcome: resolved), Chest pain, Dyspnoea exertional, Fatigue, Musculoskeletal stiffness, and Myalgia. Dose 2 was postponed.

18-24 years of age (1)

- One (1) subject, from [redacted] who developed pericarditis 9 days after vaccination (dose no. unknown):
  - A [redacted] subject, medical history not provided. Reported PTs: pericarditis outcome: resolved), Chest pain, Discomfort, Extrasystoles.

25-29 years of age (4)

- Four (4) subjects, who developed pericarditis between 1 and 7 days after dose 1 administration:
  - A [redacted] subject, from [redacted] medical history not provided. Reported PTs: Pericarditis constrictive (1 day after vaccination; outcome: not resolved), Chest pain, Hypertension, Painful respiration, Palpitations, and Pyrexia.
  - A [redacted] subject, from [redacted] medical history not provided, concomitantly treated with nimesulide. Reported PTs: Pericarditis (6 days after vaccination, outcome: resolved), Dyspnoea, Chest pain.
  - A [redacted] subject, from [redacted] tobacco user. Reported PTs: Pericarditis (4 days after vaccination; outcome: resolved), Chest pain, Dyspnoea, Respiratory disorder.
  - A [redacted] subject, from [redacted] ex-tobacco user and with a past history of suspected pericarditis in 2018. Reported PTs: Pericarditis (7 days after vaccination; outcome: resolving), Asthenia, Blood pressure diastolic increased.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

30-39 years of age (1)

- One (1) subject from [redacted] who developed Pericarditis 3 days after dose no. 1:
  - A [redacted] subject, concurrently suffering from chronic asthma. Reported PTs: Pericarditis (outcome: resolving), Asymptomatic COVID-19, Chest pain, Palpitations.

40 years and older (11)

- A [redacted] subject, from [redacted] concurrently suffering from hepatic steatosis and hypercholesterolemia. Reported PTs: Pericarditis (1 day after dose 2; outcome: resolving), Chest pain, Cough, C-reactive protein increased, Dermatitis, Dyspnoea, Hypercholesterolemia, Inappropriate schedule of product administration, Iron deficiency anaemia, Pyrexia, Rash.
- A [redacted] subject, from [redacted] medical history not provided. Reported PTs: Pericarditis (21 days after dose 2; outcome: resolving), Chest pain, Pericardial effusion.
- A [redacted] subject, from the [redacted] medical history not provided. Reported PTs: Pericarditis (3 days after dose 1; outcome: resolved), Arthralgia, Asthenia, Atelectasis, Atrial tachycardia, Chest pain, Dyspnoea, Fatigue, Gait disturbance, Headache, Influenza like illness, Malaise, Myalgia, Pain, Palpitations, Pericardial effusion, Pulmonary embolism, Pyrexia, Supraventricular tachycardia.
- A [redacted] subject, from [redacted] with a pre-existing pericarditis. Reported PTs: Pericarditis (4 days after dose 1; outcome: resolving), Cardiac failure, Dyspnoea, Malaise, Oedema peripheral, Pyrexia, Tachycardia.
- A [redacted] subject, from [redacted] suffering from history of pericarditis. Reported PTs: Pericarditis (1 day after dose 2; outcome: not resolved), Asthenia, Chest pain, Condition aggravated, Dizziness, Dyspnoea, Headache, Pallor, Pyrexia, Vomiting.
- A [redacted] subject, from [redacted] medical history not provided. Reported PTs: Pericarditis (1 day after dose 3; outcome: unknown), Interchange of vaccine product, Off label use. First 2 doses of the COVID-19 vaccine: Coronavac.
- A [redacted] subject, from [redacted] medical history not provided. Reported PTs: Pericarditis (6 days after dose 2; outcome: resolved).
- A [redacted] ex-tobacco user, [redacted] subject, from France, with a medical history of asthma, cholecystectomy and aspirin-exacerbated respiratory disease. Reported PTs: Pericarditis (17 days after dose 2; outcome: resolving), Pleural effusion.
- A [redacted] subject, from [redacted] with a medical history of cerebral infarction, dyslipidaemia, hypertension and hyperuricaemia. Reported PT: Pericarditis (8 days after dose 2; outcome: resolving).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- A [redacted] subject, from [redacted] with a past medical history relevant for aortic stenosis, atrial fibrillation, ischaemic cardiomyopathy, transcatheter aortic valve implantation, and ventricular tachycardia. Reported PTs: Pericarditis and Myocarditis (14 days after an unknown dose of vaccine; outcome: resolving), Atrial fibrillation, Cardiac murmur, Chest pain, Dilatation atrial, Dyspnoea, Left ventricular dysfunction, Mitral valve incompetence, Pericardial effusion, Pericardial rub, Renal failure, Systemic inflammatory response syndrome, Ventricular hypokinesia.

During the reporting period there were 1461 cases of medically confirmed pericarditis with a latency 21 days or less. Out of them, there were 22 cases assessed as BC level 1. For this cluster of BC level 1 cases, there were 13 males and 9 females between 12 and 93 years of age (mean=40.6, median=38.5). All cases were assessed as serious due to hospitalisation and/or medically significant (15) or due to medically significant (7); none had a serious outcome. In 16 cases pericarditis occurred within 1 week post vaccine administration. The reporting countries in that BC level 1 cluster were France (10), Japan (3), Czech Republic, Italy (2 each), the remaining 5 cases originated from 5 different countries. Insufficient description of cardiovascular and/or non-cardiovascular medical history and diagnostic to rule out other aetiologies in majority of these cases continues to preclude proper medical adjudication of causality assessment between administration of the vaccine and occurrence of Pericarditis.

Conclusion

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16.3.2. Evaluation of Important Potential Risks

Evaluation of incremental data for the important potential risk VAED/VAERD is provided below.

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.

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.[56]

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-authorisation 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.

Of note, there were 4 cases reporting the PT Vaccine associated enhanced disease. None of them met the criteria to be considered as a true VAED case.

Clinical Trial Data

There were no cases reporting COVID-19 infection associated to one of the PTs utilised to identify potential severe or atypical cases of COVID-19.

---

[56] Munoz FM, Cramer JP, Dekker CL, et al. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021;39(22):3053-66.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

Of the 1501 cases retrieved based on search strategy, 11 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- In 2 cases the lack of efficacy PT did not refer to BNT162b2 vaccine.
- In 1 case, the subject 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.
- In 3 cases the PT Drug ineffective was erroneously coded; upon review, none of them developed COVID-19 infection.
- In 5 cases the PT Vaccine associated enhanced disease was coded; upon review, none of the 5 subjects developed a COVID-19 infection.

Overview

- Number of cases: 1490 (0.2% of 657,528 cases, the total PM dataset), compared to 584 (0.2%) retrieved in the PSUR #1. All cases are serious.
- MC cases (1164), NMC cases (326).
- Country of incidence: France (569), UK (146), Spain (141), US (117), Italy (80), Estonia (69), Germany (59), Belgium (34), Portugal, Switzerland (30 each), Austria (27), Philippines (23), Malta (18), South Africa (15), Croatia (13), Hungary, Norway (11 each); the remaining 97 cases originated from 28 different countries.
- Gender: female (720), male (743), and unknown (27).
- Age in years (n = 1435), range: 12 – 104, mean: 68.0, median: 73.0.
- Relevant event seriousness: 1688 serious, 396 non-serious.
- Reported relevant PTs by organ system:
  - Respiratory system PTs (1413): COVID-19 pneumonia (684), Dyspnoea (444), Hypoxia, Respiratory failure (67 each), Pulmonary embolism (53), Acute respiratory distress syndrome (51), and Tachypnoea (47).
  - Gastrointestinal/Hepatic system PTs (350): Diarrhoea (208), Vomiting (89), Abdominal pain (52), and Jaundice (1);
  - Cardiovascular system PTs (146): Myocarditis (77), Cardia failure (45), Arrhythmia (18), Acute myocardial infarction (4), and Cardiogenic shock (2);
  - Renal and urinary system PTs (71): Acute kidney injury (44), and Renal failure (27);
  - Nervous system PTs (45): Cerebrovascular accident, Seizure (15 each), Altered state of consciousness (13), and Encephalopathy (2);
  - Vascular system PTs (19): Deep vein thrombosis (9), Peripheral ischaemia (5), Shock (4), and Vasculitis (1);
  - Blood and lymphatic system PTs (16): Thrombocytopenia (16).
  - Immune system PTs (7): Vaccine associated enhanced disease (4), and Multisystem inflammatory syndrome in children (3);

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Other PTs (17): Multiple organ dysfunction syndrome (14), Chillblains (2), and Erythema multiforme (1).

- Case outcome: fatal (278), not resolved (417), resolved/resolving (608), resolved with sequelae (15), and unknown (172).

COVID-19 positivity and severity of events

- Suspected COVID-19 infection: 161 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (156 cases) or to Vaccination failure (5 cases)][57];
- Confirmed COVID-19 infection: 1329 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (585 cases) or Vaccination failure (744 cases, 4 of these cases also co-reported Vaccine associated enhanced disease)].
- Seriousness criteria for the total 1329 cases:
  - Medically significant: 305 (of which 12 serious also for disability);
  - Hospitalisation required (non-fatal/non-life threatening): 636 (of which 8 serious also for disability);
  - Life threatening: 122 (of which 7 serious also for disability);
  - Death: 266 (of which 2 serious also for disability).

Seriousness criteria: medically significant (413)

- In 305 of 413 cases where the seriousness criterion was "medically significant", the subjects had a confirmed COVID-19 infection after vaccination, while 108 subjects had suspected COVID-19 infection. These 108 subjects did not require hospitalisation.
- In the 305 confirmed COVID-19 cases, subjects' age ranged from 17 to 100 years (n = 286, mean: 53.2, median: 48.5) (2 paediatrics, 198 adults, 87 elderly, 18 unknown); gender was reported as female (194), male (99), and unknown (12).
- Time to event onset of COVID-19 infection was reported for 238 of these 305 cases:
  - Day 14 to 402 after dose 1 (34 cases);
  - Day 0 to 288 after dose 2 (178 cases);
  - Day 0 to 140 after dose 3 (16 cases)
  - Day 3 to 68 after vaccination [dose number not reported] (10).

- These 305 cases reported 359 relevant events[58]. The most commonly (≥5 occurrences) reported relevant PTs were: Dyspnoea (113), Diarrhoea (101), Myocarditis (37), COVID-19 pneumonia (34), Vomiting (27), Abdominal pain (14), and Arrhythmia (7).
- The outcome[47] of the COVID-19 infection related events reported in these 305 cases was: resolved/resolving (165), resolved with sequelae (3), not resolved (70), and unknown (124).

---

[57] In these 5 cases COVID-19 infection was neither clinically confirmed nor laboratory confirmed.

[58] PTs included in the search strategy excluding Drug ineffective and Vaccination failure.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Seriousness criteria: hospitalisation (non-fatal, non-life threatening) (671)

- Hospitalisation occurred in 671 subjects, for 35 of them COVID-19 infection was not confirmed.
- In the 636 COVID-19 confirmed cases, subjects' age (n = 629) ranged from 12 to 104 years, (mean: 72.5, median: 77.0) (4 paediatric, 155 adults, 472 elderly, 5 unknown); gender was reported as female (256), male (376), and unknown (4).
- Time to event onset of COVID-19 infection was reported for 513 of these 636 cases.
  - Day 14 to 158 after dose 1 (27 cases);
  - Day 1 to 277 days after dose 2 (452 cases);
  - Day 0 to 161 days after dose 3 (26 cases);
  - Day 0 to 93 after vaccination [dose number not reported] (8 cases).
  - These 636 cases reported 875 relevant events.[58] The most commonly (≥5 occurrences) reported relevant PTs were: COVID-19 pneumonia (396), Dyspnoea (167), Diarrhoea (47), Respiratory failure (33), Hypoxia (32), Pulmonary embolism (30), Vomiting (24), Cardiac failure (23), Acute kidney injury (21), Tachypnoea (20), Abdominal pain (17), Acute respiratory distress syndrome (14), Myocarditis, Renal failure (13 each), and Cerebrovascular accident (7).
  - The outcome[47] of the COVID-19 infection related events reported in these 636 cases was: resolved/resolving (433), not resolved (170), resolved with sequelae (3), and unknown (273).

Seriousness criteria: life-threatening (non-fatal) (128)

- In 122 of the 128 cases characterised as life-threatening, the subjects had a confirmed COVID-19 infection after vaccination, while 6 subjects had suspected COVID-19 infection.
- In these 122 confirmed COVID-19 cases, subjects' age ranged from 13 to 96 years (n = 119), (mean: 68.9 years, median: 73.0 years), (2 paediatric, 31 adults, 86 elderly, 3 unknown); gender was reported as female (49), male (72), and unknown (1).
- Time to event onset of COVID-19 infection was reported for 97 of these 122 cases.
  - Day 17 to 143 after dose 1 (4 cases);
  - Day 2 to 266 after dose 2 (86 cases);
  - Day 8 to 176 after dose 3 (5 cases);
  - Day 19 and 32 after vaccination [dose number not reported] (2 cases).
  -
- These 122 cases reported 181 relevant events. The most commonly (≥5 occurrences) reported relevant PTs COVID-19 pneumonia (79), Dyspnoea (26), Diarrhoea (11), Acute respiratory distress syndrome, Pulmonary embolism (10 each), Hypoxia and Tachypnoea (5 each).
- The outcome[47] of the COVID-19 infection related events reported in these 122 cases was: resolved/resolving (64), not resolved (55), resolved with sequelae (3), and unknown (60).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Seriousness criteria: Death (278 cases)

- Two-hundred and seventy-eight (278) subjects died, of which COVID-19 was not confirmed in 12 cases; the remaining 266 confirmed cases are described below.
- Age: 17 to 101 years (n = 262), mean = 81.5 years, median = 84.0 years.
- Country of incidence: France (118), Spain (23), Malta (18), Estonia (15), Germany (11), Hungary (9), Italy (8), South Africa, Switzerland (7 each), Belgium, UK, US (6 each), Norway (5); the remaining 27 cases originated from 14 different countries.
- Gender: female (118), male (145), and unknown (3).
- Medical history (n = 238) included PTs in the following SOCs; Most frequently (≥5 occurrences) reported PTs by SOC are presented below:
  - Vascular disorders - 154 cases (64.7%): Hypertension (139), Peripheral arterial occlusive disease (7), Arteriosclerosis and Essential hypertension (6 each);
  - Cardiac disorders - 121 cases (50.8%): Atrial fibrillation (60), Cardiac failure (22), Myocardial ischaemia (18), Myocardial infarction (12), Arrythmia (7), Cardiac failure congestive (6), Cardiac disorder, Cardiac failure chronic, Cardiac valve disease, and Coronary artery disease (5 each);
  - Metabolism and nutrition disorders - 115 cases (48.3%): Type 2 diabetes mellitus (35), Diabetes mellitus (26), Dyslipidaemia (25), Obesity (21), Hypercholesterolaemia (15), Overweight (8), and Type 1 diabetes mellitus (5);
  - Nervous system disorders - 96 cases (40.3%): Cerebrovascular accident (19), Cognitive disorder (16), Dementia (15), Dementia Alzheimer's type (9), Epilepsy, Ischaemic stroke, and Parkinson's disease (5 each);
  - Surgical and medical procedures - 77 cases (32.4%): Cholecystectomy (9), Appendicectomy (8), Cardiac pacemaker insertion, Colectomy, Coronary artery bypass (6 each), Hip arthroplasty and Renal transplant (5 each);
  - Respiratory, thoracic and mediastinal disorders - 65 cases (27.3%): Chronic obstructive pulmonary disease (30), Sleep apnoea syndrome (11), Asthma (7), Lung disorder and Pulmonary embolism (6 each);
  - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - 60 cases (25.2%): Chronic lymphocytic leukaemia (10), Prostate cancer (9), and Colon cancer (6);
  - Other medical histories were reported under the following SOCs: Social circumstances (56), Renal and urinary disorders (50), Infections and infestations (41), Gastrointestinal disorders (37), Musculoskeletal and connective tissue disorders (36), Endocrine disorders (34), Psychiatric disorders (26), Eye disorders (23), Blood and lymphatic system disorders, Reproductive system and breast disorders (17 each), Injury, poisoning and procedural complications (15), Congenital, familial and genetic disorders, Immune system disorders (13 each), General disorders and administration site conditions (11), Ear and labyrinth disorders (9), Hepatobiliary disorders (8), Skin and subcutaneous tissue disorders (7), Investigations (5), and Pregnancy, puerperium and perinatal conditions (1).
- Time to event onset of COVID-19 infection was reported for 215 of the 266 cases:
  - Day 14 to 155 after dose 1 (17 cases);

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Day 0 to 294 after dose 2 (183 cases);
- Day 0 to 107 after dose 3 (14 cases);
- Day 18 after vaccination [dose number not reported] (1 case).

- The most frequently (≥10 occurrences) reported causes of death in these 266 cases were coded to the PTs COVID-19 pneumonia (151), Vaccination failure (132), COVID-19 (127), Drug ineffective (57), Dyspnoea (33), Acute respiratory distress syndrome (22), Respiratory failure (18), Pyrexia (16), Cardiac failure (13), Multiple organ dysfunction syndrome (11), Acute kidney injury and Acute respiratory failure (10 each). Of note, in 11 cases limited information regarding the cause of death was reported (PT Death).
  - In 174 of the 266 fatal cases, vaccination failure was reported (cross ref. Section 16.3.4.5 *Lack of Therapeutic efficacy*).
  - Two hundred and forty-one (241) of these 266 cases involved elderly subjects (aged 65 to 74 years [48] or ≥75 years [193]), including 217 subjects with underlying medical history of clinical significance.
  - Among the remaining 25 cases; 21 of them had concurrent medical histories (aged 17 years [1], 31 to 50 years [6], 51 to 64 years [11], and unknown [3]) that could impact the severity and evolution of the COVID-19 infection, including but not limited to cardiac history (atrial fibrillation, arrhythmia, cardiac disorder, cardiac failure, hypertension, myocardial ischaemia), renal disorders (chronic kidney disease, end stage renal disease) respiratory disorders (interstitial lung disease, pulmonary arterial hypertension), and immunodeficient conditions (organ transplant, leukaemia, myelodysplastic syndrome).
  - Of the remaining 4 cases where medical history was not reported, in 2 cases (and years old) concomitant medications included aciclovir, atorvastatin, hydrocortisone, ramipril, salbutamol, and sulfasalazine. The residual 2 cases (and year-old) were poorly documented. The latency to onset of COVID-19 infection from dose 2 in these 4 cases are as follows: 1, 35, 125, and 181 days. The causes of death were reported as COVID-19 (2), COVID-19 pneumonia and Drug ineffective (1). Of note, in 1 case provided limited information regarding cause of death (PT Death).

There were 4 cases reporting the PT Vaccine associated enhanced disease (3 in the "fatal dataset," 1 in the "hospitalisation required" dataset). Upon review, these 4 cases were considered "unlikely" of a true VAED case due to unknown serostatus and COVID-19 history. In addition, although the disease was severe, the subject's elderly age and baseline medical condition already posed a higher risk of severe COVID-19. Though in these cases some inflammatory markers were elevated but no description of cytokine storm or an atypical presentation of COVID. A description of these 4 cases is presented below.

– An subject with a medical history of lacunar stroke, benign prostatic hyperplasia, and carotid artery stenosis developed COVID-19 pneumonia (latency not provided) post dose 2. The subject required intubation and recovered after treatment with anti-viral, corticosteroid, and antibiotics.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- An [redacted] subject with a medical history of dyslipidemia, hypertension, and type 2 diabetes mellitus developed COVID-19 pneumonia (time to onset of event:100 days) post dose 2. Further details of the treatment provided, if any, was not reported. [redacted] died due to COVID-19 pneumonia 6 days after initial presentation.
- An [redacted] subject with a medical history of atrial fibrillation, hypertension, and osteoarthritis developed COVID-19 pneumonia (latency to onset of event 177 days) post dose 2. During admission, the subject was placed on peripheral parenteral nutrition due to feeding intolerance and poor general condition. [redacted] received treatment with oxygen therapy, corticosteroids, antibiotics, and low molecular weight heparin. Four (4) days later the subject died due to COVID-19 pneumonia and respiratory failure.
- A [redacted] subject with a medical history of chronic kidney disease, hyperlipidaemia, hypertension, diverticulum intestinal, hyperuricaemia, and mitral valve incompetence developed COVID-19 pneumonia (latency to onset of event 98 days) post dose 2. Unspecified therapeutic measures were taken, and the patient died after 25 days.
- VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 1329 subjects with confirmed COVID-19 following vaccine administration; 1036 of the 1329 cases were severe, resulting in hospitalisation, disability, life threatening consequences or death. None of the 1329 cases could be definitively considered as having VAED/VAERD.

Conclusion

The purpose of this review of subjects with COVID-19 following vaccination is to identify cases of potential vaccine associated enhanced disease. The nature of spontaneously reported data provides a challenge because of the lack of a comparison group. Further, the background rate of VAED is not known. Considering the limitations of the review, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.

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

There were no 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 categorised as important in which new information has become available during the reporting interval that allows further characterisation of a previously recognized recognised risk.

16.3.3.1. Adverse Events of Special Interest (AESIs)

The company's AESI list takes into consideration the lists of AESIs from several expert groups and regulatory authorities including but not limited to the following: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general. The AESI

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

list includes MedDRA PTs, HLTs, HLGTs or MedDRA SMQs and will be changed as appropriate based on the evolving safety profile of the vaccine.

Overlapping terms among multiple categories were assigned to one category only based on their most clinical relevance.

Please refer to Appendix 6B for the observed versus expected analysis for 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; Chest pain; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia.

Clinical Trial Data

- Number of cases: 35 (blinded therapy [6], BNT162b2 [26] and placebo [3]) (4.9% of 721 cases, the total CT dataset) compared to 33 cases (4.7%) retrieved in the PSUR #1.
- Country of incidence: US (31), Argentina (3), [redacted] (1).
- Subjects' gender: female (8), and male (27).
- Subjects' age in years (n = 35), range: 18-83, mean: 61.6, median: 62.0.
- Medical history (n = 33): the reported relevant medical conditions (>2 occurrence) included Hypertension (13), Blood cholesterol increased, Coronary artery disease, Type 2 diabetes mellitus (3 each).
- COVID-19 medical history: None.
- Co-suspect medications: alendronate, dulaglutide, fexofenadine, fluoxetine, glipizide, losartan, and metformin (1 each).
- Reported relevant PTs: Coronary artery disease (10), Acute myocardial infarction (9), Myocardial infarction (8), Chest pain (5), Cardiac failure, Cardiogenic shock, Postural orthostatic tachycardia syndrome, and tachycardia (1 each).
- BNT162b2 related event coded to the PT: Tachycardia (1). Time to onset of event 7 days and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-Authorisation Data

- Number of cases: 29,486 (4.5% of 657,528 cases, the total PM dataset), compared to 8398 (2.6%) cases retrieved in the PSUR #1.
- MC cases (11,537), NMC cases (17,949).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence (>100 occurrence): Germany (5148), UK (4302), France (3244), Australia (2539), Italy (2350), US (1615), Japan (1498), Netherlands (1456), Canada (624), Spain (475), Taiwan, Province of China (465), Norway (426), Sweden (422), Finland (407), Mexico (361), Austria (313), New Zealand (296), Ireland (267), Greece (266), Czech Republic, Denmark (253 each), Belgium (245), Philippines (234), Brazil (209), Malaysia (167), Lithuania (159), Romania (135), Portugal (132), Croatia (121), and Switzerland (108); the remaining 996 cases were distributed among 56 countries.
- Subjects' gender: female (17,914), male (11,003) and unknown (568).
- Subjects' age in years (n = 27,696), range: 2 – 109, mean: 43.1, median: 41.0.
- Medical history (n = 12,050 cases): the most frequently (>200 occurrence) reported relevant medical conditions included Hypertension (1874), Diabetes mellitus (440), Obesity (373), Tobacco user (371), Atrial fibrillation (343), Type 2 diabetes mellitus (293), Depression (289), Arrhythmia (275), Chest pain (255), Anxiety (242), Myocardial infarction (232), and Dyslipidaemia (213).
- COVID-19 Medical history (n = 1670 cases): the medical conditions reported included COVID-19 (946), Suspected COVID-19 (693), Post-acute COVID-19 syndrome (28), COVID-19 pneumonia (13), Asymptomatic COVID-19 (12), Coronavirus infection, SARS-CoV-2 test positive (11 each), Exposure to SARS-CoV-2 (9), SARS-CoV-2 antibody test positive (3).
- Co-suspects (n = 282 cases): the frequently (>5 occurrences) reported relevant co-suspect medication was adalimumab (8).
- Number of relevant events: 32,034.
- Relevant event seriousness: serious (16,434), non-serious (15,606).
- Relevant PTs: Chest pain (17,526), Tachycardia (8253), Arrhythmia (3294), Myocardial infarction (1211), Cardiac failure (807), Acute myocardial infarction (479), Cardiac failure acute (113), Postural orthostatic tachycardia syndrome (104), Coronary artery disease (101), Cardiogenic shock (92), and Stress cardiomyopathy (54).
- Time to event onset (n = 23,422 occurrences),[59] range: <24 hours to 377 days, median: 1 day.
  - <24 hours: 6983 events (60 fatal events);
  - 1 day: 4868 events (77 fatal events);
  - 2-7 days: 6759 events (201 fatal events);
  - 8-14 days: 2003 events (88 fatal events);
  - 15-30 days: 1557 events (72 fatal events);
  - 31-181 days: 1217 events (57 fatal events);
  - 182-377 days: 35 events (7 fatal events).

[59] This number does not include 37 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Duration of relevant events (n = 4196 out of 8137 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 214 days, median: 1 day.

  - <24 hours: 1230 events;
  - 1 day: 825 events;
  - 2-7 days: 1290 events;
  - 8-14 days: 294 events;
  - 15-30 days: 292 events;
  - 31-181 days: 262 events;
  - 182-214 days: 3 events.

- Relevant event outcome:[47] fatal (803), resolved/resolving (13,481), resolved with sequelae (844), not resolved (9970), unknown (7065).

  - In the 729 cases (reporting 803 relevant events with a fatal outcome), the reported cause of death (>20 occurrences) were coded to PTs Myocardial infarction (248), Cardiac failure (167), Acute myocardial infarction (92), Chest pain (62), Arrhythmia (59), Cardiac arrest (58), Cardio-respiratory arrest (56), Cardiac failure acute (54), Dyspnoea (52), Death (32), Pyrexia (30), Cardiogenic shock (28), Myocarditis (22), and Tachycardia (21). Of the 729 cases, 374 cases involved elderly subjects. Significant medical conditions included hypertension (185), diabetes mellitus (60), cardiac failure (47), atrial fibrillation (43), chronic kidney disease (32), chronic obstructive pulmonary disease, myocardial infarction (31 each), obesity (28), myocardial ischaemia (27), dyslipidaemia (26), type 2 diabetes mellitus (25), coronary artery disease (24), dementia (23), asthma, tobacco user (22 each), arteriosclerosis, cardiac failure chronic, cerebral infarction, and hyperlipidaemia (21 each).

Analysis by age group

- CT: Adults (18), and Elderly (17).

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

- PM: Paediatric (1587), Adults (22,658), Elderly (3874) and Unknown (1367).

Higher reporting proportion of events coded to the PTs Acute myocardial infarction, Arrhythmia, Cardiac failure, and Myocardial infarction was reported in elderly population when compared to adult and paediatric population (Acute myocardial infarction [1.2% in adults vs 0.2% in paediatrics vs 5.3% in elderly], Arrhythmia [10.7% in adults vs 3.4% in paediatrics vs 18.6% in elderly], Cardiac failure [1.1% in adults vs 0.2% in paediatrics vs 13.4% in elderly], and Myocardial infarction [2.8% in adults vs 0.5% in paediatrics vs 11.6% in elderly]).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by presence of comorbidities

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

O/E Analysis

- O/E analysis was performed for Acute myocardial infarction/Myocardial infarction; Arrhythmia; Coronary artery disease; Heart failure (PTs: Cardiac failure; Cardiac failure acute); Postural orthostatic tachycardia syndrome; Stress cardiomyopathy (see Appendix 6B *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.

16.3.3.1.3. Haematological AESIs

Search criteria - HLTs (All Path) Leukopenias NEC; Neutropenias OR PT Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms).[60]

Clinical Trial Data

- Number of cases: 17 (BNT162b2 [9] and blinded therapy [8]) (2.4% of 721 cases, the total CT dataset) compared to 19 cases (2.7%) retrieved in the PSUR #1.
- Country of incidence: US (9), South Africa, UK (3 each), (1 each).
- Subjects' gender: female (14) and male (3).
- Subjects' age in years (n = 17), range: 23 - 76, mean: 49.8, median: 39.0.
- Medical history (n = 16): the relevant medical conditions reported more than twice were coded to the PTs Caesarean section, Live birth, and Pregnancy (3 each).
- COVID-19 Medical history (n = 1): relevant medical condition was coded to the PT COVID-19 (1).
- Co-suspects (n = 3): relevant co-suspect medications were dabigatran, dinoprostone, ibuprofen, and oxytocin (1 each).

[60] Many terms are evaluated under different categories.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Number of relevant events: 18.
- Reported relevant PTs (≥2 occurrences): Postpartum haemorrhage, Premature separation of placenta (3 each), and Heavy menstrual bleeding (2). None of the SAEs were assessed as related to BNT162b2 or blinded therapy.

Post-Authorisation Data

Number of cases: 37,329. Upon review, 2 cases were determined to be non-contributory and were not included in the discussion since these 2 cases involved babies exposed to the vaccine through breastfeeding. [61]

- Number of relevant cases: 37,327 (5.7% of 657,528 cases, the total PM dataset), compared to 9430 cases (2.9%) retrieved in the PSUR #1.
- MC cases (6988), NMC cases (30,339).
- Country of incidence: UK (10,051), Netherlands (7296), Germany (3932), France (3443), US (1544), Norway (1342), Italy (1269), Spain (1025), Japan (980), Denmark (932), Australia (806), Sweden (773), Canada (610); the remaining 3324 cases were distributed among 66 countries.
- Subjects' age in years (n = 34,165), range: 2 months-111 years, mean: 53.4, median: 37.0.
- Medical history (n = 16,298): the most frequently (≥200 occurrences) reported relevant medical conditions were coded to the PTs Hypertension (1149), Menopause (705), Disease risk factor (599), Contraception (515), Hypothyroidism (455), Endometriosis (361), Pregnancy (342), Amenorrhoea (251), Diabetes mellitus (249), Dysmenorrhoea (205), and Polycystic ovaries (203).
- COVID-19 Medical history (n = 2834): Medical conditions reported more than once were coded to the PTs Suspected COVID-19 (1435), COVID-19 (1389), Postacute COVID-19 syndrome (17), SARS-CoV-2 test positive (15), COVID-19 pneumonia (9), Asymptomatic COVID-19 (7), Exposure to SARS-CoV-2 (5) and Coronavirus infection (3).
- Co-suspects: 460 cases. The most frequently (≥10 occurrences) reported relevant co-suspect vaccines/medications were adalimumab, COVID-19 AstraZeneca (31 each), levonorgestrel (20), acetylsalicylic acid (18), apixaban (16), ethinylestradiol/levonorgestrel (11), desogestrel, levonorgestrel/ethinyl estradiol, and rivaroxaban (10 each).
- Number of relevant events: 41,143.

[61] These cases will be included in Section 16.3.5.3 *Use in Pregnant/Lactating Women.*

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Relevant event seriousness[20]: serious (14,003) and non-serious (27,153).

- Most frequently reported relevant PTs (≥2%): Heavy menstrual bleeding (16,613), Intermenstrual bleeding (7412), Contusion (2561), Epistaxis (2461), Haematoma (1544), Postmenopausal haemorrhage (1428), Haemorrhage (1411), and Petechiae (993).

- Time to event onset (n = 29,788 events), [62] range: <24 hours to 271 days, median: 4 days.

  - <24 hours: 4203 events (13 of which had a fatal outcome);
  - 1 day: 4759 events (25 of which had a fatal outcome);
  - 2-7 days: 9367 events (50 of which had a fatal outcome);
  - 8-14 days: 4231 events (17 of which had a fatal outcome);
  - 15-30 days: 4499 events (29 of which had a fatal outcome);
  - 31-181 days: 2690 events (12 of which had a fatal outcome);
  - 182-271 days: 39 events.

- Duration of relevant events (n = 6374 out of 10,754 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 235 days, median 6 days.

  - 1 day: 880 events;
  - 2-7 days: 3083 events;
  - 8-14 days: 1114 events;
  - 15-30 days: 768 events;
  - 31-181 days: 522 events;
  - 182-235 days: 7 events.

- Relevant event outcome[47]: fatal (212), resolved/resolving (16,654), resolved with sequelae (453), not resolved (15,052), and unknown (9158).

  - In 180 cases (reporting 212 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Gastrointestinal haemorrhage (21), Haematemesis (18), Cardiac arrest (17), Aortic aneurysm rupture (16), Cardiorespiratory arrest (14), Dyspnoea, Pulmonary embolism (12 each), Haemorrhage and Pyrexia (11 each). Of note, in 9 cases limited information regarding the cause of death was provided (PT Death). Most (137 of 180 cases) of these fatal cases involved elderly subjects. When the medical history was provided (124 cases), significant medical conditions included atrial fibrillation, cardiac failure, cerebral infarction, chronic kidney disease, chronic obstructive pulmonary disease, renal failure and various malignancies. Of note, few patients received anticoagulants or chemotherapeutic agents as co-suspect/concomitant medications.

[62] This number does not include 101 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by age group

- CT: Adults (11) and Elderly (6).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (987), Adults (31,137), Elderly (2740) and Unknown (2463).
  - A significantly higher reporting proportion of events coded to the PTs Heavy menstrual bleeding and Intermenstrual bleeding was observed in paediatric and adult population when compared to elderly population (Heavy menstrual bleeding [32.5% in paediatrics vs 48.2% in adults vs 0.2% in elderly] and Intermenstrual bleeding [13.4% in paediatrics vs 22.5% in adults vs 0.6% in elderly]). It is expected that the women of reproductive age will have more bleeding than the elderly population. While the reporting proportion of PTs Epistaxis and Petechiae were significantly higher in paediatric and elderly population when compared to adult population (Epistaxis [18.5% in paediatrics vs 17.3% in elderly vs 5.3% in adults] and Petechiae: [7.3% in paediatrics vs 7.0% in elderly vs 2.2% in adults]). In general, epistaxis and petechiae can occur at any age however they are more commonly seen in paediatrics and elderly. The reporting proportion of PT Haematoma was higher in elderly population (12.2%) when compared to paediatrics (3.9%) and adult (3.7%) population.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3953 (10.6% of the CT and PM cases reporting haematological AESIs).
- The reporting proportion of haematological AESIs with fatal outcome (2.1%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.3%).

O/E Analysis

O/E analysis was performed for Haemorrhage (see Appendix 6B *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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16.3.3.1.4. COVID-19 AESIs

Search criteria – PTs: Ageusia; Anosmia; OR SMQ COVID-19 (Narrow and Broad)[63].

Of the 25,532 cases, 76 cases were determined to be non-contributory and were not included in the discussion since these subjects were exposed to the vaccine during the mother' pregnancy or through breastfeeding. [61]

Clinical Trial Data

- Number of cases: 3 (blinded therapy [2] and BNT162b2 [1]) (0.4% of 721 cases, the total CT dataset) compared to 18 cases (2.6%) retrieved in the PSUR #1.
- Country of incidence: US (2) and ██████ (1).
- Subjects' gender: female (2), and male (1).
- Subjects' age in years (n = 3), range: 32 - 64, mean: 52.3, median: 61.0.
- Medical history (n = 1): the reported relevant medical conditions included Anaemia, Anxiety, Depression, Female sterilisation, Gastrectomy, Gastric ulcer, Hernia repair, Malnutrition, Migraine, Motion sickness, Nausea, Osteoporosis, Rhinitis allergic and Vitamin D deficiency (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs: COVID-19 pneumonia (2) and COVID-19 (1). None of the events were related to BNT162b2 or blinded therapy.

Post-Authorisation Data

- Number of relevant cases: 25,453 (3.9% of 657,528 cases, the total PM dataset), compared to 12,058 cases (3.7%) retrieved in the PSUR #1.
- MC cases (17,715) NMC cases (7738).
- Country of incidence (≥ 2%): Austria (9068), US (2616), France (2189), Germany (1785), UK (1627), Portugal (1537), Italy (974), Japan (628), Spain (560) and Netherlands (514).

---

[63] The PT Anti-platelet factor 4 antibody positive is evaluated in Section 16.3.3.1.8 Immune-mediated/autoimmune AESIs; the PT Thrombosis with thrombocytopenia syndrome is evaluated in Section 16.3.3.1.18 Thromboembolic AESIs, the PTs Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children are evaluated in Section 16.3.3.1.9 Multisystem Inflammatory Syndrome in Children /Adults.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Subjects' gender: female (14,031), male (10,025) and unknown (1397).
- Subjects' age in years (n = 22,688), range: 5 - 106, mean: 51.6, median: 50.0.
- Medical history (n = 5823): the most frequently (≥2%) reported relevant medical conditions included Hypertension (1478), Diabetes mellitus (381), Asthma (373), Type 2 diabetes mellitus (343), Atrial fibrillation (335), Obesity (318), Suppressed lactation[19] (285), Hypothyroidism (255), Dyslipidaemia (235), Chronic obstructive pulmonary diseases (223), Depression (204), Chronic kidney disease (194), Drug hypersensitivity (176), Myocardial ischaemia (161), Rheumatoid arthritis (147), Hypersensitivity (143), Cardiac failure (142), Non-tobacco user (141), Hypercholesterolemia (129), Benign prostatic hyperplasia (123), Seasonal allergy (120) and Tobacco user (116).
- COVID-19 Medical history: the most frequently (≥2%) reported medical conditions included COVID-19 (675) and Suspected COVID-19 (352).
- Co-suspects (n = 275): the most frequently (>5) reported relevant co-suspect vaccines/medications were adalimumab (110), COVID-19 AstraZeneca vaccine (47), COVID-19 Moderna vaccine (27), COVID-19 vaccine (22), influenza vaccine (20), upadacitinib (15), risankizumab (13), etanercept (8), ocrelizumab, rituximab (7 each), prednisone and tofacitinib citrate (6 each).
- Number of relevant events: 27,468.
- Relevant event seriousness: serious (23,274), non-serious (4199).
- Most frequently reported relevant PTs (≥2%): COVID-19 (19,642), Ageusia (2002), Suspected COVID-19 (1974), Anosmia (1558), Asymptomatic COVID-19 (789) and COVID-19 pneumonia (733).
- Time to event onset (n = 21835),[64] range: <24 hours to 525 days, median: 71 days.
  - <24 hours: 749 events (6 fatal events);
  - 1 day: 910 events (7 fatal events);
  - 2-7 days: 1775 events (33 fatal events);
  - 8-14 days: 910 events (35 fatal events);
  - 15-30 days: 1596 events (41 fatal events);
  - 31-181 days: 13,574 events (308 fatal events);
  - ≥ 182 days: 2418 events (129 fatal events).

[64] This number does not include 14 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Duration of relevant events (n = 2557 out of 7125 occurrences with outcome of resolved/resolved with sequelae), range: 24 hours to 238 days, median: 11 days:
  - <24 hours: 74 events;
  - 1 day: 95 events;
  - 2-7 days: 478 events;
  - 8-14 days: 1118 events;
  - 15-30 days: 469 events;
  - 31-181 days: 321 events;
  - ≥ 182 days: 2 events.

- Relevant event outcome:[47] fatal (764), resolved/resolving (6962), resolved with sequelae (163), not resolved (3071), unknown (16,533).
  - In 702 cases (reporting 764 relevant events with fatal outcome), the reported causes of death (>20 occurrences) were coded to PTs COVID-19 (542), Vaccination failure (376), Drug ineffective (267), COVID-19 pneumonia (170), Dyspnoea (53), Pyrexia (37), Suspected COVID-19 (34) and Respiratory failure (21). Of note, in 19 cases limited information regarding the cause of death was provided (PT Death [17], Sudden death [2]). Most (581 of 702 cases) of the fatal cases involved elderly subjects. When the medical history was provided (453 cases), the most frequently (≥ 20 occurrences) relevant medical conditions included hypertension, cardiac disorders (eg atrial fibrillation, cardiac failure, myocardial ischaemia), type 2 diabetes mellitus, chronic kidney disease, diabetes mellitus, obesity, dyslipidaemia, COVID-19, cerebrovascular accident and chronic obstructive pulmonary disease.

Analysis by age group

- CT: Adults (3)
  - No comparison between the different age groups is possible.

- PM: Paediatric (509), Adults (15,852), Elderly (6417).
  - No significant difference was observed in the reporting proportion of the most frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population, but the multisystem inflammatory syndrome that is reported with a higher proportion in the paediatric population (6.9%) compared to adult (0.1%) and elderly (0.03%) populations.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2966 (0.5% of 658,249 cases, the total dataset).

  The reporting proportion of COVID-19 AESIs with fatal outcome (12.4%) is higher in subjects with comorbid conditions, compared to the reporting proportion observed in the individuals without comorbidities (1.4% of fatal events).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

O/E Analysis

O/E analysis was performed for Ageusia and Anosmia (see Appendix 6B *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.

16.3.3.1.5. Dermatological AESIs

Search criteria - PTs: Chillblains; Erythema multiforme.

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 339 (0.05% of 657,528 cases, the total PM dataset), compared to 178 (0.05%) cases retrieved in the PSUR #1.
- MC cases (235), NMC cases (104).
- Country of incidence: Japan (70), France (60), UK (43), Italy (31), Australia (30), Germany (21), Netherlands (11), US (9), Ireland, Spain (8 each), Finland (7), Norway (5); the remaining 36 cases were distributed among 19 countries.
- Subjects' gender: female (210), male (120) and No data (9).
- Subjects' age in years (n = 317[65]), range: 12-98, mean: 49.7, median: 49.0
- Medical history (n = 157): the most frequently (≥ 4 occurrences) reported relevant medical conditions included Erythema multiforme (9), Seasonal allergy (7), Drug hypersensitivity, Food allergy (6 each), Hypothyroidism (5), Allergy to animal, Chillblains (4 each).
- COVID-19 Medical history (n = 13): COVID-19 (8), Suspected COVID-19 (4), and Asymptomatic COVID-19 (1).
- Co-suspects (n = 11): Influenza Vaccine (surface antigen, inactivated, adjuvanted) (1).

[65] Of note there was 1 case with contradictory demographic information (physical characteristics not matching with the reported age value).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Number of events: 339.
- Relevant event seriousness: serious (249), non-serious (90).
- Reported relevant PTs: Erythema multiforme (231), Chillblains (108)
- Time to event onset (n = 244[66]), range: <24 hours to 77 days, median: 3 days.
  - <24 hours: 23 events;
  - 1 day: 27 events;
  - 2-7 days: 115 events;
  - 8-14 days: 41 events;
  - 15-30 days: 26 events;
  - 31-180 days: 12 events.
- Duration of relevant events (n = 45 out of 95 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 49 days, median: 9 days:
  - 1-7 days: 11 events;
  - 8-14 days: 16 events;
  - 15-30 days: 8 events;
  - 31-180 days: 10 events.
- Relevant event outcome:[47] resolved/resolving (178), resolved with sequelae (6), not resolved (112), unknown (44).

Analysis by age group

- PM: Paediatric (21), Adults (212), Elderly (91) and Unknown (15).
  - Due to low volume of paediatric cases a meaningful comparison of the same with the other age groups is not possible. No significant difference observed in the reporting proportion of events chillblains and erythema multiforme between adult and elderly population.

Analysis by presence of comorbidities

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

[66] This number does not include 97 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

O/E Analysis

O/E analysis was performed for Chillblains and Erythema multiforme (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Erythema multiforme was a safety topic determined to be validated signal, categorised as "no risk". No other safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.6. Facial Paralysis

Search criteria – PTs: Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis.

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: [67] 4515 (0.7% of 657,528 cases, the total PM dataset), compared to 2392 cases (0.7%) retrieved in the PSUR #1.
- MC cases (2232), NMC cases (2283).
- Country of incidence: Germany (925), France (669), UK (409), Australia (339), Italy (266), Hong Kong (234), Japan, US (173 each), Netherlands (154), Sweden (113), Spain (112); the remaining 948 cases were distributed among 45 countries.
- Subjects' gender: female (2478), male (1845), and unknown (192).
- Subjects' age in years (n = 4151), range: 12 – 99, mean 54.5, median 47.0
- Medical history (n = 1826): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (392), Diabetes mellitus (101), Obesity (80), Hypothyroidism (76), Facial paralysis, Type 2 diabetes mellitus (65 each), Bell's palsy (56), Migraine (55), Tobacco user (51), Depression (46), Dyslipidaemia (39), Cerebrovascular accident and Hypercholesterolaemia (37 each).

[67] Compared to previous PSUR, an updated approach to include in the review also cases apparently not consistent with peripheral facial nerve palsy (BC Category 5) as co-reporting other disorders (i.e., stroke) was conservatively adopted since SMSR 9.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- COVID-19 Medical history (n = 149): reported medical conditions were coded to the PTs COVID-19 (90), Suspected COVID-19 (58), Coronavirus infection (2), Exposure to SARS-CoV-2, Post-acute COVID-19 syndrome, and SARS-CoV-2 test positive (1 each).

- Co-suspects (n = 47): the relevant co-suspect vaccines/medications were botulinum toxin type A and Diphtheria vaccine toxoid, HIB vaccine, Pertussis vaccine, Polio vaccine inact, Tetanus vaccine toxoid (1 each).

- Number of relevant events:[68] 4515.

- Relevant event seriousness:[20] serious (4246) and non-serious (284).

- Reported relevant PTs: Bell's palsy (1539), Facial paralysis (2289), Facial paresis (686), and Oculofacial paralysis (1).

- Time to event onset (n = 3425 events),[69] range: <24 hours to 273 days, median 6 days.

  - <24 hours: 560 events;
  - 1 day: 382 events;
  - 2-7 days: 963 events (1 of which had a fatal outcome);
  - 8-14 days: 518 events;
  - 15-30 days: 596 events;
  - 31-181 days: 402 events;
  - 182-273 days: 4 events.

- Duration of of relevant events (n = 396 out of 861 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 201 days, median: 5 days.

  - 1 day: 118 events;
  - 2-7 days: 101 events;
  - 8-14 days: 40 events;
  - 15-30 days: 80 events;
  - 31-181 days: 56 events.
  - 182-201 days: 1 event.

- Relevant event outcome: fatal (1), resolved/resolving (1630), resolved with sequelae (120), not resolved at the time of reporting (1737), and unknown (1042).

---

[68] 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.

[69] This number does not include 5 events for which partial administration and/or event onset date was reported.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- In the single fatal case, the cause of death was coded to the PTs Aphasia, Brain oedema, Cerebral haematoma, Cerebrovascular accident, Facial paralysis, Fall, Haematoma, Hemiplegia, and Respiratory distress. The case involved an [redacted]-year-old [redacted] subject with a medical history of articular calcification, atrial fibrillation, cerebral amyloid angiopathy, and haemorrhagic stroke.

Analysis by age group

- PM: Paediatric (142), Adults (3241), Elderly (803), and Unknown (329).
  - There was no significant difference observed in the reporting proportion of facial paralysis events between age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 745 (16.5% of PM cases reporting facial paralysis, no CT cases reported).
- Only 1 case reported a fatal outcome for the relevant event coded to the PT Facial paralysis and hence a meaningful comparison cannot be made.

O/E Analysis

O/E analysis was performed for Bell's palsy (PTs: Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis) (see Appendix 6B *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).

16.3.3.1.7. Hepatic AESIs

Search criteria - SMQ Liver related investigations, signs and symptoms (Narrow and Broad) OR PT Liver injury.

Upon review, 10 cases were determined to be non-contributory and were not included in the discussion since these cases involved subjects exposed to the vaccine through breastfeeding.[61]

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

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

Post-Authorisation Data

- Number of relevant cases: 1393 (0.2% of 657,528 cases, the total PM dataset), compared to 550 cases (0.2%) retrieved in the PSUR #1.
- MC cases (867), NMC cases (526).
- Country of incidence: Japan (317), France (239), Germany (165), UK (102), US (92), Italy (85), Spain (48), Netherlands (43), Australia (42), Canada (27), Norway (24), Denmark (19), Finland (18), Austria (17), Sweden (16), New Zealand (13), Greece (12), Belgium, Taiwan, province of China (11 each), Czech Republic (10), Brazil, Portugal (8 each), Switzerland (7), Hungary (6), Ireland, Poland, Romania (5 each); the remaining 38 cases were distributed among 19 countries.
- Subjects' gender: female (797), male (557), and no data (39).
- Subjects' age in years (n = 1306), range: 12 – 109, mean: 52.6, median: 52.0.
- Medical history (n = 823): the most frequently reported relevant medical conditions (≥ 5 occurrences) included Dyslipidaemia (42), Diabetes mellitus (37), Hypothyroidism, Type 2 diabetes mellitus (34 each), Obesity (29), Cholecystectomy, Hypercholesterolaemia (19 each), Alcohol use (16), Hyperlipidaemia (13), Hepatic steatosis (9), Hepatic function abnormal (7), Hepatic cirrhosis, Type 1 diabetes mellitus (6 each), and Liver disorder (5).
- COVID-19 Medical history (n = 61): the medical conditions reported included COVID-19 (36), Suspected COVID-19 (20), COVID-19 pneumonia (2), Asymptomatic COVID-19, COVID-19 immunisation, and Exposure to SARS-CoV-2 (1 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Co-suspects (n = 62): the relevant co-suspect medications reported were methotrexate (4), adalimumab (3), amoxicillin, apixaban, paclitaxel (2 each), atorvastatin, amiodarone, cyclophosphamide, etoposide, ibuprofen and palbociclib (1 each).

- Number of relevant events: 1917

- Relevant event seriousness: serious (933) and nonserious (984)

- Most frequently reported relevant PTs (≥50 occurrences): Alanine aminotransferase increased (241), Aspartate aminotransferase increased (206), Hepatic function abnormal (199), Hepatic enzyme increased (165), Gamma-glutamyltransferase increased (164), Liver function test abnormal (113), Transaminases increased (103), Hepatic pain (102), Blood bilirubin increased (83), Liver function test increased (73), Ascites, Blood alkaline phosphatase increased (72 each), Hepatomegaly (63).

- Time to event onset (n = 1275 events)[70], range: <24 hours to 174 days, median: 7 days.

  - <24 hours: 95 events; (1 of which had a fatal outcome);
  - 1 day: 133 events;
  - 2-7 days: 418 events (5 of which had a fatal outcome);
  - 8-14 days: 215 events; (1 of which had a fatal outcome);
  - 15-30 days: 247 events;
  - 31-180 days: 167 events (3 of which had a fatal outcome).

- Duration of relevant events (n = 133 out of 299 occurrences with outcome of resolved/resolved with sequelae), range: 10 minutes to 180 days, median: 25 days.

  - <24 hours: 2 events
  - 1 day: 2 events;
  - 2-7 days: 43 events;
  - 8-14 days: 31 events;
  - 15-30 days: 26 events;
  - 31-180 days: 29 events.

- Relevant event outcome:[47] fatal (14), resolved/resolving (638), resolved with sequelae (23), not resolved at the time of reporting (330), and unknown (913).

  - In 13 cases (reporting 14 relevant events with a fatal outcome), the cause of death were coded to the PTs Hepatic function abnormal (5), Ascites (4), Congestive hepatopathy (2), Hepatic enzyme increased, Hepatomegaly, and Transaminase increased (1 each). Nine (9) of the 13 cases involved subjects who were ≥60 years of age.

[70] This number does not include 643 events for which partial administration or event onset dates were reported.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- When the medical history was provided (11 cases), the subject's medical condition included Type 2 diabetes mellitus (6), Diabetes mellitus (5), Hepatic cirrhosis (2), Hepatic cancer, Hepatic encephalopathy, Hyperlipidaemia, Hypothyroidism, Hepatic neoplasm and Transaminases increased (1 each).

Analysis by age group

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

Analysis by presence of comorbidities

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

O/E Analysis

O/E analysis was performed for Acute liver injury/Liver injury (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Hepatic events were a safety topic determined to be validated signal, categorised as "no risk". No other safety signals have emerged based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

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 Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity; Hypersensitivity myocarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis; Thyroiditis subacute.[60, 71]

---

[71] Based on PRAC Assessment on the updated signal assessment on myocarditis and pericarditis with BNT162b2 (Procedure number: EMEA/H/C/5735/SDA/032), the MAH was requested to include 'Myocarditis and pericarditis' as an important identified risk in the EU RMP. The EU RMP Version 2.3 addressing this

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 20 (BNT162b2 [13], blinded therapy [7], and placebo [1]) (2.8% of 721 cases, the total CT dataset) compared to 15 cases (2.1%) retrieved in the PSUR #1.
- Country of incidence: US (14), Argentina, China (2 each), [redacted] (1 each).
- Subjects' gender: female (6) and male (14).
- Subjects' age in years (n = 20), range: 6 – 78, mean 54.0, median 57.0.
- Medical history (n = 16): the relevant medical conditions reported more than once were coded to the PTs Seasonal allergy and Type 2 diabetes mellitus (3 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of relevant events: 20
- Reported relevant PTs (≥2 occurrences): Pancreatitis (4), Diabetic ketoacidosis, Interstitial lung disease, and Myocarditis (2 each). Among the 20 cases, in 2 cases Myocarditis was assessed as related to BNT162b2. Time to onset of event myocarditis was <24 hours and 3 days (1 case each). Outcome of the events was reported as resolved/resolving (2 cases). All the other SAEs were assessed as not related to BNT162b2 or blinded therapy or placebo.

Post-Authorisation Data

- Number of cases: 21,994 (3.3% of 657,528 cases of the total PM dataset), compared to 6902 cases (2.1%) retrieved in the PSUR #1.
- MC cases (12,176), NMC cases (9818).
- Country of incidence: Germany (3216), Australia (2901), UK (2685), France (2460), Japan (1612), US (1403), Italy (1280), Netherlands (803), Canada (708), Sweden (515), Spain (433), Norway (396), Finland (316), Austria (307), Greece (283), Denmark (241), New Zealand (239), Belgium (237); the remaining 1959 cases were distributed among 66 countries.
- Subjects' gender: female (11,541), male (9716), and unknown (737).
- Subjects' age in years (n = 19,982), range: 2 – 109, mean: 52.2, median: 41.0.

---

request with the inclusion of Myocarditis/Pericarditis as an important identified risk was approved on 30 September 2021 (procedure EMEA/H/C/005735/II/0059).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Medical history (n = 9513): the most frequently (≥150 occurrences) reported relevant medical conditions were coded to the PTs Asthma (799), Drug hypersensitivity (610), Seasonal allergy (583), Food allergy (486), Hypersensitivity (460), Hypothyroidism (381), Psoriasis (329), Diabetes mellitus (309), Pericarditis (240), Type 2 diabetes mellitus (229), Colitis ulcerative (228), Autoimmune thyroiditis (185), and Rheumatoid arthritis (155).

- COVID-19 Medical history (n = 971): the most frequently (≥2 occurrences) reported medical conditions were coded to the PTs COVID-19 (580), Suspected COVID-19 (359), Post-acute COVID-19 syndrome (13), Asymptomatic COVID-19, Coronavirus infection, COVID-19 pneumonia, SARS-CoV-2 test positive (9 each), Exposure to SARS-CoV-2 (4), SARS-CoV-2 antibody test positive (3), and Occupational exposure to SARS-CoV-2 (2).

- Co-suspects (n = 436): the most frequently (≥10 occurrences) reported relevant co-suspects were adalimumab (107), COVID-19 AstraZeneca vaccine (30), COVID-19 Moderna vaccine (18), and influenza vaccine (14).

- Number of relevant events: 23,596.

- Relevant event seriousness:[20] serious (19,121) and non-serious (4480).

- Most frequently reported relevant PTs (≥2%): Myocarditis (6338), Pericarditis (5274), Hypersensitivity (3917), Psoriasis (597), and Polymyalgia rheumatica (450).

- Time to event onset (n = 14,410),[72] range: <24 hours to 247 days, median: 4 days.
  - <24 hours: 2835 events (11 of which had a fatal outcome);
  - 1 day: 1829 events (9 of which had a fatal outcome);
  - 2-7 days: 4611 events (46 of which had a fatal outcome);
  - 8-14 days: 1747 events (22 of which had a fatal outcome);
  - 15-30 days: 1758 events (14 of which had a fatal outcome);
  - 31-181 days: 1599 events (19 of which had a fatal outcome);
  - 182-247 days: 31 events (1 of which had a fatal outcome).

- Duration of relevant events (n = 1597 out of 4371 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 210 days, median 5 days.
  - 1 day: 405 events;
  - 2-7 days: 545 events;
  - 8-14 days: 224 events;
  - 15-30 days: 200 events;

[72] This number does not include 28 events for which partial administration and/or event onset dates were reported.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 31-181 days: 221 events;
  - 182-210 days: 2 events.

- Relevant event outcome: fatal (194), resolved/resolving (9095), resolved with sequelae (459), not resolved at the time of reporting (7921), and unknown (5976).

  - In 184 cases (reporting 194 relevant events with a fatal outcome), the reported cause of death (≥10 occurrences) were coded to the PTs Myocarditis (69), Interstitial lung disease (31), Dyspnoea (12), Cardiac arrest, Respiratory failure (11 each), Cardiac failure and Myocardial infarction (10 each). Of note, in 8 cases limited information regarding the cause of death was provided (PT Death). Most (103 of 184 cases) of the fatal cases involved elderly subjects. When the medical history was provided (126 cases), significant medical conditions included aortic aneurysm, arrhythmia, atrial fibrillation, autoimmune disorder, cardiac disorder, cardiac failure, chronic obstructive pulmonary disease, hypertension, interstitial lung disease, myocardial infarction, myocardial ischaemia, and various malignancies.

Analysis by age group

- CT: Paediatric (2), Adults (12), and Elderly (6).

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

- PM: Paediatric (1649), Adults (15,537), Elderly (3195) and Unknown (1613).

  - 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 and adult population when compared to elderly population (Myocarditis [61.4% in paediatrics vs 27.9% in adults vs 13.4% in elderly] and Pericarditis [24.6% in paediatrics vs 26.9% in adults vs 12.8% in elderly]). While a higher reporting proportion of events coded to the PTs Psoriasis and Polymyalgia rheumatica were observed in elderly population when compared to paediatric and adult population (Psoriasis [0.4% in paediatrics vs 2.7% in adults vs 4.2% in elderly]; Polymyalgia rheumatica [none in paediatrics vs 0.6% in adults vs 10.7% in elderly]). A higher reporting proportion of events coded to the PT Hypersensitivity was observed in adults and elderly population when compared to paediatric population (8.1% in paediatrics vs 18.4% in adults vs 15.2% in elderly).

Analysis by presence of comorbidities

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

The reporting proportion of immune mediated/autoimmune AESIs with a fatal outcome (1.7%) is higher in subjects with comorbid conditions when compared to the reporting

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

proportion observed in the subjects without comorbidities (0.6% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Autoimmune thyroiditis, Encephalitis, Myasthenia gravis, Transverse myelitis, Myocarditis, Pericarditis, Polymyalgia rheumatica,[73] Thrombocytopenic purpura,[74] Thrombotic thrombocytopenic purpura,[74] Type 1 diabetes mellitus, and Urticarial vasculitis[73] (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

- Primary analysis (global): overall O/E, only myocarditis using the low, mid, and high background rates meet the signal criteria with the upper limit of the O/E 95% CI >1 in at least one risk window.
- Age-specific analyses (EEA and US): MIS, myocarditis, and myocarditis/pericarditis are noted to have O/E > 1 in at least one age-group and risk window.

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

16.3.3.1.9. Multisystem Inflammatory Syndrome in Children / Adults[75]

Search criteria - PTs: Autoinflammatory disease; Cytokine release syndrome; Cytokine storm; Distributive shock; Haemophagocytic lymphohistiocytosis; Hypotensive crisis; Kawasaki's disease; Macrophage activation; Macrophages increased; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Septic shock; Systemic inflammatory response syndrome; Toxic shock syndrome; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease.

---

73 Included under Cutaneous vasculitis in Appendix 6B.

74 Included under Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia in Appendix 6B.

75 This category was requested by EMA: the PTs Multiple organ dysfunction syndrome and Systemic inflammatory response syndrome were included in the Other AESI category in PSUR #1; Cytokine release syndrome under Immune-mediated/autoimmune AESI, Haemophagocytic lymphohistiocytosis under Haemophagocytic syndrome. The PTs Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease are also included in the search strategy to retrieve cases for the important identified risk VAED/VAERD. The PTs Toxic shock syndrome, Distributive shock, Macrophage activation, and Macrophages increased were not included in the TME List but added to align the search strategy (PTs) for MIS-C/A AESIs review to the one used in the signal procedure as per EMA PRAC request.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 2 (BNT162b2 [2]) (0.3% of 721 cases, the total CT dataset) compared to 3 cases (0.3%) retrieved in the PSUR #1.
- Country of incidence: [redacted] (1 each).
- Subjects' gender: [redacted] (2).
- Subjects' age: [redacted]
- Medical history (n = 2): Hypertension (2), Bronchospasm, Cardiac failure congestive, Chronic obstructive pulmonary disease, Emphysema, Ex-tobacco user, Implantable defibrillator insertion, Post menopause, Rubber sensitivity, Ventricular tachycardia (1 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PT: Septic shock (2), not related to BNT162b2.

Post-Authorisation Data

- Number of relevant cases[76]: 438 (0.07% of 657,528 cases of the total PM dataset), compared to 183 (0.1%) retrieved in PSUR #1.[77]
- MC cases (326), NMC cases (112).
- Country of incidence: France (84), Germany (73), Japan (66), Spain (29), Italy (25), US (24), UK (19), Australia (11); the remaining 109 cases were distributed among 35 countries.
- Subjects' gender: female (200), male (232), and no data (6).
- Subjects' age in years (n = 418), range: 12 – 98, mean: 56.7, median 62.0.
- Medical history (n = 284): the most frequently (≥10 occurrences) reported medical conditions included Hypertension (104), Atrial fibrillation (30), Diabetes mellitus (23), Dyslipidaemia (21), Type 2 diabetes mellitus (20), Obesity (17), Chronic kidney disease (16), Depression (15), Chronic obstructive pulmonary disease, Non-tobacco user (13

[76] One additional case was not included because made invalid after the PSUR DLP (Literature article with no identifiable patients).

[77] MIS-C/A was not identified as an AESIs in the PSUR #1.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

each), Asthma, Benign prostatic hyperplasia, Cardiac failure (12 each), Dementia, Epilepsy, Ex-tobacco user (11 each), Rheumatoid arthritis (10).

- COVID-19 medical history (n = 30): COVID-19 (22), COVID-19 pneumonia, Suspected COVID-19 (3 each), Asymptomatic COVID-19, (9), Exposure to SARS-CoV-2 (1 each).

- Co-suspects (n = 14): relevant co-suspect vaccines/medications included: influenza vaccine inact sag 3v (2), abemaciclib, acalabrutinib, adalimumab, anastrozole, calcium folinate, COVID-19 AstraZeneca vaccine , dronedarone hydrochloride, fluorouracil, influenza vaccine, influenza vaccine inact split 4v, influenza vaccine live reassort 4v, leflunomide, linezolid, metformin, methotrexate sodium, methylprednisolone, moxifloxacin1, oxaliplatin, piperacillin, tazobactam, saccharated iron oxide, and trastuzumab (1 each).

- Number of relevant events: 475.

- Relevant event seriousness: serious (472), nonserious (3)

- Most frequently reported relevant PTs (≥10 occurrences): Multiple organ dysfunction syndrome (135), Septic shock (110), Systemic inflammatory response syndrome (73), Hemophagocytic lymphohistiocytosis (38), Multisystem inflammatory syndrome in children (34), Cytokine storm (16), Hypotensive crisis, Kawasaki's disease, Toxic shock syndrome (10 each).

- Time to relevant event onset (n = 308),[78] range: <24 hours to 225 days, median: 16 days.

  - <24 hours: 31 events (10 of which had a fatal outcome);
  - 1 day: 28 events (6 of which had a fatal outcome);
  - 2-7 days: 88 events (23 of which had a fatal outcome);
  - 8-14 days: 48 events (16 of which had a fatal outcome);
  - 15-30 days: 50 events (13 of which had a fatal outcome);
  - 31-70 days: 31 events (15 of which had a fatal outcome)
  - 71-225 days: 32 events (21 of which had a fatal outcome);

- Duration of relevant events was reported in 35 out of 56 occurrences with outcome of resolved/resolved with sequelae; it ranged from 5 minutes (hypotensive crisis in 1 case) to 171 days.

  - <24 hours: 2 events;
  - 1 day: 2 events;
  - 2-7 days: 7 events;
  - 8-14 days: 9 events;

[78] This number does not include 167 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 15-30 days: 9 events;
- 31-171 days: 6 events.

- Relevant event outcome (476): fatal (156), resolved or resolving (123), resolved with sequelae (7), not resolved at the time of reporting (68), and unknown (121).
  - In 142 cases, reporting 156 fatal events of interest, the reported clinical cause of death (≥6 occurrences) was coded to the PTs Multiple organ dysfunction syndrome (83), Septic shock (48), Acute kidney injury (15), Dyspnoea, (12), COVID-19 pneumonia, Pneumonia (11 each), Pyrexia (10), COVID-19, Myocardial infarction, Respiratory failure, Sepsis, Thrombocytopenia (9 each), Acute respiratory distress syndrome (8), Cardiac arrest, and Renal failure (7 each), Cardiac failure, Hypotension, Oxygen saturation decreased, Systemic inflammatory response syndrome (6 each).

Analysis by age group

- CT: Adult (1), Elderly (1).
- PM: Paediatric (53 - Adolescent), Adult (167), Elderly (201), Unknown (17).
  - Among the frequently (≥2%) reported relevant multisystem inflammatory syndrome events, it was observed that:
    - PT Multisystem inflammatory syndrome in children was reported, as expected, only in the pediatric population (62.3% of the paediatric cases).
    - PT Kawasaki disease was more frequently reported in the paediatric population when compared to the adult population (11.3% in paediatric vs 2.4% in adults).
    - PT Multiple organ dysfunction syndrome was reported at a significantly higher frequency in the elderly population compared to the adults (45.8 % in elderly vs 22.4% in adults, no case in paediatric population).
    - PT Systemic inflammatory response syndrome was more frequently observed in adults compared to elderly and paediatric population (25.8% in adults, 12.9% in elderly, 7.6% in children).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 189 (43.0% of the cases reporting Multisystem Inflammatory Syndrome AESIs).
- The reporting proportion of Multisystem Inflammatory Syndrome AESIs with fatal outcome is higher in subjects with comorbid conditions (49.2%) when compared to the reporting proportion observed in the subjects without comorbidities (25.5% of events with fatal outcome).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

O/E Analysis

O/E analysis was performed for Multisystem inflammatory syndrome (includes PTs: Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome) (see Appendix 6B Observed versus Expected Analyses for Adverse Events of Special Interest).

Conclusion

Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C) was evaluated as signal in the reporting interval and closed as "no risk".

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

16.3.3.1.10. Musculoskeletal AESIs

Search criteria - PTs Arthralgia; Arthritis; Chronic fatigue syndrome; Polyarthritis; Post viral fatigue syndrome; Rhabdomyolysis; Rheumatoid arthritis.

Clinical Trial Data

- Number of cases: 4 (BNT162b2 [2], placebo and blinded therapy [1 each]) (0.6% of 721 cases, the total CT dataset) compared to 2 cases (0.28%) retrieved in the PSUR #1.
- Country of incidence: US (3) and (1).
- Subjects' gender: (4).
- Subjects' age: years.
- Medical history (n=3): relevant medical history included Arthritis (2), Ehlers-Danlos syndrome, vitamin D deficiency (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (2): Arthralgia, and Arthritis (2 each), not related to BNT162b2/blinded therapy.

Post-Authorisation Data

- Number of relevant cases: 58,250 (8.9% of 657,528 cases, the total PM dataset), compared to 36,146 cases (11.0%) retrieved in the PSUR #1.
- MC cases (25,111), NMC cases (33,139).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence (≥100 occurrences): Japan (15,276), Netherlands (14,007), UK (5002), US (3189), Italy (2291), Germany (2101), France (2094), Australia (1464), Belgium (1272), Mexico (1213), Sweden (1186), Denmark (1101), Czech Republic (1048), Austria (1034), Spain (862), Norway (651), Canada (496), Portugal (410), Finland (385), Ireland (289), Malaysia (266), Lithuania (240), Croatia (204), Brazil (181), Slovenia (177), Poland (165), Philippines (154), Romania (150), Estonia (141), Switzerland (118), and Iraq (115); the remaining 968 cases were distributed among 45 countries.

- Subjects' gender: female (42,378), male (14,378), and Unknown (1494).

- Subjects' age in years (n = 53,257), range: 1 day – 104 years, mean: 45.0 years, median: 44.0 years.

- Medical history (n = 15,714 cases): the most frequently (≥100 occurrences) reported medical conditions included Hypertension (1845), Disease risk factor (1391), Asthma (1274), Drug hypersensitivity (1162), Seasonal allergy (1070), Hypersensitivity (905), Suppressed lactation[19] (903), Food allergy (845), Rheumatoid arthritis (583), Hypothyroidism (572), Diabetes mellitus (449), Depression (407), Fibromyalgia, Migraine (377 each), Osteoarthritis (375), Arthralgia (354), Arthritis (337), pain (315), Anxiety (271), Gastrooesophageal reflux disease (261), Type 2 diabetes mellitus (255), Mite allergy (252), Autoimmune thyroiditis (243), Immunodeficiency (233), Allergy to animal (229), Breast cancer (200), Obesity (187), Tobacco user (172), Rhinitis allergic (171), Non-tobacco user (169), Osteoporosis (167), Blood cholesterol increased (163), Irritable bowel syndrome, Psoriasis (161 each), Atrial fibrillation, Back pain (159 each), Endometriosis (149), Allergy to metals (145), Hypercholesterolaemia (144), Chronic obstructive pulmonary disease, Clinical trial participant (136 each), Headache, Pregnancy (132 each), Hyperlipidaemia (131), Dyslipidaemia (125), Crohn's disease (122), Rubber sensitivity (117), Dust allergy (115), Thyroid disorder (114), Steroid therapy (110), Psoriatic arthropathy (109), Allergy to plants (108), Cardiac disorder (106), Systemic lupus erythematosus (104).

- COVID-19 medical history (n = 5172 cases): COVID-19 (3087), Suspected COVID-19 (2064), Post-acute COVID-19 syndrome (32), SARS-CoV-2 test positive (19), Asymptomatic COVID-19 (9), Coronavirus infection (8), COVID-19 pneumonia (7), Exposure to SARS-CoV-2 (6), Occupational exposure to SARS-CoV-2 (5), SARS-CoV-2 antibody test positive (2), and Coronavirus test positive (1).

- Co-suspects (n = 558 cases): relevant co-suspect vaccines/medications included adalimumab (96), influenza vaccine (47), COVID-19 AstraZeneca vaccine (30), hepatitis A vaccine, methotrexate (20 each), upadacitinib (19), etanercept (16), tofacitinib (15), influenza vaccine (surface antigen, inactivated, adjuvanted) (13), COVID-19 Moderna vaccine (11).

- Number of relevant events: 58,929.

- Relevant event seriousness:[20] serious (8765), non-serious (50,185)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Most frequently reported relevant PTs (≥80 occurrences): Arthralgia (56610), Arthritis (1181), Rheumatoid arthritis (627), Rhabdomyolysis (157), Polyarthritis (156), and Chronic fatigue syndrome (120).
- Time to relevant event onset (n = 45,612 occurrences),[79] range: <24 hours to 379 days, median: 1 day.
  - <24 hours: 16,736 events (3 of which had a fatal outcome);
  - 1 day: 18,528 events (6 of which had a fatal outcome);
  - 2-7 days: 6899 events (6 of which had a fatal outcome);
  - 8-14 days: 1520 events (1 of which had a fatal outcome);
  - 15-30 days: 1073 events (1 of which had a fatal outcome);
  - 31-180 days: 827 events (1 of which had a fatal outcome);
  - 181-379 days: 29 events.
- Duration of relevant events was reported in 9980 out of 21,208 occurrences with outcome of resolved/resolved with sequelae; it ranged from <24 hours to 213 days; median: 1 day.
  - <24 hours: 835 events;
  - 1 day: 3453 events;
  - 2-7 days: 4904 events;
  - 8-14 days: 372 events;
  - 15-30 days: 239 events;
  - 31-213 days: 177 events.
- Relevant event outcome (59210): fatal (22), resolved or resolving (30875), resolved with sequelae (442), not resolved at the time of reporting (16789), and unknown (11082).
  - In 22 cases, the reported cause of death (>2 occurrences) was coded to the PTs Arthralgia (14), Fatigue (8), Dyspnoea, Myalgia (7 each), Malaise (6), Headache, Pyrexia (5 each), Cardiac arrest (4), Hyperhidrosis, Nausea (3 each). Twelve (12) of 22 fatal cases involved elderly subjects. When the medical history was provided (10 cases), significant medical conditions included back pain (2), femur fracture, lumbar spinal stenosis, osteomyelitis chronic (1 each).

Analysis by age group

- CT: Adult (2) and Elderly (2).
- PM: Paediatric (616), Adult (47,590), Elderly (6980), Unknown (3064).

[79] This number does not include 70 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Higher reporting proportion of events coded to the PT Rheumatoid arthritis was reported in elderly population when compared to adult and paediatric population ([0.8% in adults vs 0.8% in paediatrics vs 2.9% in elderly]).
- Higher reporting proportion of event coded to the PT Rhabdomyolysis was reported in paediatric population when compared to adult and elderly population ([0.2% in adults vs 3.2% in paediatrics vs 0.8% in elderly]).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 6044 (10.4% of the cases reporting musculoskeletal AESIs).
- A higher reporting proportion of musculoskeletal AESIs was reported in subjects without significant comorbidities (89.6%) when compared to subjects with significant comorbidities.
- The reporting proportion of musculoskeletal AESIs with outcome resolved (25.3%) is higher in subjects without comorbid conditions when compared to the reporting proportion observed in the subjects with comorbidities (21.5% 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 6B *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.

16.3.3.1.11. 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.[80]

[80] The PTs Anti-myelin-associated glycoprotein antibodies positive, Anti-myelin-associated glycoprotein associated polyneuropathy, Clinically isolated syndrome, Immune-mediated neuropathy and Myelin oligodendrocyte glycoprotein antibody-associated disease are evaluated in Section 16.3.3.1.8 Immune-mediated/autoimmune AESI while Eclampsia is evaluated in Section 16.3.5.3 Use in Pregnant/Lactating Women.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 7 (BNT162b2 [2], blinded therapy [5] (0.97% of 721 cases, the total CT dataset) compared to 8 cases (1.14%) retrieved in the PSUR #1.
- Country of incidence: US (4), Poland (2), [redacted] (1).
- Subjects' gender: female (3), male (4).
- Subjects' age in years (n = 7), range: 4 – 59, mean: 20.7, median: 12.0.
- Medical history (n=7): relevant medical history included Cerebral haemorrhage, Epilepsy, Febrile convulsion, and Hemiparesis, Neurogenic bladder, Optic nerve hypoplasia, Seizure, Syncope (1 each).
- COVID-19 medical history: None.
- Co-suspects: None.
- Reported relevant PTs: Epilepsy (3), Alcoholic seizure, Intracranial pressure increased, Neuropathy peripheral, Status epilepticus (1 each). However, none of the SAE were assessed as related to BNT162b2/blinded therapy/placebo.

Post-Authorisation Data

- Number of relevant cases: 7197 (1.1% of 657,528 cases, the total PM dataset), compared to 3471 cases (1.1%) retrieved in the PSUR #1.
- MC cases (3657), NMC cases (3540).
- Country of incidence (>50 occurrences): Germany (1158), Japan (907), UK (906), France (819), US (524), Italy (480), Netherlands (316), Australia (288), Spain (146), Finland (141), Canada (126), Sweden (113), Mexico (106), Belgium (100), Austria (99), New Zealand (97), Norway (85), Ireland (83), Czech Republic (63), Greece (62), and Denmark (54); the remaining 524 cases were distributed among 52 countries.
- Subjects' gender: female (4376), male (2652), and unknown (169).
- Subjects' age in years (n = 6700), range: 5 – 102, mean: 45.0, median: 43.0.
- Medical history (n = 3846 cases): the most frequently (≥50 occurrences) reported relevant medical conditions included Hypertension (523), Epilepsy (522), Multiple sclerosis (282), Asthma (212), Drug hypersensitivity (194), Fibromyalgia (192), Seizure (184), Seasonal allergy (172), Suppressed lactation[19] (142), Migraine (134), Depression (119), Food allergy (117), Diabetes mellitus, Hypothyroidism (113 each), Hypersensitivity (109), Tobacco user, Type 2 diabetes mellitus (86 each), Anxiety (84), Rheumatoid arthritis (69), Dyslipidaemia (68), Mite allergy (64), Cerebrovascular accident, Non-tobacco user (62 each), Neuropathy peripheral (60), Atrial fibrillation (59),

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Gastrooesophageal reflux disease, Obesity (58 each), Pain (55), Hypercholesterolaemia (52), and Surgery (51).

- COVID-19 Medical history (n = 317 cases): COVID-19 (204), Suspected COVID-19 (101), COVID-19 pneumonia (6), SARS-CoV-2 test positive (5), Coronavirus infection (4), Post-acute COVID-19 syndrome (3), Asymptomatic COVID-19 (2), Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, and SARS-CoV-2 antibody test positive (1 each).

- Co-suspects (n = 157 cases): the reported relevant co-suspect medications (>5 occurrence) were adalimumab, ocrelizumab (12 each), etanercept (6).

- Number of relevant events: 8014.

- Relevant event seriousness: serious (7364), non-serious (650).

- Most frequently reported relevant PTs (≥50 occurrences): Seizure (2041), Guillain-Barre syndrome (812), Neuropathy peripheral (796), Epilepsy (786), Trigeminal neuralgia (340), Generalised tonic-clonic seizure (307), Fibromyalgia (300), Multiple sclerosis (233), Multiple sclerosis relapse (224), Optic neuritis (219), Polyneuropathy (218), Ataxia (176), Myelitis transverse (98), Meningitis (96), Demyelination (91), Acute disseminated encephalomyelitis (89), Status epilepticus (85), Encephalopathy (78), Aura (77), Febrile convulsion (69), Partial seizures (68), Meningitis aseptic (66), Intracranial pressure increased (65), Petit mal epilepsy (63), Tonic convulsion (58), Tongue biting (52).

- Time to relevant event onset (n = 5793 occurrences)[81], range: <24 hours to 365 days, median: 2 days.

  - <24 hours: 1720 events (12 of which had a fatal outcome);
  - 1 day: 875 events (11 of which had a fatal outcome);
  - 2-7 days: 1353 events (15 of which had a fatal outcome);
  - 8-14 days: 684 events (10 of which had a fatal outcome);
  - 15-30 days: 649 events (9 of which had a fatal outcome);
  - 31-180 days: 499 events (9 of which had a fatal outcome);
  - 181-365 days: 13 events (1 of which had a fatal outcome).

- Duration of relevant events (n = 1163 out of 2190 occurrences with outcome of resolved/ resolved with sequelae), range: from <24 hours to 202 days, median: <24 hours.

  - <24 hours: 638 events;
  - 1 day: 119 events;

[81] This number does not include 13 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 2-7 days: 169 events;
  - 8-14 days: 61 events;
  - 15-30 days: 72 events;
  - 31-202 days: 104 events.

- Relevant event outcome: fatal (87), resolved or resolving (3347), resolved with sequelae (293), not resolved at the time of reporting (2328), and unknown (1979). In 80 cases, the reported cause of death (>3 occurrences) was coded to the PTs Seizure (28), Guillain-Barre syndrome (10), Pyrexia (8), Cardiac arrest, Epilepsy (7 each), Dyspnoea, Encephalopathy, Status epilepticus (5 each), Acute disseminated encephalomyelitis, Arrhythmia, Headache, Loss of consciousness, Muscular weakness, Sepsis (4 each). Of the 80 cases, 40 fatal cases involved elderly subjects. When the medical history was provided (26 cases), significant medical conditions (>2 occurrence) included hypertension (13), atrial fibrillation (5), diabetes mellitus, myocardial infarction (4 each), cardiac failure, chronic obstructive pulmonary disease, hypothyroidism, prostate cancer (3 each).

Analysis by age group

- CT: Adult (3), Adolescent (1) and Child (3).

- PM: Adult (4978), Elderly (1268), Paediatric (524), Unknown (427).

  - Higher reporting proportion of event coded to the PT Ataxia was reported in elderly population when compared to adult and paediatric population ([1.7% in adults vs 0.6% in paediatrics vs 6.1% in elderly]).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1753 (24.4% of the cases reporting neurological AESIs). A higher reporting proportion of neurological AESIs was reported in subjects without significant comorbidities (75.6%) when compared to subjects with significant comorbidities.

The reporting proportion of neurological AESIs with fatal outcome (1.6%) is higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (0.5% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for ADEM, Encephalopathy, Fibromyalgia, Guillain-Barre syndrome, Meningitis, Meningitis aseptic, Multiple sclerosis, Multiple sclerosis relapse, Myelitis transverse, Neuropathy peripheral, Optic neuritis, Polyneuropathy and Seizure/Seizure disorders (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Conclusion

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

16.3.3.1.12. Other AESIs

Search criteria - HLT (All Path) Herpes viral infections OR PTs Adverse event following immunisation; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Occupational exposure to communicable disease; Patient isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive.

Upon review, 310 PM cases were determined to be non-contributory and were not included in the discussion since these 310 cases involved subjects exposed to the vaccine during the mother' pregnancy or through breastfeeding.[61]

Clinical Trial Data

- Number of cases: 2 (blinded therapy [1] and BNT162b2 [1]) (0.28% of 721 cases, the total CT dataset) compared to 3 cases (0.43%) retrieved in the PSUR #1.
- Country of incidence: (1 each).
- Subjects' gender: (2).
- Subjects' age in years (n = 2), reported ages were years
- Relevant Medical history: None
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PT: Pyrexia (2), not related to BNT162b2. In 1 case, the event Pyrexia is related to BNT162b2.

Post-Authorisation Data

- Number of cases: 118,843 (18.1% of 657,528 cases, the total PM dataset), compared to 70,105 cases (21.4%) retrieved in the PSUR #1.
- MC cases (62,819), NMC cases (56,024).
- Country of incidence (≥100 occurrences): Japan (40,066), Netherlands (11,361), Germany (9893), UK (7424), US (6941), Italy (5921), Spain (5696), France (4749),

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Denmark (2718), Australia (2185), Sweden (2151), Belgium (1698), Austria (1692), Czech Republic (1655), Mexico (1344), Malaysia (1152), Norway (1069), Canada (1012), Philippines (981), Croatia (835), Lithuania (776), Portugal (743), Finland (680), Brazil (630),Ireland (527), Greece (496), Switzerland (468), Romania (442), Poland (421), Estonia (401), Iraq (263), New Zealand, South Africa (192 each), Bahrain (189), Israel (181),Hungary (168), Taiwan, province of China (167), Latvia (162), Iceland, Panama (129 each); the remaining 944 cases were distributed among 56 countries.

- Subjects' gender: female (82,640), male (31,838), and unknown/no data (4365).
- Subjects' age in years (n = 1,06,902)[82], range: 5 – 109, mean: 43.3, median: 42.
- Medical history (n = 33,885): the most frequently (≥50 occurrences) relevant medical conditions included Herpes zoster (431), Breast cancer (365), Immunodeficiency (355), Neoplasm malignant (136), Prostate cancer (102), Neoplasm (63), Lung neoplasm malignant (56), Colon cancer (53).
- COVID-19 Medical history (n = 7724): the most frequently (≥10 occurrences) reported medical conditions included COVID-19 (5203), Suspected COVID-19 (2300), SARS-CoV-2 test positive (56), COVID-19 pneumonia (42), Post-acute COVID-19 syndrome (39), Exposure to SARS-CoV-2 (21), Asymptomatic COVID-19 (18), COVID-19 immunisation (15), SARS-CoV-2 test negative (11), SARS-CoV-2 test (10)
- Co-suspects (n = 339): the reported relevant co-suspect medications were adalimumab (45), methotrexate (17), infliximab (9), etanercept (6), rituximab (3), apixaban (2).
- Number of relevant events: 1,20,223.
- Relevant event seriousness: serious (15,826), nonserious (1,04,411).
- Most frequently reported relevant PTs (≥ 50 occurrences): Pyrexia (105720), Herpes zoster (9297), Inflammation (2216), Oral herpes (1209), Ophthalmic herpes zoster (346), Herpes simplex (273), Herpes virus infection (267), Genital herpes (193), Herpes zoster oticus (94), Varicella (89), Herpes zoster reactivation (78), Varicella zoster virus infection (58), Herpes ophthalmic (52).
- Time to relevant event onset (n = 93499),[83] range: <24 hours to 180 days, median: 1 day.
    - <24 hours: 30,784 events (35 of which had a fatal outcome);
    - 1 day: 43,309 events (47 of which had a fatal outcome);
    - 2-7 days: 10,725 events (46 of which had a fatal outcome);

[82] Of note there were 20 cases with contradictory demographic information (physical characteristics not matching with the reported age value).

[83] This number does not include 27,172 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 8-14 days: 3281 events (28 of which had a fatal outcome);
  - 15-30 days: 3060 events (16 of which had a fatal outcome);
  - 31-180 days: 2340 events (24 of which had a fatal outcome).

- Duration of relevant events (n = 26698 out of 57129 occurrences with outcome of resolved/ resolved with sequelae), range: from 1 second to 169 days; median: 8 hrs

  - <24 hours: 2826 events;
  - 1 day: 10648 events;
  - 2-7 days: 11295 events;
  - 8-14 days: 975 events;
  - 15-30 days: 767 events;
  - 31-180 days: 187 events.

- Relevant event outcome[47]: fatal (257), resolved or resolving (76980), resolved with sequelae (1023), not resolved at the time of reporting (18418), and unknown/no data (23832).

- In 257 cases, the reported cause of death (≥50 occurrences) was coded to the PTs Pyrexia (223). Most (178 of 257 cases) of the fatal cases involved elderly subjects.

Analysis by age group

- CT: Paediatric (2).

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

- PM: Paediatric (3389), Adult (73,062), Elderly (34382), and Unknown (8010).

  - Among the frequently (≥2%) reported relevant Other AESI events, PTs Pyrexia and Inflammation were reported significantly higher in elderly population when compared to adult population (Pyrexia [36% in adults vs 61.9% in elderly], Inflammation [0.6% in adult vs 1.9% in elderly]).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 12002 (10.1% of the cases reporting other AESI). A higher reporting proportion of other AESIs was reported in population without significant comorbidities (89.9%) when compared to population with significant comorbidities.

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

O/E Analysis

O/E analysis was performed on Herpes zoster, Multisystem inflammatory syndrome (see Appendix 6B *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.
- No safety signals have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

16.3.3.1.13. 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; Renal failure neonatal; Renal impairment neonatal; Stillbirth; Uterine rupture; Vasa praevia.

For relevant cases, please refer to the Section 16.3.5.3 *Use in Pregnant/Lactating Women.*

16.3.3.1.14. Renal AESIs

Search criteria - PTs Acute kidney injury; Renal failure.

Upon review, 2 cases were determined to be noncontributory and were not included in the discussion since these cases involved subjects exposed to the vaccine during the mother' pregnancy or through breastfeeding.

Clinical Trial Data

- Number of cases: 7 (BNT162b2 [4] and blinded therapy [3]) (0.97% of 721 cases, the total CT dataset) compared to 3 cases (0.43%) retrieved in the PSUR #1.
- Country of incidence: US (7).
- Subjects' gender: female (3), male (4).
- Subjects' age in years (n = 7), range: 44 – 78, mean: 63.9, median: 68.
- Medical history (n = 3): the relevant medical histories included Chronic kidney disease and Type 2 diabetes mellitus (2 each), Obesity, Blood cholesterol increased, Hypothyroidism (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PT (7): Acute kidney injury (7). Of the above SAEs, none was assessed as related to BNT162b2/blinded therapy.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 612 (0.09% of 657,528 cases, the total PM dataset), compared to 387 cases (0.12%) retrieved in the PSUR #1.
- MC cases (415), NMC cases (197).
- Country of incidence: France (141), Germany (122), Italy (42), Japan (41), US (40), Spain (31), UK (30), New Zealand (15), Austria (14), Netherlands (13), Australia (12), Malta (11); the remaining 100 cases were distributed among 29 countries.
- Subjects' gender: female (261), male (345), and Unknown (6).
- Subjects' age in years (n = 583), range: 12 – 104, mean: 65, median: 70.0.
- Medical history (n = 462): the most frequently (≥5 occurrences) reported medical conditions included Diabetes mellitus (59), Chronic kidney disease (51), Type 2 diabetes mellitus (49), Obesity (30), Renal failure (18), Renal transplant (14), Acute kidney injury (8), Blood cholesterol increased (6), Renal disorder, Renal impairment (5 each).
- COVID-19 Medical history (n = 20): COVID-19 (14), Suspected COVID-19 (5), Asymptomatic COVID-19 (1).
- Co-suspects (n= 36): the reported relevant co-suspect medications included methotrexate sodium, ibuprofen (2 each), cyclosporin, zoledronic acid (1 each).
- Number of relevant events: 626
- Relevant event seriousness: serious (624), nonserious (2).
- Most frequently reported relevant PTs: Acute kidney injury (337), Renal failure (289).
- Time to relevant event onset (n = 346)[84], range: <24 hours to 180 days, median: 9 days.
  - <24 hours: 17 events (4 of which had a fatal outcome);
  - 1 day: 31 events (31 of which had a fatal outcome);
  - 2-7 days: 105 events (18 of which had a fatal outcome)
  - 8-14 days: 59 events (12 of which had a fatal outcome);
  - 15-30 days: 58 events (9 of which had a fatal outcome);
  - 31-180 days: 76 events (8 of which had a fatal outcome).
- Duration of relevant events (n = 18 out of 85 occurrences with outcome of resolved/resolved with sequelae), range: 3 - 68 days; Median 68 days
  - 2-7 days: 5 events;
  - 8-14 days: 4 events;
  - 15-30 days: 5 events;
  - 31-180 days: 4 events.

[84] This number does not include 280 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Relevant event outcome:[47] fatal (102), resolved or resolving (152), resolved with sequelae (21), not resolved at the time of reporting (133), and unknown (218).
- In 102 cases, the reported cause of death was coded to the PTs Renal failure (50), Acute kidney injury (37). Most (87 of 102 cases) of the fatal cases involved elderly subjects. When the medical history was provided (73 cases), significant medical conditions included Diabetes mellitus (20), Chronic kidney disease (14), Type 2 diabetes mellitus (11), Renal failure (10), Obesity (6), Renal impairment (3), Renal cancer, Renal disorder (2 each).

Analysis by age group

- CT: Adult (3), Elderly (4).
- PM: Paediatric (18), Adult (215), Elderly (355) and Unknown (24).
  - No significant `difference observed in the reporting proportion of frequently reported renal AEs (≥2%) between adult and elderly population. However, a higher reporting proportion of events coded to the PT Renal failure was observed in elderly population when compared to adult population (Renal failure [29.8% in adults vs 37.1% in elderly].

Analysis by presence of comorbidities

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

O/E Analysis

O/E analysis was performed for Acute kidney injury and Renal failure (see Appendix 6B *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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16.3.3.1.15. Respiratory AESIs

Search criteria - HLTs (All Path) Lower respiratory tract infections NEC; Respiratory failures (excl neonatal); Viral lower respiratory tract infections OR PTs Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Respiratory disorder.[85]

Upon review, 8 cases were determined to be non-contributory and were not included in the discussion since these cases involved subjects exposed to the vaccine during the mother' pregnancy or through breastfeeding.[61]

Clinical Trial Data

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

---

[85] The PTs Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, Coronavirus pneumonia, Pneumonia viral, Post-acute COVID-19 syndrome and Suspected COVID-19 are evaluated in Section 16.3.3.1.4 *COVID-19 AESIs*; the PT Embolic pneumonia is evaluated in Section 16.3.3.1.18 *Thromboembolic AESIs* while Herpes simplex bronchitis, Herpes simplex pneumonia, Lower respiratory tract herpes infection, Pneumonia herpes viral and Varicella zoster pneumonia are evaluated in Section 16.3.3.1.12 *Other AESIs*.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 3356 (0.51% of 657,528 cases, the total PM dataset), compared to 2263 cases (0.7%) retrieved in the PSUR #1.
- MC cases (2014), NMC cases (1342).
- Country of incidence: Japan (614), France (515), Germany (375), UK (258), US (188), Italy (187), Netherlands, Belgium (140 each), Spain (119), Australia (98), Finland (53), Sweden (52), Norway (51), Austria (50); the remaining 516 cases were distributed among 45 countries.
- Subjects' gender: female (1738), male (1560), and unknown (58).
- Subjects' age in years (n = 3169), range: 6 – 100, mean: 61.3, median: 65.0.
- Medical history (n = 2190): the most frequently (≥5 occurrences) reported medical conditions included Asthma (195), Chronic obstructive pulmonary disease (147), Pneumonia (80), Seasonal allergy (62), Pulmonary embolism (36), Lower respiratory tract infection (29), Lung neoplasm malignant (23), Pneumonia aspiration (22), Respiratory failure (20), Bronchitis (18), Chronic respiratory failure (17), Bronchitis chronic (15), Lung disorder (14), Pulmonary fibrosis (13),Respiratory tract infection (8), Upper Respiratory infection (5).
- COVID-19 Medical history (n = 208): the most frequently reported medical conditions (≥2 occurrences) included COVID-19 (138), Suspected COVID-19 (48), COVID-19 pneumonia (10), Exposure to SARS-CoV-2 (6), Asymptomatic COVID-19, SARS-CoV-2 test positive (2 each).
- Co-suspects (n = 119): the reported relevant co-suspect medications included adalimumab (12), atorvastatin, methotrexate (5 each), etanercept (2), amiodarone hydrochloride (1)
- Number of relevant events: 3624
- Relevant event seriousness: serious (3162), nonserious (462).
- Most frequently reported relevant PTs (≥ 100 occurrences): Pneumonia (1249), Respiratory disorder (492), Cardio-respiratory arrest (370), Respiratory failure (335), Bronchitis (309), Hypoxia (240), Lower respiratory tract infection (205), Pneumonia aspiration (109), Acute respiratory failure (106) and Acute respiratory distress syndrome (103).
- Time to relevant event onset (n = 2378),[86] range: <24 hours to 180 days, median: 4 days.
  - <24 hours: 347 events (58 of which had a fatal outcome);
  - 1 day: 373 events (109 of which had a fatal outcome);
  - 2-7 days: 723 events (166 of which had a fatal outcome);

[86] This number does not include 1251 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 8-14 days: 281 events (59 of which had a fatal outcome);
  - 15-30 days: 283 events (67 of which had a fatal outcome);
  - 31-180 days: 371 events (75 of which had a fatal outcome).

- Duration of relevant events (n = 202 out of 560 occurrences with outcome of resolved/resolved with sequelae), range: from 2 minutes to 150 days, median: 7 days

  - <24 hours: 16 events;
  - 1 day: 20 events;
  - 2-7 days: 50 events;
  - 8-14 days: 39 events;
  - 15-30 days: 39 events;
  - 31-180 days: 38 events.

- Relevant event outcome:[47] fatal (737), resolved or resolving (1076), resolved with sequelae (82), not resolved at the time of reporting (709), and unknown (1024).

  - In 737 cases, the reported cause of death (≥10 occurrences) was coded to the PTs Cardio-respiratory arrest (269), Pneumonia (159), Respiratory failure (100), Pneumonia aspiration (42), Acute respiratory distress syndrome (41), Acute respiratory failure (39), Hypoxia (30), Respiratory disorder (21), Cardiopulmonary failure (16). Most (546 of 737 cases) of the fatal cases involved elderly subjects. When the medical history was provided (600 cases), significant medical conditions included Chronic obstructive pulmonary disease (52), Asthma (28), Pneumonia (23), Tobacco user (20), Lung neoplasm malignant, Pneumonia aspiration (18 each), Interstitial lung disease (15), Pulmonary embolism (13).

Analysis by age group

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

- PM: Paediatric (73), Adult (979), Elderly (2163) and Unknown (141).

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

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 1362 (40.1% of the cases reporting respiratory AESIs). A higher reporting proportion of respiratory AESIs was reported in

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

subjects without significant comorbidities (59.9 %) when compared to subjects with significant comorbidities.

- The reporting proportion of respiratory events with resolved (14.9%) is higher in individuals without comorbid conditions when compared to the reporting proportion observed in the individuals with comorbidities (5.4% of events with resolved).

O/E Analysis

- O/E analysis was performed for Acute respiratory distress syndrome (see Appendix 6B *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.

16.3.3.1.16. Stroke

Search criteria - HLT Central nervous system haemorrhages and cerebrovascular accidents (All path); Cerebrovascular venous and sinus thrombosis (Primary Path).[87]

Clinical Trial Data

- Number of cases: 19 (blinded therapy [10] and BNT162b2 [9]) (2.6% of 721 cases, the total CT dataset) compared to 20 cases (2.8%) retrieved in the PSUR #1.
- Country of incidence: US (14), China (3), [redacted] (1 each).
- Subjects' gender: female (8) and male (11).
- Subjects' age in years (n = 19), range: 17 – 82, mean: 62.7, median: 66.0.
- Medical history (n = 18): the relevant medical conditions reported more than twice were coded to the PTs Hypertension (12), Hyperlipidaemia, Obesity, Thrombosis, and Type 2 diabetes mellitus (3 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs (20): Cerebrovascular accident (10), Cerebral infarction (3), Cerebral haemorrhage, Ischaemic stroke (2 each), Brain stem infarction, Cerebral venous thrombosis, and Intraventricular haemorrhage (1 each). None of the SAEs were assessed as related to BNT162b2 or blinded therapy.

[87] The PT Septic cerebral embolism is evaluated in Section 16.3.3.1.18 Thromboembolic AESIs.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 4834 (0.7% of 657,528 cases, the total PM dataset), compared to 2930 cases (0.9%) retrieved in the PSUR #1.
- MC cases (2571), NMC cases (2263).
- Country of incidence: Germany (1098), Japan (720), France (659), UK (325), US (269), Italy (230), Netherlands (209), Denmark (119), Australia (118), Sweden (107), New Zealand (100); the remaining 880 cases were distributed among 54 countries.
- Subjects' gender: female (2428), male (2299), and unknown (107).
- Subjects' age in years (n = 4528), range: 12 – 102, mean: 57.0, median: 66.0.
- Medical history (n = 2982): the most frequently (≥100 occurrences) reported relevant medical conditions were coded to the PTs Hypertension (1109), Diabetes mellitus (240), Atrial fibrillation (201), Dyslipidaemia (191), Cerebrovascular accident (190), Tobacco user (187), Type 2 diabetes mellitus (177), Obesity (140), Cerebral infarction (122), and Hypercholesterolaemia (115).
- COVID-19 medical history (n = 144): the medical conditions reported more than once were coded to the PTs COVID-19 (102), Suspected COVID-19 (36), Coronavirus infection (4), Asymptomatic COVID-19 (3), and COVID-19 pneumonia (2).
- Co-suspects (n = 130 cases): Frequently (≥3 occurrences) reported relevant co-suspect vaccines/medications were COVID-19 AstraZeneca vaccine (12), ethinylestradiol/levonorgestrel (8), desogestrel/ethinylestradiol, rivaroxaban (4 each), adalimumab, apixaban, levonorgestrel/ethinyl estradiol, and methotrexate (3 each).
- Number of relevant events: 5538.
- Relevant event seriousness: serious (5538) [88].
- Most frequently reported relevant PTs (≥2%): Cerebrovascular accident (1830), Cerebral infarction (984), Ischaemic stroke (609), Cerebral haemorrhage (534), Cerebral venous sinus thrombosis (250), Cerebral thrombosis (173), Cerebral venous thrombosis (138), and Cerebral ischaemia (124).
- Time to relevant event onset (n = 4310) [89], range: <24 hours to 265 days, median: 8 days.
  - <24 hours: 377 events (33 of which had a fatal outcome);
  - 1 day: 462 events (40 of which had a fatal outcome);
  - 2-7 days: 1301 events (132 of which had a fatal outcome);
  - 8-14 days: 748 events (48 of which had a fatal outcome);
  - 15-30 days: 803 events (74 of which had a fatal outcome);

[88] For 1 event coded to the PT Cerebrovascular accident, the seriousness was upgraded from non-serious to serious after data lock point.

[89] This number does not include 3 events for which partial administration and/or event onset dates were reported.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 31-181 days: 604 events (55 of which had a fatal outcome);
- 182-265 days: 15 events (4 of which had a fatal outcome).

- Duration of relevant events (n = 339 out of 1246 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 156 days, median 9 days.

  - 1 day: 59 events;
  - 2-7 days: 102 events;
  - 8-14 days: 44 events;
  - 15-30 days: 82 events;
  - 31-180 days: 52 events.

- Relevant event outcome:[47] fatal (524), resolved or resolving (1719), resolved with sequelae (696), not resolved at the time of reporting (1267), and unknown (1342).

  - In 441 cases (reporting 524 relevant events with a fatal outcome), the reported cause of death (≥15 occurrences) were coded to the PTs Cerebral haemorrhage (126), Cerebrovascular accident (123), Cerebral infarction (51), Haemorrhagic stroke, Ischaemic stroke (30 each), Headache (18), Cerebral venous sinus thrombosis (17), Cardiac arrest and Cerebral thrombosis (15 each). Of note, in 16 cases limited information regarding the cause of death was provided (PT Death) or not reported cause of death. Most (312 of 441 cases) of the fatal cases involved elderly subjects. When the medical history was provided (293 cases), significant medical conditions included atrial fibrillation, cardiac failure, cerebrovascular accident, cerebral haemorrhage, cerebral infarction, chronic kidney disease, chronic obstructive pulmonary disease, hypertension, and myocardial ischaemia.

Analysis by age group

- CT: Paediatric (1), Adult (8), and Elderly (10)

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

- PM: Paediatric (40), Adult (2096), Elderly (2437), Unknown (261).

  - Due to low volume of paediatric cases a meaningful comparison of the same with the other age groups was not possible. Among the frequently (≥2%) reported relevant stroke events, PTs Cerebral venous sinus thrombosis and Cerebral venous thrombosis were reported significantly higher in adult population (9.0% and 5.2%, respectively) when compared to elderly population (1.7% and 1.1%, respectively).

Analysis by presence of comorbidities

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- The reporting proportion of stroke AESIs with fatal outcome (13.1%) is slightly higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (8.0% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Ischemic stroke and Hemorrhagic stroke (see Appendix 6B *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.

16.3.3.1.17. Sudden Death

Search criteria - PT Sudden Death.

Please refer to Section 16.3.4.1.

16.3.3.1.18. Thromboembolic AESIs

Search criteria - HLGT (All path) Embolism and thrombosis (excluding PTs reviewed as Stroke AESIs) OR PT Coagulopathy.[90]

Clinical Trial Data

- Number of cases: 15 (BNT162b2 [8], blinded therapy [6] and placebo [1]) (2.1% of 721 cases, the total CT dataset) compared to 23 cases (3.3%) retrieved in the PSUR #1.
- Country of incidence: US (9), Argentina (4), [redacted] (1 each).
- Subjects' gender: female (7) and male (8).
- Subjects' age in years (n = 15), range: 43 – 79, mean: 63.1, median: 68.0.
- Medical history (n = 13): the frequently (≥2 cases) reported relevant medical conditions were coded to the PTs Hypertension, Obesity (6 each), Asthma (4), Ex-tobacco user, Type 2 diabetes mellitus (3 each), and Deep vein thrombosis (2).
- COVID-19 medical history: None.
- Co-suspects: None.

[90] The PTs Antiphospholipid syndrome and Heparin-induced thrombocytopenia are evaluated in Section 16.3.3.1.8 Immune-mediated/autoimmune AESIs. Other PTs are evaluated in Section 16.3.3.1.16 Stroke.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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

Post-Authorisation Data

- Number of cases: 6507 (1.0% of 657,528 cases, the total PM dataset), compared to 4725 cases (1.4%) retrieved in the PSUR #1.
- MC cases (4108), NMC cases (2399).
- Country of incidence: Germany (1227), France (1225), UK (500), Italy (454), Australia (371), Netherlands (335), Sweden (252), Japan (251), Spain (217), US (198), Norway (151), Denmark (140), Austria (137), New Zealand (129), Belgium (127), Finland (114); the remaining 679 cases were distributed among 45 countries.
- Subjects' gender: female (3223), male (3176) and unknown (108).
- Subjects' age in years (n = 6245), range: 6 months –100 years, mean: 55.4, median: 57.0.
- Medical history (n = 3804): the most frequently (≥2%) reported relevant medical conditions were coded to the PTs Hypertension (944), Obesity (294), Deep vein thrombosis (266), Tobacco user (238), Asthma (223), Pulmonary embolism (201), Dyslipidaemia (180), Type 2 diabetes mellitus (158), Hypothyroidism (140), Hypercholesterolaemia (122), Diabetes mellitus (118), Chronic obstructive pulmonary disease (114), Atrial fibrillation, Overweight (97 each), Ex-tobacco user (93), Osteoarthritis (88), and Thrombosis (87).
- COVID-19 Medical history (n = 269): the medical conditions reported more than twice were coded to the PTs COVID-19 (200), Suspected COVID-19 (48), COVID-19 pneumonia (13), SARS-CoV-2 test positive (5), Asymptomatic COVID-19 (4), and Exposure to SARS-CoV-2 (3).
- Co-suspects (n = 216): the most frequently (≥5 occurrences) reported relevant co-suspect vaccines/medications were COVID-19 AstraZeneca vaccine (40), ethinylestradiol/levonorgestrel (24), drospirenone/ethinylestradiol (14), and adalimumab (5).
- Number of relevant events: 7443.
- Relevant event seriousness: serious (7299), non-serious (144).
- Most frequently reported relevant PTs (≥2%): Pulmonary embolism (3408), Deep vein thrombosis (2171), Coagulopathy (221), Retinal vein occlusion (215), Embolism and Pulmonary thrombosis (132 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Time to event onset (n = 5725),[91] range: <24 hours to 256 days, median: 11 days.
  - <24 hours: 251 events (16 of which had a fatal outcome);
  - 1 day: 424 events (29 of which had a fatal outcome);
  - 2-7 days: 1557 events (64 of which had a fatal outcome);
  - 8-14 days: 1122 events (45 of which had a fatal outcome);
  - 15-30 days: 1266 events (55 of which had a fatal outcome);
  - 31-181 days: 1080 events (38 of which had a fatal outcome);
  - 182-256 days: 25 events.
- Duration of relevant events (n = 276 out of 998 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 153 days, median: 13 days.
  - 1 day: 16 events;
  - 2-7 days: 81 events;
  - 8-14 days: 51 events;
  - 15-30 days: 62 events;
  - 31-181 days: 66 events.
- Relevant event outcome:[47] fatal (374), resolved/resolving (3200), resolved with sequelae (297), not resolved at the time of reporting (2159), and unknown (1430).
  - In 327 cases (reporting 374 relevant events with a fatal outcome), the reported cause of death (≥15 occurrences) was coded to the PTs Pulmonary embolism (213), Deep vein thrombosis (27), Cardiac arrest (23), Dyspnoea (19), Embolism (17), and Disseminated intravascular coagulation (16). Of note, in 15 cases limited information regarding the cause of death was provided (PT Death) or not reported the cause of death. Most (190 of 327 cases) of these fatal cases involved elderly subjects. When the medical history was provided (223 cases), significant medical conditions included atrial fibrillation, asthma, cardiac failure, chronic obstructive pulmonary disease, deep vein thrombosis, hospitalisation, pulmonary embolism, renal failure, myocardial ischaemia, surgeries, and various malignancies.

Analysis by age group

- CT: Adults (7) and Elderly (8).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

[91] This number does not include 4 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- PM: Paediatric (70), Adults (3938), Elderly (2278) and Unknown (221).
  - Except for the PT Coagulopathy, no significant difference observed in the reporting proportion of frequently (≥2%) reported thromboembolic AESIs, between paediatric, adult and elderly population. The reporting proportion of PT Coagulopathy was significantly higher in paediatric population (17.1%) when compared to adult and elderly population (3.5% and 2.4% in adult and elderly population, respectively).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1750 (26.8% of the CT and PM cases reporting thromboembolic events).
- The reporting proportion of thromboembolic events with fatal outcome (7.7%) is slightly higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (4.1%).

O/E Analysis

O/E analysis was performed for Deep vein thrombosis, Disseminated intravascular coagulation, and Pulmonary embolism (see Appendix 6B *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.

16.3.3.1.19. Vasculitic events

Search criteria - HLT (All Path) Vasculitides OR PTs Microangiopathy; Peripheral

Upon review, 1 case was determined to be non-contributory and was not included in the discussion since involved a subject exposed to the vaccine through breastfeeding.[61]

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 854 (0.13% of 657,528 cases, the total PM dataset), compared to 360 cases (0.1%) retrieved in the PSUR #1.
- MC cases (546), NMC cases (308).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence: France (164), Germany (149), Japan (96), Italy (68), UK (64), Netherlands (44), US (40), Spain (28), Sweden (21), Australia (20); the remaining 160 cases were distributed among 31 countries.
- Subjects' gender: female (508), male (325), and unknown (21).
- Subjects' age in years (n = 326), range: 13 – 99, mean: 58.9, median: 68.
- Medical history (n = 506): the most frequently (≥ 5 occurrences) reported relevant medical conditions included Hypertension (133), Type 2 diabetes mellitus (25), Diabetes mellitus, (24), Tobacco user, Drug hypersensitivity (22 each), Obesity (19), Hypercholesterolaemia (17), Behcet's syndrome, Rheumatoid arthritis (14 each), Vasculitis (13), Dyslipidaemia (11), Hypersensitivity (7), and Myocardial infarction (5).
- COVID-19 Medical history (n = 39): COVID-19 (28), Suspected COVID-19 (8), and Asymptomatic COVID-19, SARS-CoV-2 antibody test negative, SARS-CoV-2 test positive (1 each).
- Co-suspects (n = 17): relevant co-suspect included propylthiouracil (1).
- Number of events: 927
- Relevant event seriousness: serious (697) and nonserious (230).
- Most frequently reported relevant PTs (≥20 occurrences): Vasculitis (330), Giant cell arteritis (119), Cutaneous vasculitis (114), Peripheral ischaemia (77), Henoch-Schonlein purpura (70), Vasculitic rash (27), Behcet's syndrome (24), Hypersensitivity vasculitis (23), Anti-neutrophil cytoplasmic antibody positive vasculitis (22).
- Time to event onset (n = 637),[92] range: <24 hours to 174 days, median: 19 days.
  - <24 hours: 43 events; (1 of which had a fatal outcome);
  - 1 day: 55 events:
  - 2-7 days: 215 events (3 of which had a fatal outcome);
  - 8-14 days: 102 events (3 of which had a fatal outcome);
  - 15-30 days: 111 events (2 of which had a fatal outcome);
  - 31-181 days: 111 events (4 of which had a fatal outcome).
- Duration of relevant events (n = 59 out of 166 occurrences with outcome of resolved/resolved with sequelae); range: 20 hrs to 164 days, median: 7 days.
  - <24 hours: 1 event;
  - 1 day: 2 events;
  - 2-7 days: 14 events;
  - 8-14 days: 13 events;
  - 15-30 days: 19 events;

[92] This number does not include 292 events for which partial administration or event onset date was reported.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 31-180 days: 10 events.

- Relevant event outcome:[47] fatal (22), resolved/resolving (355), resolved with sequelae (27), not resolved at the time of reporting (307), and unknown (217).
  - In 22 cases (reporting 22 relevant events with a fatal outcome), the reported cause of death (≥2 occurrences) were coded to the PTs Vasculitis (10), Peripheral ischaemia (7), Anti-neutrophil cytoplasmic antibody positive vasculitis, Giant cell arthritis (2 each) and Henoch-Schonlein purpura (1 each). Most (14 of 22 cases) of these fatal cases involved subjects who were ≥65 years of age. When the medical history was provided, medical conditions included chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, giant cell arteritis, chronic lymphocytic leukaemia, follicular lymphoma, rheumatoid arthritis.

Analysis by age group

- PM: Paediatric (44), Adults (437), Elderly (328) and Unknown (45).
  - 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 (26.9% in elderly vs 5.3% 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: 302 (35.4% of the PM cases reporting vasculitic events).
- The reporting proportion of vasculitic AESIs with a fatal outcome (3.4%) is higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subject without comorbidities (1.8% for fatal outcome).

O/E Analysis

O/E analysis was performed for Behcet's syndrome, Cutaneous vasculitis, Giant cell arteritis, Limb ischaemia, Vasculitic rash, and Vasculitis (see Appendix 6B *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.

16.3.3.1.20. 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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

additional data on vaccine immunogenicity, effectiveness and safety on population groups represented in Low- and Middle-Income Countries (LMICs) including individuals with conditions such as malnutrition and populations with existing co-morbidities such as tuberculosis, human immunodeficiency virus (HIV) infection and other high prevalent infectious diseases.

Search criteria - PT Decode (History): Acute HIV infection; Asymptomatic HIV infection; Congenital HIV infection; HIV infection; HIV infection CDC Group I; HIV infection CDC Group II; HIV infection CDC Group III; HIV infection CDC Group IV subgroup A; HIV infection CDC Group IV subgroup B; HIV infection CDC Group IV subgroup C1; HIV infection CDC Group IV subgroup C2; HIV infection CDC Group IV subgroup D; HIV infection CDC Group IV subgroup E; HIV infection CDC category A; HIV infection CDC category B; HIV infection CDC category C; HIV infection CDC group IV; HIV infection WHO clinical stage I; HIV infection WHO clinical stage II; HIV infection WHO clinical stage III; HIV infection WHO clinical stage IV; Malnutrition; Perinatal HIV infection; Prophylaxis against HIV infection; Tuberculosis.

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 393 (0.06% of 657,528 cases, the total PM dataset), compared to 294 cases (0.09%) retrieved in the PSUR #1.

Patients with pre-existing HIV Infection: 201 (0.03% of 657,528 cases, the total PM dataset).

- MC cases (98), NMC cases (103).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence[93]: France (80), US (39), UK (18), Italy (10), Germany (8), Netherlands (6), South Africa, Switzerland (5 each), Belgium, Canada (4 each), Sweden (3), Austria, Brazil, Panama, Portugal, Spain, Taiwan (2 each). The remaining 7 cases were distributed among 7 countries.
- Subjects' gender: female (43), male (148) and unknown (10).
- Subjects' age in years (n = 190), range: 18 – 89, mean: 48.3, median: 50.
- COVID-19 Medical history (n = 17): COVID-19 (12), Suspected COVID-19 (5).
- Co-suspect vaccines/medications (7): Bictegravir/emtricitabine/tenofovir (2), Anakinra, caffeine/papaver somniferum tincture/paracetamol, celecoxib, COVID-19 vaccine (unspecified), cyproterone/ethinylestradiol, dexamethasone, emtricitabine, fluconazole, paracetamol, sulfamethoxazole/trimethoprim, tenofovir, tramadol (1 each).
- Of the 201 cases reporting a pre-existing HIV condition, 13 subjects reported cardiac disorders. The events in these cases were coded to PTs Myocarditis (5), Palpitations (3), Angina pectoris (2), Atrial fibrillation, Bundle branch block right, Myocardial infarction, Myocarditis post infection, Pericardial haemorrhage, Pericarditis, Tachycardia (1 each). Of the 17 events 16 were assessed as serious and 1 event were non-serious. Outcome of the events was reported as fatal (1), resolved with sequelae (2), resolved/resolving (6), not resolved (3), and unknown (5).
- Of the 201 cases, 78 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (32), Dizziness (14), Paraesthesia (9), Facial paralysis (8), Somnolence (5), Hypoaesthesia (4), Balance disorder, Cerebrovascular accident, Paralysis, Parosmia, Partial seizures, Seizure (2 each), Ageusia, Anaesthesia, Axonal and demyelinating polyneuropathy, Bell's palsy, Burning sensation, Cerebral venous thrombosis, Disturbance in attention, Epilepsy, Guillain-Barre syndrome, Hemiparesis, Hemiplegia, Hyperaesthesia, Hypersomnia, Ischaemic cerebral infarction, Loss of consciousness, Migraine, Nervous system disorder, Paraparesis, Polyneuropathy, Postictal paralysis, Sensory disturbance, and Tremor (1 each). Forty-nine (49) were assessed as serious and 57 were non-serious. Outcome of the events[47] was reported as fatal (1), resolved/resolving (47), resolving with sequelae (1), not resolved (32), and unknown (26).
- Of the 201 cases, 24 subjects reported infectious events. The events in these cases were coded to PTs COVID-19 (8), Herpes zoster (3), Cellulitis, COVID-19 pneumonia, Eye infection, Herpes simplex, Herpes simplex reactivation, Infection, Influenza, Labyrinthitis, Nasopharyngitis, Rhinitis, Secondary syphilis, Suspected COVID-19, Syphilis, Syphilis genital, Tonsilitis, Vestibular neuronitis (1 each). Of the 27 events, 18 were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (1), resolved/resolving (11), not resolved (7), and unknown (8).

[93] There were 7 cases reported from low- and middle-income countries (Brazil, Panama [2 each], Albania, Malaysia, and Mexico [1 each]).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Time to event onset (n = 515)[94], range: <24 hours to 185 days, median: 1 day.
  - <24 hours: 167 events (none of which had a fatal outcome);
  - 1 day: 106 events (none of which had a fatal outcome);
  - 2-7 days: 123 events (none of which had a fatal outcome);
  - 8-14 days: 41 events (7 of which had a fatal outcome);
  - 15-30 days: 37 events (1 of which had a fatal outcome);
  - 31-181 days: 39 events (5 of which had a fatal outcome);
  - 185 days: 2 events (none of which had a fatal outcome).
- Duration of events (n = 69)[95], range: <1 day to 60 days, median 2 days.
  - <1 day: 5 events;
  - 1 day: 25 events;
  - 2-7 days: 27 events;
  - 8-14 days: 7 events;
  - 15-30 days: 4 events;
  - 31-60 days: 1 event.
- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing HIV infection when compared to the subjects without the disease.
- Of the 201 cases, 166 cases involved adults, 25 cases involved elderly and in 10 cases age group was not reported. Due to the low volume of cases reported in elderly, it was not possible to make a meaningful comparison between the adults and elderly patient population.

Patients with pre-existing tuberculosis: 139 (0.02% of 657,528 cases, the total PM dataset).

- MC cases (75), NMC cases (64).
- Country of incidence[96]: France (64), US (17), UK (11), Germany, Japan (9 each), Spain (6), Iceland, Italy, South Africa (3 each), Croatia and Sweden (2 each). The remaining 10 cases were distributed among 10 countries.
- Subjects' gender: female (90), male (48), Unknown (1).
- Subjects' age in years (n = 138), range: 22 – 98, mean: 64, median: 67.
- COVID-19 Medical history (n = 7): COVID-19 (5), and Suspected COVID-19 (2).

---

[94] This number does not include 1 event which occurred prior to vaccine administration.

[95] 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.

[96] The cases were not reported from any low- and middle-income countries

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Co-suspect vaccines/medications (3): COVID-19 AstraZeneca vaccine, influenza vaccine, levofloxacin (1 each).
- Of the 139 cases reporting a pre-existing tuberculosis, 30 subjects reported cardiac disorders. The events in these cases were coded to PTs Tachycardia (8), Palpitations (5), Arrhythmia (4), Atrial fibrillation, Cardiac failure, Myocarditis, Pericarditis (3 each), Angina pectoris, Cardiomegaly (2 each), Atrioventricular block complete, Cardiac arrest, Cardiac failure congestive, Cardiac fibrillation, Cardiomyopathy, Cardiovascular disorder, Extrasystoles, Myocardial infarction, Pericarditis constrictive, Supraventricular tachycardia, and Ventricular fibrillation (1 each). Of the 44 events, 35 were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (4), resolved/resolving (28), not resolved (4), and unknown (8).
- Of the 139 cases, 42 subjects reported nervous system disorders. The events in these cases were coded to PTs Headache (15), Dizziness (14), Paraesthesia (6), Tremor (4), Hypoaesthesia, Loss of consciousness (3 each), Hypotonia, Migraine, Sinus headache, Speech disorder (2 each), Ageusia, Altered state of consciousness, Anaesthesia, Anosmia, Aphasia, Axonal and demyelinating polyneuropathy, Axonal neuropathy, Burning sensation, Carotid artery stenosis, Cerebral atrophy, Cerebral ventricle dilatation, Cluster headache, Depressed level of consciousness, Disturbance in attention, Dysstasia, Hemiparesis, Ischaemic stroke, Lacunar stroke, Movement disorder, Myasthenia gravis, Polyneuropathy, Quadriparesis, Sciatic nerve palsy, Syncope, Tension headache, and Transient global amnesia (1 each). Of the 79 events, 38 were assessed as serious and 41 events were non-serious. Outcome of the events was reported as fatal (5), resolved/resolving (36), not resolved (9), resolved with sequelae (2), and unknown (27).
- Of the 139 cases, 25 subjects reported infectious events. The events in these cases were coded to PTs COVID-19 (9), COVID-19 pneumonia (7), Pneumonia (5), Asymptomatic COVID-19 (2), Candida infection, Herpes zoster, Influenza, Oropharyngeal candidiasis, Pericarditis tuberculous, Rhinitis, Sepsis, Septic shock, Sialoadenitis, Superinfection bacterial, and Vulvovaginal candidiasis (1 each). Of the 34 events, 30 were assessed as serious and 4 events were non-serious. Outcome of the events was reported as fatal (5), resolved/resolving (6), not resolved (7), and unknown (16).
- Time to event onset (n = 507), range: <24 hours to 254 days, median: 4 days.
  - <24 hours: 108 events (3 of which had a fatal outcome);
  - 1 day: 62 events (none of which had a fatal outcome);
  - 2-7 days: 153 events (12 of which had a fatal outcome);
  - 8-14 days: 36 events (none of which had a fatal outcome);
  - 15-30 days: 35 events (none of which had a fatal outcome);
  - 31-181 days: 93 events (none of which had a fatal outcome);
  - 182-254 days: 20 events (none of which had a fatal outcome).
- Duration of events (n = 77),[95] range: 1 day to 87 days, median 2 days.
  - 1 day - <2 days: 18 events;
  - 2 - 7 days: 32 events;
  - 8-14 days: 16 events;

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 15-30 days: 6 events;
  - 31-87 days: 5 events.

- There was no trend in the reporting of infections, cardiac disorders and nervous disorders in subjects with pre-existing tuberculosis when compared to the subjects without the disease.

- Of the 139 cases, 63 cases involved adults, and 75 cases involved elderly, and the age group was not reported in 1 case. The reporting proportion of infectious events was higher in elderly (15.8%) compared to the adult population (2.2%); and more adult subjects reported nervous system disorders as compared to the elderly (20.1% in adults vs 9.4% in elderly). No significant difference was observed in the reporting proportion of cardiac events (12.2% in elderly vs 9.4% in adults) between the elderly and adult population.

Patients with pre-existing malnutrition: 52 (<0.01% of 657,528 cases, the total PM dataset).

- MC cases (48), NMC cases (4).
- Country of incidence:[96] France (31), Japan (4), Czech Republic, Germany (3 each), Norway (2); the remaining cases were reported from 9 countries.
- Subjects' gender: female (29), male (23).
- Subjects' age in years (n = 50), range: 22 – 95, mean: 74, median: 79.
- COVID-19 Medical history (n = 2): COVID-19 (1), and Suspected COVID-19 (1).
- Co-suspect medications (3): amiodarone, atorvastatin/ezetimibe, bisoprolol, buspirone, fentanyl, furosemide, levofloxacin, macrogol, metformin, metoclopramide/pancreatin, morphine, paracetamol, phloroglucinol/trimethyl phloroglucinol, potassium chloride, quetiapine, risedronate (1 each).
- In these 52 cases, the most frequently reported events (≥5 occurrences) were COVID19 (13), Dyspnoea (10), Drug ineffective, Vaccination failure (9 each), Asthenia, Inappropriate schedule of product administration (6 each), Cough, General physical health deterioration, and Pyrexia (5 each).
- Of the 52 cases reporting pre-existing malnutrition, 15 subjects reported PTs Asthenia (6), General physical health deterioration (5), Condition aggravated, Decreased appetite (4 each), and Adult failure to thrive, Malnutrition (1 each). Of the total 21 events, 12 events were assessed as serious and 9 events were non-serious. Outcome of the events was reported as fatal (3), resolved/resolving (5), not resolved (2), and unknown (11).
- Time to event onset (n = 244), range: <24 hours to 265 days, median: 12 days.
  - <24 hours: 36 events (9 of which had a fatal outcome);
  - 1 day: 32 events (5 of which had a fatal outcome);
  - 2-7 days: 50 events (20 of which had a fatal outcome);
  - 8-14 days: 13 events (2 of which had a fatal outcome);

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 15-30 days: 22 events (1 of which had a fatal outcome);
- 31-181 days: 70 events (10 of which had a fatal outcome);
- 182-265 days: 21 events (none of which had a fatal outcome).

- Duration of events (n = 17),[95] range: <1 day to 62 days, median 1 week.

  - <1 day: 2 events;
  - 2-7 days: 7 events;
  - 8-14 days: 1 event;
  - 15-62 days: 7 events.

  - Of the 52 cases, 39 were reported in elderly and 13 cases involved adults. Due to the low volume of cases reported in adults, it was not possible to make a meaningful comparison between the adults and elderly patient population.

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 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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 21,269 cases, 29 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- In 4 case the event of interest was due to underlying conditions (thyroid mass/goitre, psoriasis flare-up, right knee infection, and total knee replacement
- In 20 cases the event of interest was attributed to another co-suspect drug and not Covid-19 mRNA vaccine
- Foetuses, neonates, or infants exposed to the vaccine during the mother' pregnancy or exposed through breastfeeding were reported in 5 cases.[61]

Therefore, 21,240 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; no cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 21,240 (3.2% of 657,528 cases, the total PM dataset), compared to 21,806 cases (6.7%) retrieved in the PSUR #1.
- MC cases (11,594), NMC cases (9646).
- Country of incidence (>2%): Japan (6678), UK (3589), Italy (1924), US (1905), Germany (1056), France (992), Netherlands (712), Malaysia (543).
- Subjects' gender: female (16,189), male (4444) and unknown (607).
- Subjects' age in years (n = 19,403), range: 0.06 - 120, mean: 45.2, median: 44.
- Medical history (n = 18,696):[97] the most frequently (≥2%) reported medical conditions included Suppressed lactation[19] (872), Hypertension (869), Seasonal allergy (722), Drug hypersensitivity (707), Asthma (699), Food allergy (656), Hypersensitivity (501), Diabetes mellitus (269), Hypothyroidism (250), Depression (212), Mite allergy (172), Migraine (170).

[97] Some cases reported more than 1 medical history event.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- COVID-19 Medical history (n = 846): COVID-19 (439), Suspected COVID-19 (382), Coronavirus infection (6), Exposure to SARS-CoV-2 (4), Post-acute COVID-19 syndrome (4), SARS-CoV-2 test positive (4), COVID-19 pneumonia (3), Asymptomatic COVID-19 (2), Coronavirus test positive (1), COVID-19 treatment (1).
- Co-suspect vaccines/medications (n = 252): those reported in ≥ 2 cases included Influenza vaccine (41), Adalimumab (12), COVID-19 AstraZeneca vaccine (10), Hepatitis A vaccine (8), Influenza vaccine (surface antigen, inactivated, adjuvanted) (6), BCG vaccine, Macrogol (5 each), COVID-19 Moderna vaccine, Influenza vaccine INACT SPLIT 4V (4 each), Alemtuzumab, Amlodipine besilate, Amoxicillin, Atorvastatin calcium, Diclofenac sodium, Infliximab, Mepolizumab, Methotrexate sodium, Ocrelizumab (3 each), Beclometasone, Cetirizine, Etanercept, Hyaluronic Acid, Influenza vaccine INACT SAG 3V, Lercanidipine Hydrochloride, Levothyroxine, Metamizole sodium, Methylprednisolone, Prednisone, Rituximab, Rosuvastatin, Sulfasalazine (2 each).
- Number of relevant events: 23,092.
- Relevant event seriousness:[20] serious (3341), non-serious (19,756).
- Most frequently reported relevant PTs (≥2%): Erythema (9951), Swelling (9293), Injection site pain (2872), Injection site erythema (560), Injection site swelling (416).
- Most frequently co-reported PTs (> 5%): Pain (4828). Headache (4522), Pyrexia (3787), Pruritus (3579), Fatigue (3195), Malaise (2872), Myalgia (2714), Arthralgia (2169), Vaccination site pain (1996), Pain in extremity (1922), Rash (1751), Lymphadenopathy (1570), Chills (1514), Nausea (1419), Immunisation[23] (1365), Peripheral swelling (1278), Off label use (1169), Axillary pain (1104), and Urticaria (1065).
- Time to event onset (n = 23,163)[98] range: < 24 hours – 175 days, median: 2 days.
  - <24 hours: 7433 cases;
  - 1 day: 4736 cases;
  - 2-7 days: 2953 cases;
  - 8-14 days: 573 cases;
  - 15-30 days: 272 cases;
  - 31-181 days: 185 cases.
- Duration of relevant events (n = 3454 out of 7777 occurrences with outcome of resolved/resolved with sequelae), range: < 24 hours to 536 days median 3.8 days.
  - <24 hours: 724 cases;
  - 1 day: 776 cases;
  - 2-7 days: 1584 cases;
  - 8-14 days: 212 cases;
  - 15-30 days: 97 cases;

[98] This number does not include 7011 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 31-181 days: 61 cases;
  - > 181 days: 3 cases.

- Relevant event outcome:[47] fatal (7), resolved/resolving (11,781), resolved with sequelae (153), not resolved (4435), unknown (6781).

  - Time to onset of fatal events were 1 day (2 events), 5 days (2 events), 7 days (1 event), 11 days (1 event), and 60 days (1 event). There were 7 cases reporting fatal events of interest (Erythema [3 cases] and Swelling [4 case]) in elderly (5 cases) and adult (2 cases) patients. Review of these cases identified additional fatal adverse events reported in these cases. The local adverse reactions were not the primary cause of death in these cases.

Analysis by age group

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

- PM: Paediatric (377), Adults (16,375), Elderly (3030) and Unknown (1458).

Event of Interest	Paediatric (n/%)	Adult (n/%)	Elderly (n/%)	Unknown (n/%)
Erythema	211 (51.7)	7110 (39.9)	1922 (59.2)	708 (44.3)
Injection site erythema	10 (2.5)	421 (2.4)	99 (3.0)	30 (1.9)
Injection site pain	47 (11.5)	2235 (12.5)	468 (14.4)	122 (7.6)
Injection site swelling	8 (2.0)	354 (2.0)	27 (0.8)	27 (1.7)
Swelling	132 (32.4)	7719 (43.3)	730 (22.5)	712 (44.5)
Total[a]	**408**	**17,839**	**3246**	**1599**

a. Some cases reported more than 1 event.

- 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

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

- PM

  - Number of subjects with comorbidities: 2676 (0.4% of 657,528 cases, the total PM dataset). Subjects with comorbidities were reported in 12.6% of the Local adverse Reactions dataset. Given the nature of the adverse events of interest reported (Erythema, Injection site erythema, Injection site pain, Injection site swelling, Swelling) and the percentage of patients with comorbidities in the dataset, there were no differences between the group with comorbidities and the one without comorbidities.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by dose

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

- PM

  - Number of post-authorisation vaccine doses[99] administered at the time of the event onset: Dose 1 in 7311 cases, Dose 2 in 7044 cases, Dose 3 in 1575 cases, Dose 4 in 1 case, and the dose number was not specified in 5319 cases.

PT	Dose 1[a] (n/%)	Dose 2[a] (n/%)	Dose 3[a] (n/%)	Dose 4[a] (n/%)	Dose Unspecified[a] (n/%)
Erythema	3621 (46.2)	3137 (40.2)	647 (37.3)	1 (100)	2581 (44.6)
Injection site erythema	171 (2.2)	157 (2.0)	35 (2.0)	-	197 (3.4)
Injection site pain	1061 (13.5)	496 (6.3)	76 (4.4)	-	1244 (21.5)
Injection site swelling	84 (1.1)	87 (1.1)	17 (1.0)	-	227 (3.9)
Swelling	2905 (37.0)	3936 (50.4)	960 (55.3)	-	1534 (26.5)
Total	**7842**	**7813**	**1735**	**1**	**5783**

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-authorisation events reported across doses were similar with the exception of injection site pain being reported more frequently in the unspecified dose group.

Conclusion

Local adverse reactions were reported in 21,240 cases representing 3.2% of the cases in the reporting period. The majority of events (85.6%) were non-serious events with 51.5% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 7 fatal cases describing local adverse reactions; two were adult and 5 were elderly subjects. Review of these cases indicated that there were additional fatal adverse events reported and the event of interests (Erythema, Swelling) were not the primary cause of death in these subjects. When reported, the majority onset of events occurred within to <24 hours, with durations lasting <24 hours to 7 days.

Evaluation of local adverse reaction cases did not reveal any significant new safety information. Local adverse reactions are appropriately described in the RSI. Surveillance of local adverse reactions will continue.

16.3.3.4. Systemic Adverse Reactions

Search criteria - PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia.

[99] Number of vaccine doses is reported by case number. Twenty-five cases reported invalid dosing details.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Of the 279,349 cases, 161 cases were determined to be non-contributory and were not included in the discussion due to the following reasons:

- neonate, or infants exposed to the vaccine through breastfeeding;[61]
- cases with contradictory demographic information (physical characteristics not matching with the reported age value);
- cases reporting unauthorized use [ie, PT Product administered to patient of inappropriate age, population] are reviewed in Section 16.3.4.6 *Off-Label Use*.

Clinical Trial Data

- Number of cases: 4 (BNT162b2 [2], and blinded therapy [2]) (0.6% of 721 cases, the total CT dataset) compared to 3 cases (0.4%) retrieved in the PSUR #1.
- Country of incidence: US (2), [redacted] (1 each).
- Subjects' gender: [redacted]
- Subjects' age (n = 4), [redacted] years, respectively.
- Medical history (n = 3): Anorexia nervosa, Atrial septal defect, Constipation, Croup infectious, Depression, Depression suicidal, Ehler-Danlos syndrome, Febrile convulsion, Gastrooesophageal reflux disease, Generalised anxiety disorder, Lymphadenopathy, Postural orthostatic Tachycardia syndrome, Seasonal allergy, and Wheezing, (1 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of relevant events: 4.
- Relevant PTs: Arthralgia, and Pyrexia (2 each). Of these SAEs, one event of pyrexia (outcome resolved) was assessed as related to BNT162b2 by the investigator and Sponsor.
- Time to event onset (n = 4): 2, 43, 70, and 112 days, respectively.
- Duration of event (n = 3): 4, 12, and 106 days.
- Relevant event outcome: resolved/resolving (4).

Post-Authorisation Data

- Number of cases: 279,184 (42.5% of 657,528 cases in the total PM dataset), compared to 157,857 cases (48.3%) retrieved in the PSUR #1.
- MC cases (112,997), NMC cases (166,187).
- Country of incidence (top 10 countries): Japan (64,971), Netherlands (49,585), Germany (30,386), UK (26,056), US (15,908), Italy (12,801), France (10,541), Spain (8,392), Australia (6,407), and Denmark (5,242).
- Subjects' gender: female (199,808), male (71,443) and unknown (7933).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Subjects' age in years (n = 254,831), range: 2 – 109, mean: 43.1; median: 41.0.
- Medical history (n = 83310): the most frequently (>1000 cases) reported medical conditions included Hypertension (8372), Asthma (6040), Suppressed lactation[19] (5873), Seasonal allergy (5455), Drug hypersensitivity (5297), Disease risk factor (4463), Food allergy (3905), Hypersensitivity (3624), Hypothyroidism (2595), Migraine (2191), Depression (2163), Diabetes mellitus (2139), Anxiety (1504), Mite allergy (1253), Pain (1226), Fibromyalgia (1224), Gastrooesophageal reflux disease (1139), Type 2 diabetes mellitus (1137), Allergy to animal (1119), Obesity (1118), Autoimmune thyroiditis (1086), Headache (1037), Immunodeficiency (1033), and Rheumatoid arthritis (1020).
- COVID-19 Medical history (n = 19,908): COVID-19 (11753), Suspected COVID-19 (7727), Post-acute COVID-19 syndrome (108), SARS-CoV-2 test positive (105), COVID-19 pneumonia (59), Coronavirus infection (55), Exposure to SARS-CoV-2 (45), Asymptomatic COVID-19 (37), Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive (8 each), and Coronavirus test positive (3).
- Co-suspects (n = 2084): the most frequently (≥20 occurrences) reported co-suspect medications included influenza vaccine (324), COVID-19 vaccine (239 [non-MAH or unspecified]), adalimumab (140), hepatitis A vaccine (56), methotrexate (37), paracetamol (31), ocrelizumab (28), ibuprofen (23), nitrofurantoin, tofacitinib (21 each), etanercept, upadacitinib (20 each).
- Number of relevant events: 545,486.
- Relevant event seriousness: serious (62,906), non-serious (482,720).
- Relevant PTs: Headache (135,032), Fatigue (109,454), Pyrexia (105,981), Myalgia (84,890), Arthralgia (56,609), and Chills (53,520).
- Time to event onset (n = 437,197)[95] range < 24 hours to 365 days, median: 0 days.
  - < 24 hours: 183,028 events (66 of which had a fatal outcome);
  - 1 day: 182,002 events (90 of which had a fatal outcome);
  - 2-7 days: 50,342 events (105 of which had a fatal outcome);
  - 8-14 days: 9726 events (41 of which had a fatal outcome);
  - 15-30 days: 6759 events (24 of which had a fatal outcome);
  - 31-181 days: 4996 events (44 of which had a fatal outcome);
  - 182-240 days: 261 events (2 of which had a fatal outcome);
  - 241-365 days: 83 events (1 of which had a fatal outcome).
- Duration of event (n = 170,217),[95] range: <24 hours to 365 days, median: <24 hours.
  - <24 hours: 22,745 events;
  - 1 day: 3830 events;
  - 2-7 days: 123,243 events;
  - 8-14 days: 9714 events;
  - 15-30 days: 6521 events;

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 31-181 days: 4106 events;
- 182-240 days: 36 events;
- 241-365 days: 22 events.

- Relevant event outcome:[47] fatal (462), not resolved (124,790), resolved/resolving (327,321), resolved with sequelae (3685), and unknown (90779).
  - In 357 cases, the relevant events (462) were reported as fatal: Pyrexia (223), Fatigue, Headache (81 each), Chills (29), Myalgia (28), and Arthralgia (20).[4] In these cases, the most frequently reported other fatal events (>20 occurrences) included Dyspnoea (84), Malaise (56), Asthenia (39), Vomiting (38), Cough (35), COVID-19 (34), Nausea (32), Pneumonia (29), Decreased appetite (27), Cardiac arrest, Immunisation[23] (25 each), Death, and Dizziness (22 each). Most (241 of 357 cases) of the cases with a fatal outcome involved elderly subjects.

Analysis by age group

- CT: Paediatric (2, PT Pyrexia), Adults (1, PT Arthralgia), Elderly (1 PT Arthralgia).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM
  - An analysis of relevant PM events by age group, event seriousness and event outcome are provided in Table 45. Per the RSI, the most frequent systemic adverse reactions in subjects 16 years of age and older (in order from highest to lowest frequencies) were fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), and pyrexia (>10%); the most frequent systemic adverse reactions in adolescents 12 through 15 years of age were fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%). Across the age groups in the table below, the greatest number of events were reported in the adult population, followed by the elderly. In general, relevant events were more likely to be assessed as non-serious and/or associated with a resolving outcome with increasing age. Generally, there were less relevant events associated with a worse outcome (not resolved/fatal).

Table 45. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 11,687 n (%)	Adults N = 456,740 n (%)	Elderly N = 50,899 n (%)	Unknown N = 26,160 n (%)
Arthralgia				
Total Events	577 (4.9%)	46,552 (10.2%)	6520 (12.8%)	2960 (11.3%)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 45. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 11,687 n (%)	Adults N = 456,740 n (%)	Elderly N = 50,899 n (%)	Unknown N = 26,160 n (%)
Serious Events	112 (1.0%)	5475 (1.2%)	1144 (2.3%)	520 (2.0%)
Event Outcome[a]: Fatal	0 (0.0%)	8 (0.0%)	10 (<0.1%)	2 (<0.1%)
Not Resolved	215 (1.8%)	12,669 (2.8%)	2350 (4.6%)	536 (2.0%)
Resolved with sequelae	3 (<0.1%)	315 (<0.1%)	63 (0.1%)	11 (<0.1%)
Resolved/Resolving	292 (2.5%)	25,731 (5.6%)	3229 (6.3%)	897 (3.4%)
Unknown	69 (0.6%)	8011 (1.8%)	909 (1.8%)	1536 (5.9%)
Chills				
Total Events	1075 (9.2%)	44,980 (9.8%)	5339 (10.5%)	2126 (8.1%)
Serious Events	161 (1.4%)	4137 (0.9%)	707 (1.4%)	446 (1.7%)
Event Outcome: Fatal	0 (0.0%)	7 (0.0%)	22 (<0.1%)	0 (0.0%)
Not Resolved	281 (2.4%)	7373 (1.6%)	968 (1.9%)	249 (1.0%)
Resolved with sequelae	5 (<0.1%)	282 (<0.1%)	39 (<0.1%)	5 (<0.1%)
Resolved/Resolving	666 (5.7%)	32,001 (7.0%)	3678 (7.2%)	917 (3.5%)
Unknown	126 (1.1%)	5374 (1.2%)	647 (1.3%)	962 (3.7%)
Fatigue				
Total Events	2184 (18.7%)	92,303 (20.2%)	10,677 (21.0%)	4290 (16.4%)
Serious Events	454 (3.9%)	10838 (2.4)	1675 (3.3%)	1199 (4.6%)
Event Outcome: Fatal	2 (<0.1%)	16 (0.0%)	58 (0.1%)	5 (<0.1%)
Not Resolved	789 (6.8%)	28,903 (6.3%)	3368 (6.6%)	959 (3.7%)
Resolved with sequelae	10 (0.1%)	642 (0.1%)	102 (0.2%)	25 (0.1%)
Resolved/Resolving	1043 (8.9%)	50,150 (11.0%)	5658 (11.1%)	1227 (4.7%)
Unknown	350 (3.0%)	12,929 (2.8%)	1535 (3.0%)	2099 (8.0%)
Headache				
Total Events	3546 (30.3%)	114,286 (25.0%)	10,813 (21.2%)	6387 (24.4%)
Serious Events	798 (6.8%)	12,859 (2.8%)	1822 (3.6%)	1256 (4.8%)
Event Outcome: Fatal	4 (<0.1%)	38 (<0.1%)	36 (<0.1%)	3 (<0.1%)
Not Resolved	1059 (9.1%)	27,916 (6.1%)	2729 (5.4%)	1200 (4.6%)
Resolved with sequelae	23 (0.2%)	861 (0.2%)	94 (0.2%)	34 (0.1%)
Resolved/Resolving	1908 (16.3%)	68,785 (15.1%)	6479 (12.7%)	2276 (8.7%)
Unknown	561 (4.8%)	16,904 (3.7%)	1500 (2.9%)	2899 (11.1%)
Myalgia				
Total Events	1228 (10.5%)	72,380 (15.8%)	7850 (15.4%)	3432 (13.1%)
Serious Events	182 (1.6%)	5666 (1.2%)	905 (1.8%)	450 (1.7%)
Event Outcome: Fatal	0 (0.0%)	9 (0.0%)	16 (<0.1%)	3 (<0.1%)
Not Resolved	452 (3.9%)	16,552 (3.6%)	2457 (4.8%)	422 (1.6%)
Resolved with sequelae	7 (<0.1%)	374 (<0.1%)	52 (0.1%)	9 (<0.1%)
Resolved/Resolving	638 (5.5%)	44,841 (9.8%)	4489 (8.8%)	1194 (4.6%)
Unknown	131 (1.1%)	10,683 (2.3%)	855 (1.7%)	1809 (6.9%)
Pyrexia				
Total Events	3077 (26.3%)	86,239 (18.9%)	9700 (19.1%)	6965 (26.6%)
Serious Events	743 (6.4%)	8420 (1.8%)	2094 (4.1%)	843 (3.2%)
Event Outcome: Fatal	6 (<0.1%)	53 (<0.1%)	157 (0.3%)	7 (<0.1%)
Not Resolved	681 (5.8%)	10993 (2.4%)	1161 (2.3%)	508 (1.9%)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 45. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 11,687 n (%)	Adults N = 456,740 n (%)	Elderly N = 50,899 n (%)	Unknown N = 26,160 n (%)
Resolved with sequelae	25 (0.2%)	605 (0.1%)	84 (0.2%)	15 (<0.1%)
Resolved/Resolving	1766 (15.1%)	60,005 (13.1%)	6332 (12.4%)	2869 (11.0%)
Unknown	607 (5.2%)	14,708 (3.2%)	1989 (3.9%)	3586 (13.7%)

a. Multiple episodes of the same event were reported with different clinical outcomes in some cases hence the sum of the events for outcome may differ.
N: Total number of events in the population subset; n: number of events; percentage (%) calculated as n/N.

Analysis by presence of comorbidities

Number of subjects with comorbidities: 25409 (3.9% of 658,249 cases in the total dataset and 9.1% of 279188 [4 CT and 278184 PM] cases reporting systemic adverse reactions).

- CT:
  - One of the CT cases reported selected comorbidities: the case involved a paediatric participant (█ years) with a history of croup infectious, febrile convulsion, lymphadenopathy and wheezing, who experienced a serious event coded to PT Pyrexia; the participant was recovering from the event.
- PM:
  - An analysis of relevant PM events by presence of selected comorbidities, event seriousness and event outcome are provided in Table 46. The total proportion of relevant events were generally evenly distributed among subjects that reported selected comorbidities and subjects that did not report selected comorbidities. In subjects with selected comorbidities, the relevant event was more likely to be assessed as non-serious and/or with a resolved or resolving event outcome. Of note, subjects that reported comorbidities were more likely to be of advanced age, polypharmacy users, report more AEs on average (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 46. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome

	Without Comorbidities N = 499,812 n (%)	With Comorbidities N = 45,674 n (%)
Arthralgia		
Total Events	51,208 (10.2%)	5401 (11.8%)
Serious Events	5634 (1.1%)	1617 (3.5%)
Event Outcome[a]: Fatal	8 (<0.1%)	12 (<0.1%)
Not Resolved	13,919 (2.8%)	1851 (4.1%)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 46. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome

	Without Comorbidities N = 499,812 n (%)	With Comorbidities N = 45,674 n (%)
Resolved with sequelae	311 (<0.1%)	81 (0.2%)
Resolved/Resolving	27,523 (5.5%)	2653 (5.8%)
Unknown	9661 (1.9%)	864 (1.9%)
Chills		
Total Events	48,967 (9.8%)	4553 (10.0%)
Serious Events	4343 (0.9%)	1108 (2.4%)
Event Outcome: Fatal	19 (<0.1%)	10 (<0.1%)
Not Resolved	7999 (1.6%)	872 (1.9%)
Resolved with sequelae	249 (<0.1%)	82 (0.2%)
Resolved/Resolving	34,292 (6.9%)	2994 (6.6%)
Unknown	6492 (1.3%)	617 (1.4%)
Fatigue		
Total Events	99,694 (19.9%)	9760 (21.4%)
Serious Events	11,265 (2.3%)	2901 (6.4%)
Event Outcome: Fatal	41 (<0.1%)	40 (0.1%)
Not Resolved	30,939 (6.2%)	3080 (6.7%)
Resolved with sequelae	594 (0.1%)	185 (0.4%)
Resolved/Resolving	53,479 (6.6%)	4645 (4.0%)
Unknown	15,025 (3.0%)	1888 (4.1%)
Headache		
Total Events	123,826 (24.8%)	11,206 (24.5%)
Serious Events	13,702 (2.7%)	3033 (6.6%)
Event Outcome: Fatal	58 (<0.1%)	23 (<0.1%)
Not Resolved	29804 (6.0%)	3100 (6.8%)
Resolved with sequelae	804 (0.2%)	208 (0.5%)
Resolved/Resolving	73241 (14.7%)	6262 (13.7%)
Unknown	20,193 (4.0%)	1671 (3.7%)
Myalgia		
Total Events	79,634 (15.9%)	5256 (11.5%)
Serious Events	5816 (1.2%)	1387 (3.0%)
Event Outcome: Fatal	20 (<0.1%)	8 (<0.1%)
Not Resolved	18,349 (3.7%)	1534 (3.4%)
Resolved with sequelae	368 (<0.1%)	74 (0.2%)
Resolved/Resolving	48,228 (9.6%)	2962 (6.5%)
Unknown	12,783 (2.6%)	695 (1.5%)
Pyrexia		
Total Events	96,483 (19.3%)	9498 (20.8%)
Serious Events	9475 (1.9%)	2625 (5.7%)
Event Outcome: Fatal	123 (<0.1%)	100 (0.2%)
Not Resolved	11811 (2.4%)	1532 (3.4%)
Resolved with sequelae	566 (0.1%)	163 (0.4%)
Resolved/Resolving	64,861 (13.0%)	6181 (13.5%)
Unknown	19,326 (3.9%)	1564 (3.4%)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 46. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome

	Without Comorbidities N = 499,812 n (%)	With Comorbidities N = 45,674 n (%)

a. Multiple episodes of the same event were reported with different clinical outcomes in some cases hence the sum of the events for outcome may differ.
N: Total number of events in the population subset; n: number of events; percentage (%) calculated as n/N.

Analysis by dose

Number of vaccine doses administered: 1 dose in 62919 cases, 2 doses in 100,838 cases; 3 doses in 10576 cases, 4 doses in 20 cases, and in 104836 cases the dose was either not specified or reported as others.

- CT:
  - Vaccination dose number: 2 doses (3) and 4 doses (1).
  - A meaningful comparison by dose is not possible due to the low number of CT cases.
- PM:
  - An analysis of relevant PM events by dose, event seriousness and event outcome are provided in Table 47. In general, the total proportion of relevant events, event seriousness, and event outcome were highest in those subjects whose vaccine doses were not reported or unclear; following this, most events were reported in those who had received two doses of the vaccine.

Table 47. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 102,844 n (%)	2 Doses N = 209,586 n (%)	3 Doses N = 20,738 n (%)	4 Doses N = 30 n (%)	Dose Not Specified/ Other N = 212,302 n (%)
Arthralgia					
Total Events	10,796 (10.5%)	23264 (11.1%)	2252 (10.9%)	0 (0.0%)	20298 (4.4%)
Serious Events	2446 (2.4%)	3135 (1.5%)	1141 (5.5%)	0 (0.0%)	529 (0.3%)
Event Outcome[a]: Fatal	10 (<0.1%)	9 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Not Resolved	2927 (2.8%)	4510 (2.2%)	828 (4.0%)	0 (0.0%)	7506 (3.5%)
Resolved with sequelae	154 (0.1%)	132 (<0.1%)	31 (0.2%)	0 (0.0%)	75 (<0.1%)
Resolved/Resolving	5282 (5.1%)	13,485 (6.4%)	980 (4.7%)	0 (0.0%)	10,429 (4.9%)
Unknown	2497 (2.4%)	5244 (2.5%)	466 (2.3%)	0 (0.0%)	2318 (1.1%)
Chills					
Total Events	7572 (7.4%)	21,030 (10.0%)	2855 (13.8%)	4 (13.3%)	22,061 (4.8%)
Serious Events	1479 (1.4%)	2304 (1.1%)	1274 (6.1%)	0 (0.0%)	395 (0.2%)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 47. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 102,844 n (%)	2 Doses N = 209,586 n (%)	3 Doses N = 20,738 n (%)	4 Doses N = 30 n (%)	Dose Not Specified/ Other N = 212,302 n (%)
Event Outcome: Fatal	8 (<0.1%)	13 (<0.1%)	3 (<0.1%)	0 (0.0%)	5 (<0.1%)
Not Resolved	1241 (1.2%)	2568 (1.2%)	602 (2.9%)	0 (0.0%)	4460 (2.1%)
Resolved with sequelae	112 (0.1%)	137 (<0.1%)	26 (0.1%)	0 (0.0%)	56 (<0.1%)
Resolved/Resolving	4694 (4.6%)	15,152 (7.2%)	1823 (8.8%)	3 (10.0%)	15,616 (7.4%)
Unknown	1529 (1.5%)	3193 (1.5%)	454 (2.2%)	1 (3.3%)	1932 (0.9%)
Fatigue					
Total Events	21,908 (21.3%)	35,082 (16.7%)	4418 (21.3%)	11 (36.7%)	48,038 (10.4%)
Serious Events	5097 (5.0%)	5782 (2.8%)	2150 (10.4%)	1 (3.3%)	1137 (0.5%)
Event Outcome: Fatal	24 (<0.1%)	37 (<0.1%)	7 (<0.1%)	0 (0.0%)	13 (<0.1%)
Not Resolved	5639 (5.5%)	9033 (4.3%)	1426 (6.9%)	2 (6.7%)	17,919 (8.4%)
Resolved with sequelae	295 (0.3%)	261 (0.1%)	29 (0.1%)	0 (0.0%)	194 (0.1%)
Resolved/Resolving	11,049 (10.7%)	19,298 (9.2%)	1843 (8.9%)	4 (13.3%)	25,933 (12.2%)
Unknown	5037 (4.9%)	6637 (3.2%)	1194 (5.8%)	5 (16.7%)	4040 (1.9%)
Headache					
Total Events	28,017 (27.2%)	49,117 (23.4%)	5107 (24.6%)	4 (13.3%)	52,791 (11.4%)
Serious Events	6139 (6.0%)	6560 (3.1%)	2534 (12.2%)	1 (3.3%)	1501 (0.7%)
Event Outcome: Fatal	28 (<0.1%)	27 (<0.1%)	2 (<0.1%)	0 (0.0%)	24 (<0.1%)
Not Resolved	6448 (6.3%)	8749 (4.2%)	1777 (8.6%)	1 (3.3%)	15,931 (7.5%)
Resolved with sequelae	349 (0.3%)	330 (0.2%)	68 (0.3%)	0 (0.0%)	265 (0.1%)
Resolved/Resolving	15,200 (14.8%)	30,756 (14.7%)	2596 (12.5%)	2 (6.7%)	30,951 (14.6%)
Unknown	6092 (5.9%)	9367 (4.5%)	741 (3.6%)	1 (3.3%)	5663 (2.7%)
Myalgia					
Total Events	17,221 (16.8%)	28,028 (13.4%)	2291 (11.0%)	4 (13.3%)	37348 (8.1%)
Serious Events	2369 (2.3%)	3192 (1.5%)	983 (4.7%)	0 (0.0%)	660 (0.3%)
Event Outcome: Fatal	8 (<0.1%)	12 (<0.1%)	1 (0.0%)	0 (0.0%)	7 (<0.1%)
Not Resolved	2629 (2.6%)	5016 (2.4%)	779 (3.8%)	1 (3.3%)	11,459 (5.4%)
Resolved with sequelae	155 (0.2%)	158 (<0.1%)	25 (0.1%)	0 (0.0%)	104 (<0.1%)
Resolved/Resolving	10,350 (10.1%)	17996 (8.6%)	1155 (5.6%)	3 (10.0%)	21,687 (10.2%)
Unknown	4112 (4.0%)	4908 (2.3%)	354 (1.7%)	0 (0.0%)	4104 (1.9%)
Pyrexia					
Total Events	17,330 (16.9%)	53,065 (25.3%)	3815 (18.4%)	7 (23.3%)	31,766 (6.9%)
Serious Events	3680 (3.6%)	5568 (2.7%)	1743 (8.4%)	1 (3.3%)	1109 (0.5%)
Event Outcome: Fatal	53 (<0.1%)	102 (<0.1%)	24 (0.1%)	0 (0.0%)	44 (<0.1%)
Not Resolved	2419 (2.4%)	4409 (2.1%)	882 (4.3%)	0 (0.0%)	5633 (2.7%)
Resolved with sequelae	231 (0.2%)	290 (0.1%)	54 (0.3%)	0 (0.0%)	154 (<0.1%)
Resolved/Resolving	10,449 (10.2%)	37,629 (18.0%)	2233 (10.8%)	5 (16.7%)	20,728 (9.8%)
Unknown	4229 (4.1%)	10,724 (5.1%)	704 (3.4%)	2 (6.7%)	5231 (2.5%)

a. Multiple episodes of the same event were reported with different clinical outcomes in some cases hence the sum of the events for outcome may differ.
N: Total number of events in the population subset; n: number of events; percentage (%) calculated as n/N.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Conclusion

Systemic adverse reactions were reported in 279,188 (4 CT and 279,184 PM) cases representing 42.5% of the cases in the total dataset for the reporting period. The majority of events (88.5%) were non-serious events with 60.7% of the events resolved, resolved with sequelae or resolving at the time of reporting. Evaluation of systemic adverse reaction cases did not reveal any significant new safety information based on analysis by age group, by presence of comorbidities or by dose. Systemic adverse reactions are appropriately described in the RSI. Surveillance of systemic adverse reactions will continue.

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-Authorisation Data

- Number of cases: 1558 (0.24% of 657,528 cases, the total PM dataset), compared to 427 cases (0.13%) retrieved in the PSUR #1.
- MC cases (126), NMC cases (1432).
- Country of incidence: Netherlands (1126), Belgium (333), Australia (33), France (25), Croatia (10), UK (8), Italy (5); the remaining 18 cases were distributed among 10 countries.
- Subjects' gender: female (1296), male (260), unknown (2).
- Subjects' age in years (n = 1505), range: 12.0 - 91.0, mean: 42.7, median: 41.0.
- Medical history (n = 625): the relevant reported medical conditions included Drug hypersensitivity (34), Hypersensitivity (30).
- COVID-19 Medical history (n = 322): medical conditions reported included COVID-19 (192), Suspected COVID-19 (129) and Asymptomatic COVID-19 (1).
- Relevant Co-suspects: Influenza vaccine (3), BCG vaccine (1)
- Number of relevant events: 1558
- Relevant event seriousness: serious (226), non-serious (1332).
- The reported relevant PT included Extensive swelling of vaccinated limb. Majority of the cases did not describe the type or extent of swelling and reported (verbatim) terms such as, "reaction at or around the injection site: extensive swelling of vaccinated limb"; many also reported additional events related to warmth, pain or redness at the injection site, with no additional relevant details; some cases described localized redness or swelling limited to the injection site and/or reports of lymph node swelling with no evidence in the case detail regarding any additional extensive swelling.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

For those cases reporting details of swelling, most appeared limited to the area surrounding the injection site with little evidence of additional extensive swelling of the rest of the limb. Majority of cases reporting swelling associated with the injection site, no treatment was required, and no case reported long lasting or permanent sequelae following the event.

- Time to event onset (n = 1441)[100], range: <24 hours to 164 days, median: 0 day.
  - <24 hours: 676 cases;
  - 1 day: 525 cases;
  - 2-7 days: 192 cases;
  - 8-14 days: 18 cases;
  - 15- 180 days: 30 cases.
- Duration of relevant events was reported in 324 occurrences with outcome of resolved; it ranged from 30 min to 30 days, median: 4 days
  - <24 hours: 11 cases;
  - 1 day: 25 cases;
  - 2-7 days: 242 cases;
  - 8-14 days: 31 cases;
  - 15-30 days: 15 cases
- Relevant event outcome:[47] resolved/resolving (859), resolved with sequelae (8), not resolved (641), unknown (51).

Analysis by age group

- PM: Paediatric (27), Adult (1340), Elderly (176), Unknown (15).
  - A higher reporting proportion of events coded to the PT Extensive swelling of vaccinated limb was observed in elderly versus adult population (Extensive swelling of vaccinated limb [20.3% in elderly vs 18.3% in adults]
- **Analysis by presence of comorbidities**
- Number of subjects reporting comorbidities: 80 (5.1% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (94.9%) when compared to patients with significant comorbidities.
- The reporting proportion of event severe reactogenicity with events resolved/resolving (63%) is higher in individuals with comorbid conditions when compared to the reporting

[100] This number does not include 118 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

proportion observed in the individuals without comorbidities (54.7% of events with resolved/resolving).

Conclusion

There was a total of 1558 cases, in the safety database reporting the PT Extensive swelling of vaccinated limb with the use of BNT162b2, and were mostly reported from the Netherlands (1126, 72%) and Belgium (333, 21.3%). Majority of cases involved females (1296, 83.2%) and were reported in subjects aged 31-64 years (958, 61.5%). Two-hundred and twenty-six (226; 14.5%) of the events were assessed as serious due to meeting medically significant criteria (there were no hospitalisations due to reported events). There was no case reporting a fatal outcome. One thousand two hundred and one (1201) cases reported time to onset of the event as the same day or the day following vaccination. For all the cases reporting swelling associated with the injection site, no treatment was required, and no case reported long lasting or permanent sequelae following the event.

Injection site swelling and lymphadenopathy are listed adverse drug reactions in the RSI for BNT162b2, and based on the data reviewed, there is insufficient evidence from reported cases to date that would warrant a change to the existing product information.

16.3.3.6. Age-Related Adverse Reactions

For the overall demographic information for all CT and PM cases refer to Section 6.3.1.1 *General Overview of the Safety Database – All Cases*.

Clinical Trial Data

- Number of cases: 721
- Time to event onset (n = 816), range <24 hours to 364 days, median: 105 days.
  - <24 hours: 27 events;
  - 1 day: 1 event;
  - 2-7 days: 28 events;
  - 8-14 days: 34 events;
  - 15-30 days: 81 events;
  - 31-181 days: 459 events;
  - >182 days: 186 events.
- Relevant event outcome: fatal (59), resolved/resolving (745), resolved with sequelae (34), not resolved (155), unknown (9).

- **Post-Authorisation Data**

- Number of cases: 657,528
- Time to event onset (n = 1,628,114), range <24 hours to 365 days, median: 1 day.
  - <24 hours: 671,438 events;
  - 1 day: 465,491 events;

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 2-7 days: 270,253 events;
- 8-14 days: 76,125 events;
- 15-30 days: 65,578 events;
- 31-181 days: 72,505 events;
- >182 days: 6724 events.

- Relevant event outcome[47]: fatal (12,608), resolved/resolving (1,030,580), resolved with sequelae (23,677), not resolved (546,986), unknown (566,691).

Analysis by age group

- CT: Paediatric (68), Adults (353), Elderly (233) and Unknown (7).

The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 48, Table 49 and Table 50. The Infections and infestations and Injury, poisoning and procedural complications SOCs were included in the top 5 SOCs for all 3 age groups.

There were 39 cases reporting 44 events in the Pregnancy, puerperium and perinatal conditions SOC for the adult age group. It is not unexpected for events of Pregnancy, puerperium and perinatal conditions to be reported more frequently in adult subjects compared to elderly and paediatric subjects.

There were 60 cases reporting 65 events in the Cardiac disorders SOC for the adult and elderly age group. Forty-six (46) cases reported relevant medical history (eg, hypertension, coronary artery disease, atrial fibrillation, congestive cardiac failure) which may have contributed to the relevant events. The most frequently reported events (≥5 occurrences) in the Cardiac disorders SOC for the adult and elderly age group were Coronary artery disease (10), Acute myocardial infarction (9), Myocardial infarction (8), Atrial fibrillation (6), and Cardiac failure congestive (5).

There were 108 cases reporting 116 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Thirty-three (33) cases reported pre-existing medical history of cancer (eg, breast cancer, basal cell carcinoma, prostate cancer, renal cell carcinoma). The most frequently reported events ≥5 occurrences) in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group were Prostate cancer (14), Breast cancer, and Invasive ductal breast carcinoma (5 each). When reported, latency ranged from 7 days to 451 days with a median of 148 days.

There were 6 cases reporting 6 events in the Psychiatric disorders SOC for the paediatric age group. The 6 events reported were Suicidal ideation (3), Anorexia nervosa, Psychotic disorder and Suicide attempt (1 each). The events were assessed as unrelated to BNT162b2 by the investigator and the Sponsor.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 48. 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	Paediatric	Elderly	Unknown
Infections and infestations	82	31	37	1
Injury, poisoning and procedural complications	61	12	41	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	54	2	62	1
Pregnancy, puerperium and perinatal conditions	44	1	0	3
Cardiac disorders	31	1	34	0

Table 49. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

SOC	Paediatric	Adult	Elderly	Unknown
Infections and infestations	31	82	37	1
Injury, poisoning and procedural complications	12	61	41	3
Nervous system disorders	8	27	22	0
Psychiatric disorders	6	29	1	0
Respiratory, thoracic and mediastinal disorders	4	19	17	1

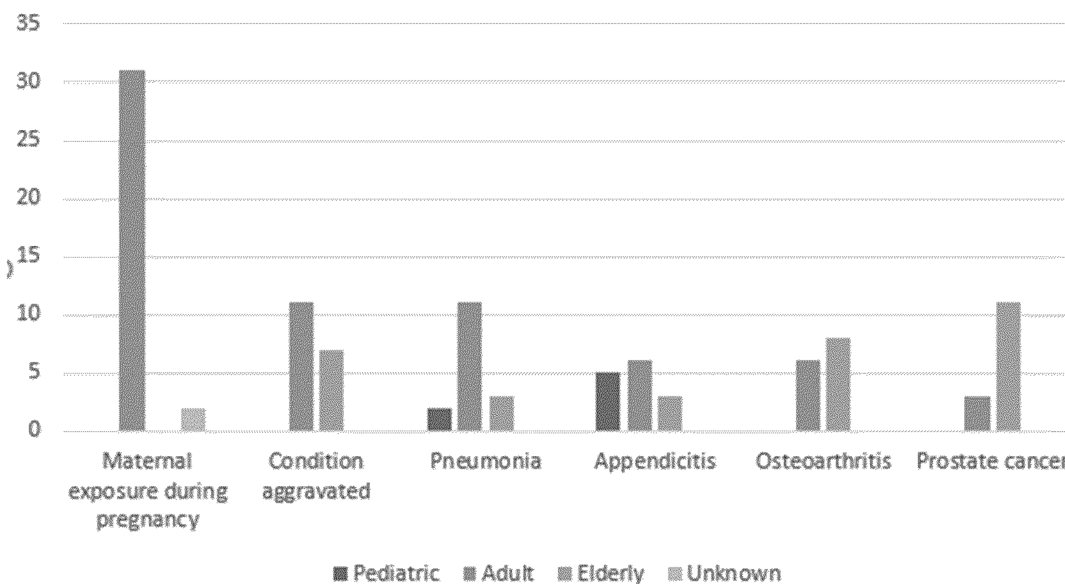
Table 50. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Elderly Age Group Compared with Other Age Groups

SOC	Elderly	Adult	Paediatric	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	62	54	2	1
Injury, poisoning and procedural complications	41	61	12	3
Infections and infestations	37	82	31	1
Cardiac disorders	34	31	1	0
Nervous system disorders	22	27	8	0

The distribution of the most frequently reported serious PTs (≥ 2%) by age group in the 661 CT cases where the participants were directly exposed to BNT162b2, is shown in Figure 13. Events of maternal exposure to be reported more frequently in adult patients compared to elderly and paediatric subjects is expected.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Figure 13. Events Reported in ≥2% of All Clinical Trial Cases by Age Group



- PM: Paediatric (19,637), Adults (492,065), Elderly (87,443) and Unknown (57,128).

The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented in Table 51, Table 52, and Table 53.. The top 5 SOCs were generally comparable for all age groups except Reproductive system and breast disorders in the adult age group, Injury, poisoning and procedural complications in the paediatric age group and Skin and subcutaneous tissue disorders in the elderly age group.

In the Reproductive system and breast disorders SOC for adult age group, event seriousness was assessed as serious (16,551) and non-serious (68,336). Event outcome was reported as resolved/resolving (29,006), not resolved (37,691), resolved with sequel (819), and unknown (17,892). The most commonly reported PTs (>1000 occurrences) in Reproductive system and breast disorders for the adult and elderly age group were Heavy menstrual bleeding (15,021), Menstrual disorder (10,459), Menstruation delayed (8342), Menstruation irregular (7656), Dysmenorrhoea (7477), Intermenstrual bleeding (6993), Amenorrhoea (5922), Polymenorrhoea (5310), Vaginal haemorrhage (2529), Breast pain (2254), Oligomenorrhoea (1654), Hypomenorrhoea (1468), and Postmenopausal haemorrhage (1321). It is not unexpected for these events of reproductive system and breast disorders to be reported more frequently in adult subjects compared to elderly and paediatric subjects.

There were 2860 cases reporting 4376 events in the in Injury, poisoning and procedural complications SOC for the paediatric age group. Of note, some cases more reported more than 1 PT. Event seriousness was assessed as serious (265) and non-serious (4111). Event outcome was reported as resolved/resolving (265), not resolved (63), resolved with sequel (7), unknown (4036) and fatal (6). The fatal cases are reviewed in Section 16.3.4.1 *Death*. The majority of cases (2481 cases) reported events indicative of medication error and/or off label use. The most commonly reported PTs (>100 occurrences) in Injury, poisoning and procedural complications for the paediatric age group were Poor quality product

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

administered (816), Off label use (401), Inappropriate schedule of product administration (400), Product administered to patient of inappropriate age (354), Expired product administered (324), Product preparation issue (251), Overdose (244), Product use issue (238), Underdose (173), Fall (160), Product preparation error (151), Incorrect dose administered (142), and Product storage error (105). Of the 160 events of Fall, 82 were assesses as non-serious and 78 were serious. The outcome was reported as resolved/resolving (92), not resolved (7), resolved with sequel (4), unknown (57). The co-reported PTs (> 20 occurrences) in these 160 cases reporting Fall were Loss of consciousness (67), Presyncope (50), Syncope (49), Malaise (28), Pyrexia (27), Dizziness (26), Headache (24), Seizure (24), and Pallor (23). Off label use, Product administered to patient of inappropriate age and Product use issue cases are reviewed in Section 16.3.4.6 *Off-Label Use*. Poor quality product administered, Inappropriate schedule of product administration, Expired product administered, Product preparation issue, Product preparation error, Incorrect dose administered, Product storage error and Underdose are reviewed in Section 9.2 *Medication Errors*. Overdose is reviewed in Section 16.3.4.2 *Overdose*.

In the Skin and subcutaneous tissue disorders SOC for elderly age group, event seriousness was assessed as serious (3919) and non-serious (11,935). Event outcome was reported as resolved/resolving (7414), not resolved (4727), resolved with sequel (149), unknown (3561) and fatal (68). The fatal cases are reviewed in Section 16.3.4.1 *Death*. The most commonly reported PTs (>250 occurrences) in Skin and subcutaneous tissue disorders for the adult and elderly age group were Rash (2902), Pruritus (2665), Erythema (1922), Urticaria (1539), Hyperhidrosis (771), Rash pruritic (611), Eczema (340), Rash erythematous (337), and Blister (273). Most of these events are listed or consistent with listed events as per the current RSI.

Table 51. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Adult Age Group Compared with Other Age Groups

SOC	Adult	Paediatric	Elderly	Unknown
General disorders and administration site conditions	598,611	16,233	81,630	41,801
Nervous system disorders	246,302	9,810	36,429	16,315
Musculoskeletal and connective tissue disorders	196,376	3,898	28,734	13,844
Gastrointestinal disorders	111,668	4,927	17,436	6,689
Reproductive system and breast disorders	84,879	2,211	688	6,050

Table 52. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

SOC	Paediatric	Adult	Elderly	Unknown
General disorders and administration site conditions	16,233	598,611	81,630	41,801
Nervous system disorders	9,810	246,302	36,429	16,315
Gastrointestinal disorders	4,927	111,668	17,436	6,689
Injury, poisoning and procedural complications	4,376	46,632	11,520	19,165
Musculoskeletal and connective tissue disorders	3,898	196,376	28,734	13,844

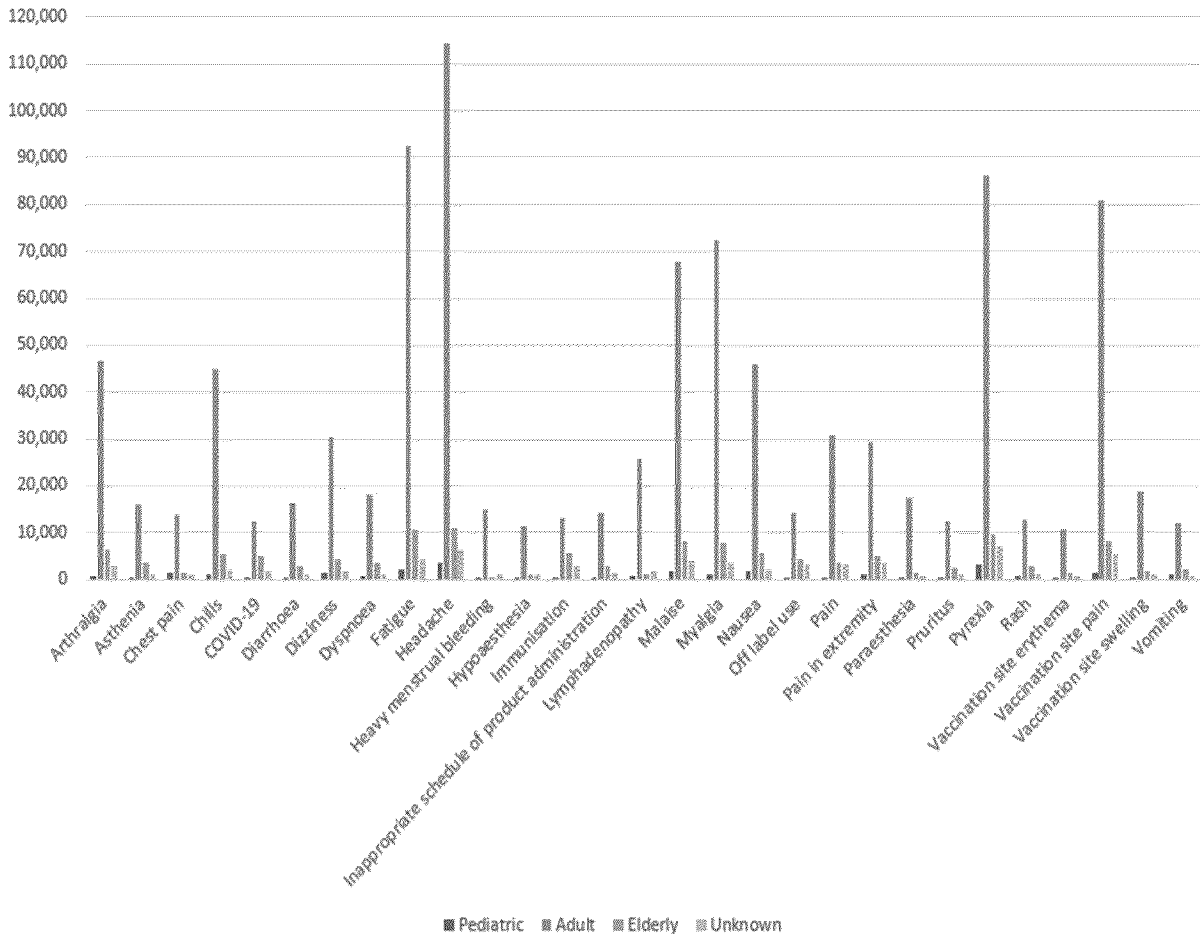
090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 53. Post-Authorisation 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	Paediatric	Unknown
General disorders and administration site conditions	81,630	598,611	16,233	41,801
Nervous system disorders	36,429	246,302	9,810	16,315
Musculoskeletal and connective tissue disorders	28,734	196,376	3,898	13,844
Gastrointestinal disorders	17,436	111,668	4,927	6,689
Skin and subcutaneous tissue disorders	15,851	71,071	3,128	6,333

The distribution of the most frequently reported overall PTs (≥ 2%) by age group is shown in Figure 14. Most of these events are listed or consistent with listed events as per the current RSI.

Figure 14. Events Reported in ≥ 2% of All Post-marketing Cases by Age Group



090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Conclusion

A review of the most frequently reported SOCs and overall PTs with the COVID-19 vaccine across the age groups were listed or consistent with listed events as per the current RSI. The analysis of age-related AEs did not identify any new safety information.

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: 15 (blinded therapy [2], BNT162b2 [13]) (2.1% of 721 cases in the total CT dataset) compared to 16 cases (2.3%) retrieved in the PSUR #1.
- Country of incidence: US (12), Argentina (2), [redacted] (1).
- Subjects' gender: female (8), male (7).
- Subjects' age in years (n = 15), range: 18 – 84, mean: 53.7, median: 56.0.
- Medical history (n = 14): the relevant medical conditions reported more than were coded to PTs Hypertension, Myocardial infarction (3 each), Depression (2).
- COVID-19 Medical history: None.
- Co-suspects: The reported co-suspects included fexofenadine, fluoxetine (1 each).
- Reported relevant PTs (15): Syncope (8), Anxiety (2), Dizziness, Dyspnoea, Loss of consciousness, Palpitations, Tachycardia (1 each). The event tachycardia was assessed as related to BNT162b2 by the investigators.
- Time to event onset (n = 15; no events reported a fatal outcome) range 7 days to 271 days.
  - < 24 hours: None;
  - 1 day: None;
  - 2-7 days: 1 event;
  - 8-14 days: None;
  - 15-30 days: 3 events;
  - 31-181 days: 9 events;
  - 181-240 days: 1 event;
  - 241-365 days: 1 event.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Duration of event (n = 11 of 15 relevant events with outcome of resolved/resolved with sequelae)[101]:
  - <24 hours: 4 events;
  - 1 day: 2 events;
  - 2-7 days: 4 events;
  - 8-14 days: 1 event;
  - 15-30 days: 1 event.

Post-Authorisation Data

Number of cases: 104,411 cases. Upon review, 6 cases were determined to be non-contributory and were not included in the discussion as these subjects were exposed to the vaccine during the mother' pregnancy or were exposed through breastfeeding.[61]

- Number of relevant cases: 104,405 (15.9% of 657,528 cases, the total PM dataset), compared to 57,806 cases (17.7%) retrieved in the PSUR #1.
- MC cases (38,436), NMC cases (65,969).
- Country of incidence (≥2%): Germany (16,624), UK (15,168), Netherlands (9240), France (8378), Japan (8126), US (7575), Italy (6119), Australia (5014), Philippines (2695), Spain (2248), Sweden (2114).
- Subjects' gender: female (73,772), male (28,408) and unknown (2225).
- Subjects' age in years (n = 97,495),[102] range: 2[103] - 121, mean: 43.9, median: 42.0.
- Medical history (n = 40,679): the most frequently (≥2%) reported relevant medical conditions included Hypertension (4847), Asthma (3930), Depression (1196), and Anxiety (1104).
- COVID-19 Medical history (n = 6145): COVID-19 (3381), Suspected COVID-19 (2551), Post-acute COVID-19 syndrome (73), SARS-CoV-2 test positive (42), COVID-19 pneumonia (27), Coronavirus infection (23), Asymptomatic COVID-19 (21), Exposure to SARS-CoV-2(18), SARS-CoV-2 antibody test positive (6), Occupational exposure to SARS-CoV-2 (2), Coronavirus test positive (1).
- Co-suspects (n = 924): the most frequently (≥ 10 occurrences) reported co-suspect vaccines/medications included influenza vaccine (125), COVID-19 vaccine NRVV AD (83), adalimumab, (33), COVID-19 Moderna vaccine, hepatitis A vaccine (26 each), ocrelizumab, ibuprofen (12 each), and treprostinil (11).

---

[101] This number does not include 1 event for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

[102] Excluded 1 case with contradictory demographic information (physical characteristics not matching with the reported age value) from reported minimum age calculation.

[103] This case reported off label use of BNT162b2 vaccine (PT Product use issue)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Number of relevant events: 133,499
- Relevant event seriousness[20]: serious (47,556), non-serious (86,005).
- Most frequently reported relevant PTs (≥2%): Dizziness (37,982), Dyspnoea (23,756), Paraesthesia (19,809), Palpitations (12822), Tachycardia (8253), Hyperhidrosis (7234), Syncope (6408), Blood pressure increased (6337), Loss of consciousness (3542), Anxiety (3084), and Paraesthesia oral (2284).
- Time to event onset (n = 101,754),[104] range < 24 hours to 365 days, median: 1 day.
  - < 24 hours: 47,621 events (61 of which had a fatal outcome);
  - 1 day: 21,717 events (78 of which had a fatal outcome);
  - 2-7 days: 20,574 events (126 of which had a fatal outcome);
  - 8-14 days: 5349 events (68 of which had a fatal outcome);
  - 15-30 days: 3765 events (37 of which had a fatal outcome);
  - 31-181 days: 2610 events (55 of which had a fatal outcome);
  - 181-240 days: 99 events (9 of which had a fatal outcome);
  - 241-365 days: 19 events (1 of which had a fatal outcome).
- Duration of event (n = 17,486 of 133,499 relevant events with outcome of resolved/resolved with sequelae)[105]:
  - <24 hours: 3969 events;
  - 1 day: 5104 events;
  - 2-7 days: 5864 events;
  - 8-14 days: 1071 events;
  - 15-30 days: 795 events;
  - 31-181 days: 667 events;
  - 182-240 days: 15 events;
  - 241-365 days: 1 event.
- Relevant event outcome[47]: fatal (552), resolved/resolving (65,522), resolved with sequelae (2163), not resolved (39,343), unknown (26,894).
  - The reported cause of death was (≥30 occurrences) coded to the PTs Dyspnoea (241), Loss of consciousness (73), Pyrexia (62), Cardiac arrest (48), Cough and Covid 19 (36 each), Syncope (33), Dizziness (32), Vomiting (31) and Cardio-respiratory arrest (30). When the medical history was provided (n = 296), significant medical conditions included (≥ 25 occurrences) Hypertension (114), Diabetes mellitus (38), and Chronic obstructive pulmonary disease (29).

[104] This number does not include 168 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.

[105] This number does not include 7 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by age group

- CT Data: 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 (3916), Adults (80,942), Elderly (13,000) and Unknown (6547).
  - No significant difference was observed in the reporting proportion of frequently (≥2%) reported relevant events between the adult and elderly population. A higher reporting proportion of relevant PT, Syncope was observed in the paediatric population when compared to the adult or elderly population (23.4% in paediatric vs 10.2% in adults vs 6.6% in elderly). This is consistent with expectations based on age-related event reports from other vaccines.[106]

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 14,406 (13.8% of the cases reporting stress/anxiety ADRs).
  - The reporting proportion of cases with fatal outcome is higher in subjects with comorbid conditions (1.4%) when compared to the reporting proportion observed in subjects without comorbidities (0.3%). In these cases, underlying comorbidities or events not related to stress/anxiety, are likely to be contributory to subject's death.

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 subject situations is described below.

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 field is set to "Yes".

[106] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- If the case contains one of the following terms: High Level Group Term: Fatal outcomes; Preferred Terms: Assisted suicide, Completed suicide.

Clinical Trial Data

- Number of cases: 44[107] (blinded therapy [19], BNT162b2 [24] and placebo [1]) (6.1% of 721 cases, the total CT dataset) compared to 46 cases (6.6%) retrieved in the PSUR #1.
- Country of incidence: the US (35), Argentina (5), [redacted] (1 each).
- Subjects' gender: female (13) and male (31).
- Subjects' age in years (n = 44), range: 20.0 – 89.0 years, mean: 62.2 years, median: 63.0 years
- Medical history (n = 40): the most frequently (>5 occurrences) reported medical conditions included Hypertension (24), Depression, Obesity (10 each), Hypercholesterolaemia, Hyperlipidaemia (8 each), Anxiety, Gastrooesophageal reflux disease (7 each), Benign prostatic hyperplasia, Insomnia, and Type 2 diabetes mellitus (6 each).
- COVID-19 Medical history: None.
- Causes of death most frequently reported (>2 occurrences): Death (7), Disease progression, Pulmonary embolism (4 each), Cardiac arrest, Cardio-respiratory arrest, Completed suicide, and Sepsis (3 each).
- Autopsy results were provided in 4 cases. Angiosarcoma, Arteriosclerosis, Cardio-respiratory arrest, Pulmonary embolism, Shock haemorrhagic, and Vascular neoplasm were singularly reported.
- Events with a fatal outcome (n = 54): The most frequently reported PTs (>2 occurrences): Death (7), Cardio-respiratory arrest, Pulmonary embolism (4 each), Completed suicide, and Sepsis (3 each). None of these events are considered related to blinded therapy/BNT162b2.
- Co-suspects were reported in 2 cases and they were cocaine and fentanyl (1 each).
- Time to event onset (n = 39),[108] range: 14 – 363 days, median: 230 days.
  - 8-14 days: 2 events;
  - 31-181 days: 10 events;

---

[107] During the current reporting interval, there were 8 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 (6) and cases which involved transplacental exposure are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.

[108] This number does not include 8 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

– >181 days: 27 events

Post-Authorisation Data

- Number of cases: 5215[109] (0.8% of 657,528 cases, the total PM dataset) compared to 5042 (1.5% of 327,125 cases, the total PM dataset) analysed in the PSUR #1.
- MC cases (3482), NMC cases (1733).
- Country of incidence (≥2%): Japan (961), Germany (797), France (643), the US (380), Italy (254), the UK (243), Austria (182), Netherlands (128), Philippines (126), Australia (123), and New Zealand (115).
- Subjects' gender: female (2089), male (2775), unknown (351).
- Subjects' age in years (n = 4608), range: 5.0 months – 106.0 years, mean: 71.4 years, median: 75.0 years.
- Medical history (n = 3132)[110]: The most frequently reported (≥100 occurrences) medical conditions included cardiac and vascular disorders (eg, Hypertension [1181], Atrial fibrillation [340], Cardiac failure [215], Dyslipidaemia [150], Myocardial ischaemia [145], Cerebrovascular accident [119], Hypercholesterolaemia [112], Myocardial infarction [107], Coronary artery disease [100]). Other most frequently reported (>100 occurrences) medical conditions included Diabetes mellitus (379), Type 2 diabetes mellitus (227), Chronic obstructive pulmonary disease (213), Chronic kidney disease (186), Dementia (174), Obesity (173), Depression (113), Asthma (105), Hypothyroidism (103), and Tobacco user (102).
- COVID-19 Medical history (n = 161): COVID-19 (117), Suspected COVID-19 (19), COVID-19 pneumonia (10), Asymptomatic COVID-19 (9), Exposure to SARS-CoV-2 (5), Coronavirus infection, SARS-CoV-2 test positive (3 each), and SARS-CoV-2 antibody test positive (1)
- Causes of death most frequently reported (>100 occurrences): Death (1229), COVID-19 (503), Cardiac arrest (323), Vaccination failure (310), Cardio-respiratory arrest (255), Myocardial infarction (251), Dyspnoea (242), Pulmonary embolism (217), Sudden death (202), Drug ineffective (199), Pyrexia (193), Cardiac failure (172), COVID-19 pneumonia (169), Pneumonia (155), Cerebral haemorrhage (127), and Cerebrovascular accident (124)
- Autopsy results were provided in 281 cases and the most commonly reported (≥10 occurrences) were: Pulmonary embolism (26), Acute myocardial infarction, Myocardial infarction (20 each), Arteriosclerosis coronary artery, Pulmonary oedema (17 each),

---

[109] During the current reporting interval, there were 261 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 (109) and cases which reported foetal death/still birth/spontaneous abortion/involved transplacental or trans-mammary exposure are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women* (152).

[110] This list excluded the medical history terms indicative of COVID-19. Of note, more than 1 medical history was reported in some cases.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Arteriosclerosis (16), Cardiomegaly (15), Myocarditis (14), Cardiac failure acute (13), Pulmonary congestion (12), Cardiac failure, and Cerebral haemorrhage (10 each)

- Co-suspect vaccines/medications (n = 145): the most frequently reported (>2 occurrences) were COVID-19 AstraZeneca vaccine (14), influenza vaccine (9), influenza vaccine INACT SAG 4V, influenza vaccine INACT SPLIT 4V (8 each), apixaban, methotrexate (7 each), levofloxacin (5), acetylsalicylate lysine, adalimumab, influenza vaccine INACT SAG 3V, paracetamol, and rivaroxaban (3 each)
- Events with a fatal outcome (n = 12,250): The most frequently reported (≥2%) events coded to the PTs: Death (1192), COVID-19 (542), Vaccination failure (379), Cardiac arrest (338), Dyspnoea (277), Drug ineffective (270), Cardio-respiratory arrest (269), Myocardial infarction (258), Immunisation[23] (257), Sudden death (245), Pulmonary embolism (224), Pyrexia (223), Cardiac failure (174), COVID-19 pneumonia (170), Pneumonia (159), Cerebrovascular accident (132), Cerebral haemorrhage (126), and Malaise (102).
- Time to fatal event onset (n = 8523),[111] range: <24 hours to 306 days, median: 6 days.
  - Same day: 1141 events;
  - 1 day: 1161 events;
  - 2-7 days: 2309 events;
  - 8-14 days: 1058 events;
  - 15-30 days: 964 events;
  - 31-181 days: 1557 events;
  - >181 days: 333 events

Analysis by age group

- CT: Adults (18-64) (25), and Elderly (65 years and older) (19).
  - A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.
- PM: Paediatric (17 years and under) (77), Adults (18-64 years) (1220), Elderly (65 years and older) (3390) and Unknown (528).
  - There is a significant difference observed in the reporting proportion for majority of the frequently reported fatal events (≥2% events listed above) in elderly population when compared to adult population due to higher proportion of fatal cases reported in subjects over 64 years of age (65.1% vs 23.4%, respectively). There is no meaningful comparison between elderly vs paediatric population possible due to the low number of paediatric fatal cases reported (1.5% vs 65.1%, respectively).

[111] This number does not include 14 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Most of the cases reporting a fatal outcome (45.8%) were in subjects over 75 years of age. This reflects one of the priority groups targeted for vaccination by many regions and countries, including Europe and the US, that is, elderly (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2.[112,113,114]

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2090 (0.3% of 658,249, the total dataset) when compared to 2760 (0.8% of 327,827 cases) in the PSUR #1.
- Upon review, there were no significant differences observed in the patterns of the most frequently reported fatal events (>100 occurrences) between the group with comorbidities and the one without comorbidities except COVID-19 pneumonia. In most of the cases reporting this event, the subject experienced vaccination failure or drug ineffective and majority of these cases reported cardiac disorders, vascular disorders, diabetes mellitus, respiratory disorders as comorbid conditions.

Analysis by dose

- Number of vaccine doses administered at the time of the subjects' death:
  - First dose (1259)
  - Second dose (2379). Of the 2379 cases, 660 cases (27.7%) reported a latency of same day to 3 days after vaccination. There were 5882 fatal events. The most frequently reported (>100 occurrences) fatal events were coded to PTs COVID-19 (432), Death (376), Vaccination failure (362), Drug ineffective (177), Cardio-respiratory arrest (158), COVID-19 pneumonia (142), Cardiac arrest (136), Pulmonary embolism (126), Dyspnoea (125), Myocardial infarction (103), and Pyrexia (102).
  - Third dose (407). Majority of these cases (>10 occurrences) originated from France (77), Germany (70), UK (59), Italy (24), Austria, the US (23 each), Sweden (19), Spain (14), Belgium, Israel (13 each), Hungary, Netherlands, Norway (11 each). There were 1272 fatal events. The most frequently reported (>20 occurrences) fatal events were coded to PTs Immunisation[23] (250), Death (111), Off label use (64), Sudden death (43), Interchange of vaccine products (38), Cardiac arrest (36), COVID-19, Pyrexia (24 each), and Pulmonary embolism (21).

---

[112] Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA. ECDC, February 2021.

[113] https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19/evidence-table-phase-1b-1c.html.

[114] 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).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- In the remaining cases (1170), it was not specified if the subjects received the first, second or the third vaccine dose at the time of the subject's death.

Analysis by dose interval

- Among the 4595 cases involving subjects, who received 3 doses of BNT162b2 with different time intervals than the recommended intervals (cross-referenced with Section 6.3.1.1.2.1 *Analysis by Dose*), there were 101 cases (360 fatal AEs) that reported death in 97 elderly and 4 adult subjects.
- The most frequently (≥ 2%) reported AEs leading to death the subjects, who received 3 doses of BNT162b2 administered with time intervals different from recommended posology [Immunisation[23] (65), Death (21), Sudden death (15), Off label use (11), Cardiac failure (10), Pyrexia (9) and Cardiac arrest (8)], are consistent with the most commonly reported fatal events in the overall PM dataset, except for the PT Immunisation that is selected per case processing conventions to collect cases reporting third/booster doses and the PT Off label use that is reported in this dataset due to the administration of dosages in unapproved time intervals.

Literature

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

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 5259 cases are in the interval reporting period (see Section 16.3.4.1 for further details for further details. According to the corePSUR19[44] summary tabulation of fatal reports by Age groups and SOCs is provided in Appendix 6C.1.

Interval Reporting Period

- CT (44 cases): Adults (18-64) (25), and Elderly (65 years and older) (19)

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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 54. 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	18-24 years	25-49 years	50-59 years	60-69 years	70+ years
Infections	10	0	2	4	3	1
General disorders	8	0	0	3	3	2
Cardiac	7	0	0	1	3	3
Injury	6	1	4	0	0	1
Respiratory	6	0	0	1	4	1

Of note, multiple AEs may be reported in a single case.

- PM (5215 cases): Paediatric (17 years and under) (77), Adults (18-64 years) (1220), Elderly (65 years and older) (3390), and Unknown (528).

The top 5 MedDRA SOCs with the most frequently reported (>1000 occurrences) events with a fatal outcome cumulative by age group in the post-authorisation data are presented in the table below.

Table 55. Post-Authorisation- 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	3309	56	29	249	249	430	1887	409
Cardiac	1943	35	17	271	198	310	1050	62
Nervous system	1407	26	23	151	152	233	774	48
Infections	1311	6	5	47	47	152	977	77
Respiratory	1285	24	12	132	113	184	792	28

Of note, multiple AEs may be reported in a single case.

Cumulative Reporting Period

This is a high-level- overview of the 10,424 relevant cumulative cases with a fatal outcome. According to the corePSUR19 guidance,[44] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 6C.2.

Clinical Trial Data

- Number of cases: 111[115] (6.3% of 1766 cases, the total CT dataset; 104 cases involved blinded therapy [60]/BNT162b2 [44]). In the remaining 7 cases subjects received placebo.

[115] There were 12 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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Causes of death most frequently reported (>3 occurrences): Disease progression (24), Cardiac arrest (14), Death (9), Cardio-respiratory arrest (7), COVID-19, Completed suicide (6 each), COVID-19 pneumonia, Multiple organ dysfunction syndrome (5 each), Myocardial infarction, Pulmonary embolism, Pneumonia, Acute myocardial infarction, Sepsis, Acute respiratory failure, Arteriosclerosis, and Road traffic accident (4 each)
- Autopsy results were provided in 10 cases. Arteriosclerosis (2), Pulmonary embolism, Death, Aortic dissection, Cardio-respiratory arrest, Hypertensive heart disease, Pericardial haemorrhage, Obesity, Shock haemorrhagic, Embolism, Accidental death, Alcohol abuse, Angiosarcoma, Gastrointestinal haemorrhage, Overdose, and Vascular neoplasm (1 each)
- Events with a fatal outcome (n = 145): The most frequently reported PTs (>3 occurrences): Death (9), Cardiac arrest, Cardio-respiratory arrest (8 each), Completed suicide (6), COVID-19 pneumonia (5), COVID-19, Myocardial infarction, Pulmonary embolism, Road traffic accident, and Sepsis (4 each). None of these events are considered related to blinded therapy/BNT162b2.

Post-Authorisation Data

- Number of cases: 10,313[116] (1.1% of 982,006 cases, the total cumulative PM dataset).
- MC cases (7490), NMC cases (2823).
- Causes of death most frequently reported (>300 occurrences): Death (2452), COVID-19 (981), Cardiac arrest (666), Dyspnoea (525), Sudden death (506), Myocardial infarction (454), Cardio-respiratory arrest (444), Pyrexia (440), Vaccination failure (423), Pulmonary embolism (392), Drug ineffective (374), Cardiac failure (373), and Pneumonia (347)
- Autopsy results were provided in 511 cases and the most commonly reported (>15 occurrences) were: Pulmonary embolism (52), Arteriosclerosis, Pulmonary oedema (42 each), Myocardial infarction (39), Arteriosclerosis coronary artery (36), Acute myocardial infarction (35), Cardiomegaly (26), Cardiac hypertrophy (23), Cardiac failure, Cardiac failure acute, Pneumonia (20 each), Cerebral haemorrhage, Myocarditis (19 each), Pulmonary congestion (18), Death (17), Coronary artery stenosis, Deep vein thrombosis, and Myocardial ischaemia (16 each)
- Events with a fatal outcome (n = 23,988): The most frequently reported (>300 occurrences) events coded to the PTs: Death (2404), COVID-19 (1039), Cardiac arrest (684), Dyspnoea (584), Sudden death (569), Vaccination failure (514), Drug ineffective

---

presenting a fatal outcome (10) and cases which involved transplacental exposure (2) are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.

[116] During the current reporting interval, there were 328 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 (152) and cases which reported foetal death/still birth/spontaneous abortion/involved transplacental or trans-mammary exposure are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women* (176).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

(499), Pyrexia (495), Cardio-respiratory arrest (463), Myocardial infarction (459), Pulmonary embolism (402), Cardiac failure (378), and Pneumonia (351).

Analysis by age group:

- CT: Adults (62), and Elderly (49).

  The top 5 MedDRA SOCs with the most frequently reported (>11 occurrences) events with a fatal outcome cumulative by age group is presented in the table below.

Table 56. 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
Infections	31	5	9	10	7
Cardiac	28	1	8	9	10
General disorders	16	2	5	6	3
Neoplasms benign	13	0	2	5	6
Respiratory	12	1	3	7	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) (81), Adults (18-64 years) (1764), Elderly (65 years and older) (7591) and Unknown (877).

  The top 5 MedDRA SOCs with the most frequently reported (>2000 occurrences) events with a fatal outcome cumulative by age group in the PM data are presented in the table below.

Table 57. Post-Authorisation 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	6617	58	31	352	361	672	4524	619
Cardiac	3678	36	26	345	292	476	2413	90
Nervous system	2784	26	24	192	213	357	1902	70
Respiratory	2654	25	14	170	171	302	1923	49
Infections	2577	6	7	55	76	241	1971	221

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 (listed above) in elderly population when compared to adult population due to higher proportion of fatal cases reported in subjects over 65

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

years of age (73.6% vs 17.1%, respectively). There is no meaningful comparison between elderly vs paediatric population is possible due to the low number of paediatric fatal cases reported (0.8% vs 73.6%, respectively).

- Most of the cases reporting a fatal outcome (57.3%) 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.[112,113,114]

O/E Analysis

O/E analysis was performed for events with a fatal outcome (see Appendix 6B *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 2037 cases, 52 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- dosage regimes or injection volumes inconsistent with BNT162b2 vaccine dosing were reported in 47 cases;
- the subjects received the 2nd dose or the booster dose with a scheduling different from the recommended one, but no evidence of overdose was reported in 2 cases;
- the reported PTs of overdose referred to fentanyl, everolimus, tacrolimus, venlafaxine and zopiclone and not to BNT162b2 in 3 cases.

Clinical Trial Data

- There were no serious clinical trial cases of overdose of the vaccine reported during the current interval period, compared to 2 cases (0.3%) retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 1985[117] (0.3% of 657,528 cases, the total PM dataset), compared to 1498 cases (0.5%) retrieved in the PSUR #1.

[117] Among these cases, 81 involved the Tris/Sucrose formulation (Section 6.3.1.1.2.2 *Tris/Sucrose Formulation.*

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- MC cases (1430), NMC cases (555).
- Country of incidence (≥2%): US (1060), Italy (231), Portugal (148), UK (97), Japan (89), Canada (75), France (58) and Germany (38).
- Subjects' gender: female (823), male (559) and unknown (603).
- Subjects' age in years (n = 1339), range: 0.17 – 98, mean: 39.6, median: 38.0.
- Medical history (n = 277): the most frequently (≥2%) reported medical conditions included: Hypertension (38), Drug hypersensitivity (27), Asthma (21), COVID-19 (18), Obesity (16), Diabetes mellitus (15), Depression, Food allergy (12 each), Hypersensitivity (8), Attention deficit hyperactivity disorder, Hypothyroidism, Rheumatoid arthritis (7 each), Allergy to metals, Dementia, Hypercholesterolaemia, Suppressed lactation,[19] Tobacco user (6 each), Fibromyalgia, Migraine, Overweight, Pain and Seasonal allergy (5 each).
- Co-suspect vaccines/medications: influenza vaccine (8), COVID-19 Moderna vaccine (4), COVID-19 AstraZeneca vaccine, sodium chloride (2 each), furosemide, vildagliptin, glatiramer acetate, influenza vaccine RHA 3V (baculovirus), letrozole, amoxicillin, simvastatin, meningococcal group B RLP2086, meningococcal vaccine A/C/Y/W conj (dip tox), prednisone, methotrexate sodium and water for injection (1 each).
- Number of relevant events: 1985.
- Relevant event seriousness: serious (57), non-serious (1928).
- Relevant PTs: Overdose (1881) and Accidental overdose (104).
- Relevant event outcome: resolved/resolving (46), not resolved (11), fatal (2), resolved with sequelae (2), unknown (1924).
- Most frequently co-reported PTs (≥2%): Product preparation error (413), Product preparation issue (369), Vaccination site pain (152), Pyrexia (147), Headache (140), Poor quality product administered (96), Fatigue (84), Incorrect dose administered (83), Immunisation[23] (82), Pain in extremity (81), and Off label use (79).

Analysis by age group

- Paediatric (267), Adults (917), Elderly (211) and Unknown (590).
  - Upon review, no significant differences in the reporting proportion of the most frequently co-reported AEs were noted between the different age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 109 (5.5% of the total cases reporting overdose).
- Upon review, no significant differences in the occurrence of the most frequently co-reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Literature

Review of the literature did not identify any significant new information regarding overdoses of BNT162b2.

Conclusion

The most frequently reported reasons (≥ 2%) for overdose were:

- administration of incorrect dose of diluted vaccine, different from the recommended 0.3 ml for the subjects aged ≥ 12 years and 2 ml for the paediatric subjects aged 5 through 11 years (728; 36.7% of the total cases reporting overdose);
- administration of undiluted vaccine (464; 23.4% of the total cases reporting overdose);
- dilution with a volume of sodium chloride different from the recommended 1.8 ml for the subjects aged ≥ 12 years and 1.3 ml for the paediatric subjects aged 5 through 11 years (270; 13.6% of the total cases reporting overdose);
- administration of a double dose of vaccine (156; 7.9% of the total cases reporting overdose);
- full adult dose of vaccine administered to paediatric subjects aged 5 through 11 years instead of the recommended 10 mcg dosage (69; 3.5% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 281 cases, the reason for overdose was not reported or unclear. No new significant safety information was identified based on the review of these cases. The most frequently co-reported AEs other than overdose and medication error PTs were events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 *Undesirable effects* of the CDS.

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

use issue; Intentional removal of drug delivery system by patient; Intentional underdose; Performance enhancing product use; Prescription drug used without a prescription; Treatment noncompliance.

Of the 121 cases, 76 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Seven (7) cases involved the abuse of illicit substances, including as most frequently reported (≥ 2) substances cannabis and cocaine (2 each);
- In 41 cases including the PTs Withdrawal syndrome (38), Dependence, Drug withdrawal headache and Drug withdrawal syndrome (1 each), the subjects developed symptoms mimicking withdrawal syndrome, but these cases did not report drug abuse, intentional, excessive or non-therapeutic use of BNT162b2;
- in 23 cases, abuse or misuse of other drugs than BNT162b2 was reported;
- in 3 cases, withdrawal syndrome (2) or tolerance decreased (1) to caffeine and/or tea occurred;
- in the remaining 2 cases, contradictory information was included (PT Drug withdrawal syndrome neonatal reported in an adult patient and PT Toxicity to various agents that it is unclear if really occurred).

Clinical Trial Data

- There were no serious clinical trial cases of abuse or misuse of the vaccine reported during the reporting period; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 45 (0.01% of 657,528 cases, the total PM dataset), compared to 65 cases (0.01%) retrieved in the PSUR #1.
- MC cases (13), NMC cases (32).
- Country of incidence (≥2%): US (15), UK (7), Canada, France (5 each), Germany (4), Japan (3), Italy (2), [redacted] (1 each).
- Subjects' gender: female (28), male (14) and unknown (3).
- Subjects' age in years (n = 36), range: 11 - 90, mean: 52.2, median: 52.5.
- Medical history (n = 20): the most frequently (≥2 occurrences) reported medical conditions included Drug hypersensitivity, Hypertension and Suppressed lactation[19] (2 each).
- COVID-19 Medical history (n = 2): COVID-19 and Exposure to SARS-CoV-2 (1 each).
- Co-suspect vaccines/medications (n = 17): adalimumab (3), COVID-19 Moderna vaccine (2), abatacept, apixaban, clozapine, COVID-19 AstraZeneca vaccine, ebastine,

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

fenofibrate, linagliptin, metformin, pantoprazole, pirfenidone, teriflunomide and valproate (1 each).

- Number of events: 233 (of which 46 were events of interest).
- Relevant event seriousness: serious (10), non-serious (36).
- Relevant PTs: Intentional product misuse (11), Intentional dose omission (10), Needle track marks (8), Toxicity to various agents and Intentional product use issue (7 each), Disturbance in social behaviour, Drug level increased and Drug tolerance decreased (1 each).
- Co-reported AEs (≥2 %): Off label use (7), Interchange of vaccine products (5), Drug ineffective, Asthenia and Pruritus (4 each).
- Time to event onset (n = 13), range: 0 - 7 days, median: 0 days.
  - <24 hours: 7 cases;
  - 1 day: 3 cases;
  - 2-7 days: 3 cases.
- Relevant event outcome: resolved/resolving (8), not resolved (11), unknown (27).

Analysis by age group

- PM: Paediatric (3), Adults (24), Elderly (11) and Unknown (9).
  - 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 15 cases, 2 doses in 8 cases, 3 doses in 3 cases and number of doses was not specified in 19 cases.
  - There are no differences between the AEs that occurred after the first, the second and the booster dose.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and abuse, dependence or misuse.

Conclusion

Overall, there were 45 cases representing 0.01% of the overall post-marketing dataset, that reported events indicative of misuse. Most of the cases involved subjects who intentionally omitted their second BNT162b2 dose or received the second dose after the recommended time frame per the RSI. In general, the most frequently co-reported events observed in these

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

cases 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; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 41 (0.01% of 657,528 cases, the total PM dataset), compared to 32 cases (0.01%) retrieved in the PSUR #1.
- MC cases (27), NMC cases (14).
- Country of incidence: Japan (17), US (12), Germany (3), Canada, Denmark, Spain (2 each), [redacted] (1 each).
- Subjects' gender: female (26), male (4) and unknown (11).
- Subjects' age in years (n = 16), range: 14 - 60, mean 38, median 35.0.
- Medical history (n = 10): Chorioretinopathy (7), Allergy to animal, Depression, Disease risk factor, Dust allergy, Food allergy, Milk allergy, Mite allergy, Seasonal allergy and Thyroid hormones decreased (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspects (n = 3): COVID-19 AstraZeneca vaccine, influenza vaccine, COVID-19 J&J vaccine and sodium chloride (1 each).
- Number of events: 94 (of which 40 were events of interest).
- Relevant event seriousness: serious (1), non-serious (39).
- Reported relevant PT: Occupational exposure to product (40).
- Co-reported AEs (≥2 occurrences): Ocular hyperaemia (3), Burning sensation, Erythema, Exposure via eye contact, Eye irritation, Interchange of vaccine products, Off label use, Product use issue and Underdose (2 each).
- Time to event onset (n = 6): < 24 hours.
- Relevant event outcome: resolving (1), unknown (39).

Analysis by age group

- PM: Paediatric (1), Adults (15), Unknown (25).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 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 41 cases representing 0.01% of the overall post-marketing dataset, that reported events indicative of occupational exposure. Review of the cases did not identify any significant new information regarding the use of BNT162b2 and occupational exposure. No safety signals have emerged that would be considered specific to this population.

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 27 September 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 by laboratory tests or reported by HCP).
- PT "Drug ineffective" is coded when either of the following applies:
  - The infection is not reported by HCP or not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied by consumers, e.g., "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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 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"

Lack of efficacy cases[118]

Search criteria - PTs Drug ineffective; Vaccination failure.

- Of the 21,543 cases, 86 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - Thirteen (13 cases) cannot be considered true lack of efficacy cases because the subjects developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the development of a vaccine preventable disease during this time is not considered a lack of effect of the vaccine.
  - Twenty-five (25) cases were invalidated in the safety database after the PSUR DLP.
  - Twenty-two (22) cases were identified as not a report of lack of efficacy because the subjects did not develop COVID-19 infection.
  - In 26 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; no cases were retrieved in the PSUR #1.

Post-Authorisation Data

- Number of cases: 21,457 (3.3% of 657,528 cases, the total PM dataset), compared to 6376 cases (1.9%) retrieved in the PSUR #1.
- MC cases (16,473), NMC cases (4984).

[118] LOE cases are assessed according to the definition provided in the EMA corePSUR19 guidance (EMA/362988/2021) and classified into confirmed vaccination failure, suspected vaccination failure, and not a vaccination failure.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Relevant lack of efficacy events[119]: 21,457 (Vaccination failure [11,934] and Drug ineffective [9523]).
- Country of incidence (≥2%): Austria (9009), US (2016), France (1865), Germany (1484), Portugal (1479), Italy (891), UK (806), Spain (480), and Japan (450).
- Please note, there is an increased number of cases from Austria as compared to the PSUR #1 (204 cases in PSUR #1). This is due to active solicitation of LOE cases, including retrospective cases, by Austrian Board of Health starting from August 2021.
- Subjects' gender: female (11,504), male (8744) and unknown (1209).
- Subjects' age in years (n = 19,261), range: 6 – 106, mean: 52.8, median: 50.0.
- Relevant event seriousness: all serious[120].

<u>Confirmed vaccination failure (10,877 cases)</u>

- Vaccination failure was reported in 10,877 cases, indicative of appropriately and fully vaccinated subjects (appropriate series of 2 doses at the appropriate interval), who developed clinical, and laboratory confirmed (e.g., COVID-19 PCR positive test, antigen test) COVID-19 infection, on or after day 7 post second dose. In 175 of these 10,877 cases, a third dose was also administered (including 1 case with administration of a fourth dose[121]).
- Age groups: Adolescent (182), Adults (7099), Elderly (3479) and Unknown (117).
- Time to event onset was known for 10,609 cases; in the remaining 268 cases, it was implied that vaccination failure was reported on or after day 7 post second dose, however detailed information was not provided.
  - Time to onset reported after the second dose.
    - day 7 to ≤ 30 days: 728 subjects
    - ≥ 31 days to ≤ 60 days: 1932 subjects
    - ≥ 61 days to ≤ 90 days: 2062 subjects
    - ≥ 91 days to ≤ 120 days: 1406 subjects
    - ≥ 121 days to ≤ 150 days: 1126 subjects
    - ≥ 151 days to ≤ 180 days: 1307 subjects
    - ≥ 181 days to ≤ 210 days: 1019 subjects
    - ≥ 211 days to ≤ 240 days: 671 subjects

[119] LOE PTs recorded in the 21,457 cases were Vaccination failure (11,773) and Drug ineffective (9685). Upon review after DLP, some cases were re-assessed: in 248 cases the PT Drug ineffective was reassessed to Vaccination failure; in 86 cases the PT Vaccination failure was reassessed to Drug ineffective, in 1 case that recorded both Drug ineffective and Vaccination failure, PT Vaccination failure was removed.

[120] Includes 17 cases where LOE was captured as non-serious and upgraded to serious after the PSUR DLP.

[121] In this case, an immunodeficient subject who had renal transplant received BNT162b2 vaccine dose 1 on 12 March, dose 2 on 19 April, dose 3 in May (date not reported), and dose 4 on 15 September of 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

    - ≥ 241 days to ≤ 270 days: 125 subjects
    - ≥ 271 days to ≤ 309 days: 76 subjects

- Time to onset reported after the third dose.
    - day 1 to ≤ 30 days: 106 subjects
    - ≥ 31 days to ≤ 60 days: 25 subjects
    - ≥ 61 days to ≤ 90 days: 14 subjects
    - ≥ 91 days to ≤ 120 days: 6 subjects
    - ≥ 121 days to ≤ 150 days: 2 subjects
    - ≥ 151 days to ≤ 186 days: 3 subjects

- Time to onset reported after the fourth dose.[121]
    - 13 days: 1 subject

- Reported COVID-19 infection related events:[122] COVID-19 (10,517), COVID-19 pneumonia (387), SARS-CoV-2 test positive (173), Suspected COVID-19[123] (33), Coronavirus pneumonia (4), Coronavirus infection (3), Post-acute COVID-19 syndrome (2), Multisystem inflammatory syndrome in children, Pneumonia viral, and SARS-CoV-2 sepsis (1 each).

- Outcome of COVID-19 infection related events:[47] resolved/resolving (2406), resolved with sequelae (20), not resolved (553), unknown (7738), and fatal (409).

- Of the 10,877 subjects with confirmed vaccination failure, in 1184 cases, the COVID-19 events were severe, resulting in:

    - Hospitalisation (non-fatal/non-life threatening): 730
    - Disability: 5
    - Life threatening: 78
    - Death: 371.

<u>Suspected vaccination failure (1777 cases)</u>

Lack of efficacy (PTs Drug ineffective or Vaccination failure) was reported in 1777 cases, wherein the subjects received 2 doses of vaccine at appropriate interval and reported to develop COVID-19 infection on or after day 7 post second dose, but laboratory confirmation of the infection (e.g., COVID-19 PCR positive test, antigen test) was not reported or clinical disease was unconfirmed (i.e., asymptomatic COVID-19). In 26 of these 1777 cases, a third dose was also administered.

[122] Some cases reported more than 1 PT referring to a COVID-19 infection.

[123] In these cases reporting Suspected COVID-19, upon review, the infection was assessed to be confirmed.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Age groups: Adolescent (25), Adults (1136), Elderly (559) and Unknown (57).

- Time to event onset was known for 1623 cases; in the remaining 154 cases, it was implied that vaccination failure was reported on or after day 7 post second dose, however detailed information was not provided.

  - Time to onset reported after the second dose.
    - day 7 to ≤ 30 days: 209 subjects
    - ≥ 31 days to ≤ 60 days: 336 subjects
    - ≥ 61 days to ≤ 90 days: 285 subjects
    - ≥ 91 days to ≤ 120 days: 189 subjects
    - ≥ 121 days to ≤ 150 days: 213 subjects
    - ≥ 151 days to ≤ 180 days: 200 subjects
    - ≥ 181 days to ≤ 210 days: 97 subjects
    - ≥ 211 days to ≤ 240 days: 45 subjects
    - ≥ 241 days to ≤ 270 days: 28 subjects
    - ≥ 271 days to ≤ 300 days: 5 subjects

  - Time to onset reported after the third dose.
    - day 1 to ≤ 30 days: 14 subjects
    - 31 days and 56 subjects: 2 subjects

- Reported COVID-19 infection related events:[122] COVID-19 (825), Asymptomatic COVID-19 (507), Suspected COVID-19 (414), COVID-19 pneumonia (42), SARS-CoV-2 test positive (27), and Coronavirus pneumonia (1).

- Outcome of COVID-19 infection related events: resolved/resolving (611), resolved with sequelae (4), not resolved (109), unknown (1057), and fatal (35).

<u>Not a vaccination failure cases (8803 cases)</u>

There were 8803 cases reporting Drug ineffective that were indicative of occurrence of the disease:

- in subjects who experienced a vaccine preventable illness from day 14 after receiving the first dose to day 6 after receipt of the second dose;

- in subjects for whom it was not possible to determine whether they received the appropriate series of 2 doses at the appropriate interval;

- in subjects for whom it was not possible to determine how many days have passed since the first or second dose administration.

- Age groups: Children (13), Adolescent (137), Adults (5046), Elderly (1832) and Unknown (1775).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Reported COVID-19 infection related events:[122] COVID-19 (7117), Suspected COVID-19 (1167), Asymptomatic COVID-19 (261), COVID-19 pneumonia (255), SARS-CoV-2 test positive (97), Post-acute COVID-19 syndrome (7), Coronavirus infection (6), Pneumonia viral (3), Coronavirus pneumonia, Multisystem inflammatory syndrome in children (2 each), Multisystem inflammatory syndrome, and SARS-CoV-2 test false negative (1 each).

- Outcome of COVID-19 infection related events:[47] resolved/resolving (2090), resolved with sequelae (56), not resolved (630), unknown (5872), and fatal (277).

According to the RSI, subjects may not be protected until at least 7 days after their second dose of the vaccine, therefore for the above 8803 cases where lack of efficacy was reported, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness.

- ***SARS-CoV-2 Variants (6526 cases)***

In 6526 of the 21,457 cases, information on SARS-CoV-2 variants was provided.

- *Delta (India) variant[124] (5833 cases)[125]*

  - Country of incidence (>2 occurrences): Austria (5362), France (324), US (52), Germany (27), Italy (17), Norway (16), Turkey (7), and Hong Kong (4)
  - Lack of efficacy events: Vaccination failure (4345) and Drug ineffective (1488)
  - Outcome of COVID-19 infection related events: [47] resolved/resolving (186), resolved with sequelae (3), not resolved (81), unknown (5465), and fatal (124).

- *Alpha (UK) variant[124] (620 cases)*

  - Country of incidence: Austria (401), France (150), Germany (24), Greece (23), Italy (17), Spain (2), (1 each)
  - Lack of efficacy events: Vaccination failure (558) and Drug ineffective (62)
  - Outcome of COVID-19 infection related events: [47] resolved/resolving (90), resolved with sequelae (4), not resolved (26), unknown (465), and fatal (55).

- *C1 variant [as reported] (36 cases)*

  - Country of incidence: France (36)
  - Lack of efficacy events: Vaccination failure (29) and Drug ineffective (7)

---

[124] As per WHO Nomenclature (Countries in which earliest samples were documented were additionally listed).

[125] Includes 356 cases reporting SARS-CoV-2 variant as Indian variant or lineage specified as B.1.617 or mutation suggestive of Indian variant, without further details.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - Outcome of COVID-19 infection related events: resolving (3), not resolved (3), unknown (27), and fatal (3).

- *Beta (South Africa) variant[124] (11 cases)*
  - Country of incidence: France (7), Germany (2), [redacted] (1 each)
  - Lack of efficacy events: Vaccination failure (8) and Drug ineffective (3)
  - Outcome of COVID-19 infection related events: resolved/resolving (4), unknown (6), and fatal (1).

- *South African or Brazilian variant [as reported] (9 cases)*
  - Country of incidence: France (9)
  - Lack of efficacy events: Vaccination failure (9)
  - Outcome of COVID-19 infection related events: resolved/resolving (4), not resolved (2), and unknown (3).

- *Lambda (Peru) variant[124] (5 cases)*
  - Country of incidence: Israel (5)
  - Lack of efficacy events: Vaccination failure (5)
  - Outcome of COVID-19 infection related events: unknown (5).

- *Omicron variant[124] (4 cases)*
  - Country of incidence: Hong Kong (2), [redacted] (1 each)
  - Lack of efficacy events: Vaccination failure (2) and Drug ineffective (2)
  - Outcome of COVID-19 infection related events: resolved (1) and unknown (3).

- *V3 variant [as reported] (4 cases)*
  - Country of incidence: France (4)
  - Lack of efficacy events: Vaccination failure (3) and Drug ineffective (1)
  - Outcome of COVID-19 infection related events: unknown (3) and fatal (1).

- *Others (4 cases)*
  - In 4 other cases, variant was reported as Eta (Nigeria)[124], Gamma (Brazil)[124], Kappa (India)[124], and B.1.1.29, respectively.

Literature

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Conclusion

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.

Please refer to Section 6.3.1.1.2.3 *Third Dose /Booster Dose* for the amendments made regarding booster doses of the BNT162b2 vaccine.

Of the 22,938 cases, 405 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Three hundred fifty-eight (358) cases reporting the PT Product administered to patient of inappropriate age were found to be indicative of a potential medication error. These cases are referenced in Section 9.2 *Medication Errors*.
- Twenty-nine (29) cases involved subjects exposed to the vaccine during the mother' pregnancy or exposed through.[61]
- Ten (10) cases reported the event Intentional product use issue (10). Three (3) 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 7 cases are referenced in Section 16.3.4.3 *Abuse, Misuse and Drug Dependency*.
- Four (4) 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*.
- Four (4) additional cases did not report relevant off label use (i.e., not considered off label use at the time of reporting, off label use not reported with the BNT162b2 vaccine).

Clinical Trial Data

- Not applicable.

Post-Authorisation Data

- Number of cases: 22,533 (3.4% of 657,528 cases, the total PM dataset), compared to 4672 cases (1.4%) retrieved in the PSUR #1.
- MC cases (5439), NMC cases (17,094).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence (≥2%): UK (13,188), Germany (1892), US (1629), the Netherlands (1137), and Canada (533).
- Subjects' gender: female (16,301), male (5050) and unknown (1182).
- Subjects' age in years (n = 18,844), range: 0.04 - 103 years, mean: 49.6, median: 50.0.
- Medical history (n = 10,789): the most frequently (≥2%) reported medical conditions included Breast feeding (1503), Suspected COVID-19 (1243), Hypertension (1050), Asthma (857), Immunodeficiency (748), COVID-19 (591), Disease risk factor (585), Clinical trial participant (570), Steroid therapy (407), Hypothyroidism (380), Rheumatoid arthritis (349), Diabetes mellitus (325), Depression (293), Drug hypersensitivity (285), Hypersensitivity (257), and Anxiety (219).
- COVID-19 Medical history (n = 1799): the most frequently (≥2%) reported medical conditions included Suspected COVID-19 (1243), and COVID-19 (591).
- Co-suspects (n = 1206): the most frequently (≥2%) reported co-suspect vaccines/medications included influenza vaccine (310), COVID-19 AstraZeneca vaccine (301), COVID-19 Moderna vaccine (169), hepatitis A vaccine (99), influenza vaccine (surface antigen, inactivated, adjuvanted) (43), influenza vaccine inact split 4v (27), influenza vaccine inact sag 3v (23), and adalimumab (20).
- Number of events: 130,024 (of which 26,044 were events of interest).
- Relevant event seriousness:[20] serious (6058), non-serious (20,003).
- Most frequently reported relevant PTs (≥2%): Off label use (22,002) and Product use issue (4001). Of note, of the 22,533 cases, 916 did not report additional events. The majority of cases described off-label use as
  - intentionally used in an unapproved population
    - It is unknown whether the BNT162b2 vaccine is excreted in human milk.
    - Administration of the vaccine in pregnancy should be considered when potential benefits outweigh any potential risks for the mother and foetus.
    - Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.
    - The administration of the BNT162b2 vaccine should be postponed in individuals suffering from acute severe febrile illness.
    - Those receiving anticoagulant therapy or with a bleeding disorder that would contraindicate an intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.
  - alternative dosing or scheduling regimens (ie. Full primary series not received, longer/shorter amount of days between doses than recommended)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - The primary series of the BNT162b2 vaccine is administered as 2 doses at greater than or equal to 21 days (preferably 3 weeks) apart. Off label is currently considered when the 2nd dose of the vaccine is administered outside the 19-42 day range from the 1st dose.

- co-administration with other vaccines (ie. influenza)
  - No interaction studies have been performed
- administration of COVID-19 vaccines from different manufacturers and third/booster/extra doses.

Analysis by dose interval

- Among these cases, 1114 (468 serious and 646 non-serious) reported administration of 3 doses of BNT162b2 with different time intervals than the recommended posology (cross-referenced with Section 6.3.1.1.2.1) and included the relevant PTs Off label use (1069), Product use issue (120) and Product administered to patient of inappropriate age (3).
- Upon review, no significant differences in the occurrence of the most frequently relevant PTs and co-reported AEs and clinical outcome in subjects, who received the 3 doses of vaccine with not recommend time intervals compared to the population receiving BNT162b2 in unapproved conditions was identified.

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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 844 (0.1% of 657,528 cases, the total PM dataset), compared to 472 cases (0.1%) retrieved in the PSUR #1.
- MC cases (101), NMC cases (743).
- Country of incidence (≥2%): US (183), Germany (168), Netherlands (126), UK (74), Turkey (34), Japan (28), Canada, France (25 each), Brazil (19) and Sweden (17).
- Subjects' gender: female (483), male (297) and unknown (64).
- Subjects' age in years (n = 526), range: 11 - 99, mean: 53.7, median: 54.0.
- Medical history (n = 654): the most frequently (≥2%) reported medical conditions included Hypertension (33), Asthma (30), Seasonal allergy (27), Arthritis, Migraine (24 each), Arthralgia (23), Multiple sclerosis (20), Fibromyalgia, Rheumatoid arthritis (19), Chronic obstructive pulmonary disease, Diabetes mellitus, Drug hypersensitivity, Hypersensitivity (17 each), Hypothyroidism, Suppressed lactation[19] (16 each), Fatigue, Psoriasis (15 each), Food allergy, Pain (14 each) and Headache (13).
- COVID-19 Medical history (n = 160): COVID-19 (65), Suspected COVID-19 (16), Post-acute COVID-19 syndrome (6).
- Co-suspects (n = 10): amoxicillin, certolizumab pegol, digoxin, etonogestrel, glimepiride, hydrocortisone acetate/neomycin sulfate/polymyxin B sulfate, influenza vaccine, insulin aspart, levothyroxine, mepolizumab, metformin, metoprolol tartrate, pioglitazone, prednisolone, risankizumab, tofacitinib citrate (1 each).
- Number of events: 1992 (of which 845 were events of interest).
- Relevant event seriousness: serious (22), non-serious (823).
- Relevant PTs: Therapeutic response unexpected (841) and Drug effective for unapproved indication (4).
- In most of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, menstrual disorders, breathing, skin conditions (including warts and psoriasis), arthritis, migraine, headache, herpes infections, taste, smell, eyesight and cognitive skills.
- Time to event onset (n = 270), range: 0 - 266 days, median: 2 days.
  - <1 day: 83 events;
  - 1 day: 63 events;
  - 2-7 days: 76 events;
  - 8-14 days: 21 events;
  - 15-30 days: 17 events;
  - 31-181 days: 8 events;
  - > 182 days: 2 events.

- Relevant event outcome: resolved/resolving (131), resolved with sequelae (5), not resolved (132), unknown (580).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by age group

- PM: Paediatric (9), Adults (377), Elderly (174) and Unknown (285).
  - There was no meaningful difference between different age groups.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and unexpected therapeutic effect.

Conclusion

In most of the cases, the unexpected therapeutic effect included improvement in the following: pain, allergies, menstrual disorders, breathing, skin conditions (including warts and psoriasis), arthritis, migraine, headache, herpes infections, taste, smell, eyesight and cognitive skills. In the majority of the cases, the subject's experienced the unexpected therapeutic effect following the first dose. No significant new information was identified with regards the use of BNT162b2 and unexpected therapeutic effects.

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

Of the 88,228 cases, 13 cases were determined to be non-contributory and were not included in the discussion for the following reason:

- upon review, it was realised that the patients' age was erroneously reported as old age.

Clinical Trial Data

- Number of cases: 233 (blinded therapy [73], BNT162b2 [149], placebo [8], BNT162b2S01 [2] and BNT162b3 [1]) (32.3% of 721 cases, the total CT dataset), compared to 255 cases (36.0%) retrieved in the PSUR #1.
- Country of incidence (≥2%): US (201), Argentina (17), Germany (6) and China (5).
- Subjects' gender: female (99), male (134).
- Subjects' age in years (n = 233), range: 65 - 91, mean: 72.8, median: 72.0.
- Medical history (n = 214): the most frequently HLGT (≥20 occurrences) reported medical conditions included vascular hypertensive disorders (124), lipid metabolism disorders (79), joint disorders (58), gastrointestinal motility and defaecation conditions (54), glucose metabolism disorders (incl diabetes mellitus) (52), allergic conditions (39), appetite and general nutritional disorders (37), cardiac arrhythmias (33), prostatic disorders (excl infections and inflammations) (32), lifestyle issues (30), thyroid gland disorders (27), coronary artery disorders, bronchial disorders (excl neoplasms) (26 each),

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

depressed mood disorders and disturbances, gastrointestinal therapeutic procedures (23 each), infections - pathogen unspecified, anxiety disorders and symptoms (21 each), bone disorders (excl congenital and fractures), sleep disorders and disturbances (20 each).

- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspects (n = 5): ibuprofen (2), dabigatran etexilate mesilate, loratadine and pravastatin sodium (1 each).
- Number of relevant events: 295
- Most frequently reported PTs (≥2%): Prostate cancer (11), Cerebrovascular accident, Coronary artery disease, Osteoarthritis, Syncope and Urinary tract infection (6 each).
- BNT162b2 related event coded to the PT Transient ischaemic attack (1).
- Time to event onset: n = 278, range: from 1 day to 418 days, median: 140 days.
  - 1 day: 1 event;
  - 2-7 days: 4 events;
  - 8-14 days: 9 events;
  - 15-30 days: 27 events;
  - 31-181 days: 145 events;
  - ≥182 days: 92 events.
- Event outcome: fatal (24), resolved/resolving (196), resolved with sequelae (8), not resolved (66), unknown (1).

Post-Authorisation Data

- Number of cases: 87,982 (13.4% of 657,528 cases, the total PM dataset), compared to 61,833 cases (18.9%) retrieved in the PSUR #1.
- MC cases (40,971), NMC cases (47,011).
- Country of incidence (≥2%): Japan (13,413), Netherlands (13,029), France (12,770), Germany (10,954), US (7058), UK (6448), Italy (4158), Austria (3244), Spain (1982) and Sweden (1697).
- Subjects' gender: female (53,863), male (32,819) and unknown (1300).
- Subjects' age in years (n = 85,323), range: 65 – 121, mean: 74.7, median: 73.0.
- Medical history (n = 38,252): the most frequently (≥2200 occurrences) reported HLGT medical conditions included vascular hypertensive disorders (12,299), glucose metabolism disorders (incl diabetes mellitus) (5318), allergic conditions (4817), viral infectious disorders (4505), lipid metabolism disorders (3380), cardiac arrhythmias (3376), bronchial disorders (excl neoplasms) (3146), joint disorders (3038), thyroid gland disorders (2684), central nervous system vascular disorders (2360), coronary artery disorders (2302) and lifestyle issues (2208).
- COVID-19 Medical history (n = 3723): the most frequently (≥27 occurrences) reported medical conditions included COVID-19 (2482), Suspected COVID-19 (1083),

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

COVID-19 pneumonia (52), Exposure to SARS-CoV-2 (28) and SARS-CoV-2 test positive (27).

- Co-suspects (n = 1535) the most frequently (≥26 occurrences) reported co-suspect vaccines/medications included influenza vaccine (165), adalimumab (105), COVID-19 AstraZeneca vaccine (66), COVID-19 Moderna vaccine (57), influenza vaccine (surface antigen, inactivated, adjuvanted) (45), apixaban (42), influenza vaccine inact SAG 3V (30), mepolizumab, methotrexate (26 each).
- Number of events: 278,931; the most frequently (≥2%) reported PTs: Headache (10,954), Fatigue (10,818), Pyrexia (9794), Vaccination site pain (8396), Malaise (8286), Myalgia (7980), Arthralgia (6642), Nausea (5773), Immunisation[23] (5693), Chills (5410), COVID-19 (5101), Pain in extremity (5022), Dizziness (4375), Off label use (4213), Vaccination failure (3754), Asthenia (3691), Dyspnoea (3600), Pain (3513), Herpes zoster (3114), Rash (2913), Diarrhoea (2826), Interchange of vaccine products (2817), Inappropriate schedule of product administration (2767), Pruritus (2694), Vomiting (2152), Drug ineffective (2137), Erythema (1938), Vaccination site swelling (1886).
- Event seriousness:[20] serious (105,076), non-serious (173,938).
- Time to event onset: n = 211,483[126], range: from <1 to 525 days, median: 1 day.
  - <1 day: 66,701 events;
  - 1 day: 47,745 events;
  - 2-7 days: 46,378 events;
  - 8-14 days: 15,449 events;
  - 15-30 days: 13,043 events;
  - 31-181 days: 19,428 events;
  - ≥182 days: 2739 events.
- Event outcome:[47] fatal (8557), resolved/resolving (121,566), resolved with sequelae (4333), not resolved (63,715), unknown (81,488).
- **Analysis by presence of comorbidities**
- Number of elderly subjects with comorbidities: 19,599 (22.2% of 88,215 cases, the total elderly dataset).
- Upon review, no significant differences in the occurrence of the most frequently reported AEs and in the fatalities in the elderly subjects with comorbidities compared to the elderly population without underlying diseases was identified.

[126] This number does not include 426 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 exposed to the vaccine before or during the mother' pregnancy or exposed through breastfeeding were excluded.

Of the 19,845 cases, 17 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- in 2 cases the data reported (eg, height, weight, clinical data, etc) were not consistent with paediatric subjects;
- upon review, one case has been reassessed as invalid, since unspecified number of subjects was reported;
- in 14 cases, the subjects were exposed to the vaccine before or during the mother' pregnancy or were exposed through breastfeeding.[61]

16.3.5.2.1. Paediatric Subjects <5 Years of Age[127]

Clinical Trial Data

- Number of cases: 25 (blinded therapy [23], BNT162b2 [1] and placebo [1]), originated from Protocol C4591007 (3.5% of 721 cases, the total CT dataset), compared to no cases retrieved in the PSUR #1.
- Country of incidence of relevant cases: US (15), Poland (7), (1 each).
- Subjects' gender: female (9), male (15).
- Subjects' age in years (n = 24), range: 0.83 – 4, mean: 1.9, median: 1.63.
- Medical history (n = 14): the most frequently (≥2) reported medical conditions included Asthma, Depression (4 each), Anxiety, Cerebral palsy, Seasonal allergy, Seizure (3 each), Acne, Atrial septal defect, Dacryostenosis acquired, Febrile convulsion, Food allergy, Generalised anxiety disorder, Hemiparesis, Iron deficiency anaemia, Major depression,

[127] The administration of BNT162b2 in this subpopulation is not approved.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Nasopharyngitis, Oppositional defiant disorder, Otitis media acute, Respiratory syncytial virus infection and Urinary tract infection (2 each).

- COVID-19 Medical history: None.
- Co-suspects (n = 1): Influenza vaccine (surface antigen, inactivated, adjuvanted) (1).
- PTs reported in the relevant cases (31): Respiratory syncytial virus bronchiolitis[128] (6), Bronchiolitis (3), Pneumonia (2), Anaphylactic reaction, Burns second degree, Cough, Diarrhoea, Enterovirus infection, Epilepsy[129], Gastroenteritis, Gastroenteritis viral, Head injury, Large intestine infection, Lower respiratory tract infection viral, Pain in extremity, Papilloedema, Pneumomediastinum, Pyrexia, Respiratory distress, Respiratory syncytial virus infection, Rhinovirus infection, Status epilepticus[130] and Upper respiratory tract infection (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy, but the AEs Pain in extremity and Pyrexia (1 each), both occurred in a █-year-old subject with a medical history of patent foramen ovale. The fever resolved within 4 days and the calf pain resolved in 3 days; the events were assessed related to second dose of BNT162b2 by the investigator and the MAH.
- Time to event onset: n = 31, range: < 1 - 111 days, median: 19 days.
  - < 1 day: 2 events;
  - 2-7 days: 17 events;
  - 8-14 days: 5 events;
  - 15-30 days: 5 events;
  - 31-111 days: 14 events.
- Duration of event: n = 28[131]: range: from 1 day to 18 days, median: 4 days.
  - 1 day: 4 events;
  - 2-7 days: 18 events;
  - 8-14 days: 3 events;
  - 15-18 days: 5 events.
- Event outcome: resolved/resolving (31).

[128] Out of the 6 cases reporting the PT Respiratory syncytial virus bronchiolitis, in 2 cases the subjects had underlying medical history of bronchiolitis, respiratory syncytial virus infection (in the first case) and neonatal respiratory distress (in the second case).

[129] The subject had a medical history of febrile convulsion.

[130] The subject had a medical history of seizure.

[131] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Post-Authorisation Data

- Number of cases: 83[132] (0.01% of 657,528 cases, the total PM dataset), compared to 64 cases (0.02%) retrieved in the PSUR #1.
- MC cases (32), NMC cases (51).
- Country of incidence (≥2%): US (19), Germany (12), Spain (7), Italy (6), France, Netherlands (5 each), Japan (4), Brazil, South Africa, UK (3 each), Canada, Dominica and Malaysia (2 each).
- Subjects' gender: female (41), male (31) and unknown (11).
- Subjects' age in years (n = 76), range: 0.04-4.08, mean: 2, median: 2.0.
- Medical history (n = 12): the reported medical conditions included Anxiety, Asthma, Atrioventricular septal defect, Attention deficit hyperactivity disorder, COVID-19, Hypertension, Generalised anxiety disorder, Milk allergy, Paraplegia, Scoliosis and Viral infection (1 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect vaccines (n = 7): influenza vaccine (6) and hepatitis B vaccine (1).
- Number of events: 248. The most frequently reported PTs (≥2%): Product administered to patient of inappropriate age (48), Off label use (21), Product use issue, Pyrexia (18 each), Wrong product administered (12), Headache (9), Malaise (7), Vaccination site pain (6), Fatigue and Incorrect route of product administration (5 each).
- Event seriousness: serious (36), non-serious (212).
- Time to event onset (n = 168), range: <1 to 185 days, median: <24 hours.
  - <1 day: 107 events;
  - 1 day: 40 events;
  - 2-7 days: 15 events;
  - 8-14 days: 1 event;
  - 15-30 days: 2 events;
  - 31-185 days: 3 events.
- Duration of event (n = 32)[133], range: <1 to 21 days, median: 1 day.
  - <1 day: 6 events;
  - 1 day: 13 events;
  - 2-7 days: 9 events;

[132] Cross-referenced with Section 16.3.4.6 *Off-Label Use*, since the administration of BNT162b2 is not approved in subjects <5 years of age.

[133] This number does not include 19 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 8-14 days: 1 event;
- 21 days: 3 events.

- Event outcome: fatal (1), resolved/resolving (72), not resolved (36), unknown (140).
  - Fatal case (country:): this NMC case involved a -old subject died 15 days after receiving one dose of BNT162b2 (fatal PT: Death and PT Off label use). The subject had no symptoms associated with COVID-19. It was not reported if an autopsy was performed. No further details were provided, preventing any meaningful assessment.

16.3.5.2.2. Paediatric Subjects ≥5 Years and ≤ 11 Years of Age[134]

Clinical Trial Data

- Number of cases: 18 (blinded therapy [14] and BNT162b2 [4]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (2.5% of 721 cases, the total CT dataset), compared to no cases retrieved in the PSUR #1.
- Country of incidence: US (9), Poland (6) and Finland (3).
- Subjects' gender: female, male (9 each).
- Subjects' age in years (n = 18), range: 5 – 11, mean: 7.4, median: 7.0
- Medical history (n = 8): the most frequently (≥2) reported medical conditions included Asthma (3), Nasopharyngitis and Hemiparesis (2 each).
- COVID-19 Medical history: None.
- Co-suspect vaccines/medications (n = 2): bamlanivimab, etesevimab and HPV vaccine (1 each).
- PTs (20): Abdominal pain, Abscess limb, Appendicitis, Arthritis bacterial, Asthma, Dehydration, Disease recurrence, Epilepsy, Epiphyseal fracture, Foreign body ingestion, Infusion related reaction, Pancreatitis, Pharyngitis streptococcal, Pneumonia respiratory syncytial viral, Pyelonephritis, Pyrexia, Testicular appendage torsion, Transient ischaemic attack, Upper limb fracture and Urinary tract infection (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy, but the AE Transient ischaemic attack, occurred in an subject on day 113 after the second dose of BNT162b2. The investigator considered the SAE related to BNT162b2 and to the concomitant Human papillomavirus vaccine, received 4 days prior to the onset of the event. The MAH considered there was not a reasonable possibility that the event was related to vaccine administration, based on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause this event and time course. A potential contributory role of concurrent viral herpangina is an alternative explanation, as neurologic complications rarely occur with enteroviruses.

[134] The administration of BNT162b2 in this subpopulation was approved by EMA on 25 November 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Time to event onset: n = 20, range: 3 - 153 days, median: 31.5 days.
  - 2-7 days: 2 events;
  - 8-14 days: 4 events
  - 15-30 days: 4 events;
  - 31-153 days: 10 events.

- Duration of event: n = 14[135], range: <1 day to 44 days, median: 6 days.
  - <1 day: 1 event;
  - 1 day: 2 events;
  - 2-7 days: 5 events;
  - 8-14 days: 3 events;
  - 15-30 days: 1 event;
  - 31-44 days: 2 events.

- Event outcome: resolved/resolving (20).

Post-Authorisation Data

- Number of cases: 1227 (0.2% of 657,528 cases, the total PM dataset), compared to 68 cases (0.02%) retrieved in the PSUR #1.
- MC cases (692), NMC cases (535).
- Country of incidence (≥2%): US (941), Canada (57), Germany, Puerto Rico (46 each) and France (27).
- Subjects' gender: female (435), male (451) and unknown (341).
- Subjects' age in years (n = 1049), range: 5 – 11, mean: 8.6, median: 9.0.
- Medical history (n = 167): the most frequently (>2) reported medical conditions included Asthma (30), Food allergy (21), Attention deficit hyperactivity disorder, Hypersensitivity (17 each), Seasonal allergy (10), Drug hypersensitivity (9), Anxiety, Autism spectrum disorder (8 each), Epilepsy (6), Eczema, Nasopharyngitis (5 each), Cardiac murmur, Coeliac disease, Constipation, Seizure (4 each), Obesity, Pyrexia (3 each).
- COVID-19 Medical history: COVID-19 (14), Suspected COVID-19 (5).
- Co-suspects (n = 28): influenza vaccine (22), COVID-19 vaccine mRNA (mRNA-1273), influenza vaccine inact split 3V (3 each), diphtheria vaccine toxoid/pertussis vaccine acellular/tetanus vaccine toxoid, HPV vaccine VLP RL 4V (yeast), influenza vaccine inact SAG 3V, influenza vaccine inact whole 3V and meningococcal vaccine (1 each).
- Number of events: 3101.

---

[135] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Event seriousness:[47] serious (255), non-serious (2847).
- Most frequently reported PTs (≥2%): Product administered to patient of inappropriate age (252), Poor quality product administered[136] (244), Off label use (216), Expired product administered[136] (183), Product preparation issue[136] (180), Product use issue (145), Overdose (102), Pyrexia (95), Headache (73), Vomiting (72), Incorrect dose administered (66) and Pain in extremity (64).
- Time to event onset (n = 2047)[137], range: <1 to 34 days, median: <1 day.
  - <1 day: 1399 events;
  - 1 day: 377 events;
  - 2-7 days: 197 events;
  - 8-14 days: 37 events;
  - 15-30 days: 34 events;
  - 34 days: 3 events.
- Duration of event (n = 143)[138], range: <1 to 28 days, median: 1 day.
  - <1 day: 66 events;
  - 1 day: 33 events;
  - 2-7 days: 34 events;
  - 8-14 days: 4 events;
  - 15-28 days: 6 events.
- Relevant event outcome: resolved/resolving (679), resolved with sequelae (10), not resolved (251), fatal (2), unknown (2160).
- Fatal cases (both reporting the fatal PT Death): the limited information reported in these cases does not allow any meaningful assessment.
  - The first NMC case involved a subject received BNT162b2 (dose unknown) and experienced a fatal outcome. An additional event reported in this case coded to PT Drug ineffective. Date of vaccination and onset date of the AEs are not provided. It was not reported if an autopsy was performed.

[136] In 151 cases from the same reporter, it was stated that the same diluent was used for several vials of the vaccine, instead of the diluent being thrown out after each use; moreover, the administered vaccines were expired (PTs Poor quality product administered, Product preparation issue and Expired product administered). No AEs were associated to these medication errors.

[137] This number does not include 15 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.

[138] This number does not include 324 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

– The second MC case reported a ██ year-old subject (gender unknown) died four days after the BNT162b2 first dose. No information on autopsy was available.

16.3.5.2.3. Paediatric Subjects ≥12 Years of Age[139]

Clinical Trial Data

- Number of cases: 24 (BNT162b2 [18] and blinded therapy [6]) originated from Protocol C4591001 (7), C4591001-OPEN LABEL (15) and C4591031 (2) (3.3% of 721 cases, the total CT dataset), compared to 27 cases (3.8%) retrieved in the PSUR #1.
- Country of incidence: US (24).
- Subjects' gender: female (11) and male (13).
- Subjects' age in years (n = 24), range: 12 – 17, mean: 14.8, median: 15.0.
- Medical history (n = 17): the most frequently (≥2) reported medical conditions included Depression (4), Anxiety (3), Acne, Cerebral palsy, Generalised anxiety disorder, Major depression, Oppositional defiant disorder, Seasonal allergy and Seizure (2 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 2): escitalopram oxalate, sertraline hydrochloride (1 each).
- PTs (26): Appendicitis (4), Suicidal ideation[140] (3), Upper limb fracture (2), Acute lymphocytic leukaemia, Anaphylactic reaction, Anorexia nervosa[140], Arthropod bite, Cerebral haemorrhage, Dyskinesia, Epilepsy, Kidney infection, Mucoepidermoid carcinoma of salivary gland, Myocarditis, Psychotic disorder[140], Radius fracture, Somnolence, Suicide attempt[140], Syringomyelia, Traumatic renal injury and Ulna fracture (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy, but the AEs Appendicitis and Myocarditis (1 each) that were assessed related to BNT162b2:

– A ██████ subject, enroled in study C4591001-OPEN LABEL, received the BNT162b2 third dose on ██████ and fourth dose on ██████. Previously, the subject had received doses of the blinded study vaccine (first dose on ██████ and second dose on ██████). The subject presented to hospital 3 days after the fourth dose with abdominal pain and vomiting, acute appendicitis was diagnosed and appendectomy was performed as an outpatient procedure. The subject recovered from the event.
The investigator considered there was a reasonable possibility that the event was related to the study vaccine BNT162b2 (dose 3 and 4), while the MAH assessed the AE unrelated to the vaccine administration, based on the short latency of 3 days after

[139] The administration of BNT162b2 in this subpopulation was approved by EMA on 31 May 2021.

[140] Out of the 6 cases reporting PTs included in the SOC Psychiatric disorders (Anorexia nervosa, Psychotic disorder, Suicide attempt and Suicidal ideation), in 4 cases the subjects suffered from underlying psychiatric disorders (ie, depression, major depression and generalised anxiety disorder).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

dose 2 and on the absence of a plausible pathophysiological mechanism by which the vaccine would be expected to cause this event.

- A [redacted] subject, enroled in study C4591001-OPEN LABEL, developed myocarditis 3 days after received the booster dose of BNT162b2 (Lot No. P220395-00911). Medical history included seasonal allergy, kidney stone, patella dislocation and anxiety. The subject received sertraline hydrochloride and isotretinoin as concomitant medications. The subject was admitted to hospital due to intense pain; ECG indicated ST elevation, troponin and creatine kinase were elevated, cardiac MRI showed abnormal cardiac MRI, left ventricular free wall subepicardial delayed gadolinium enhancement, consistent with myocarditis. The subject received treatment and was recovering at the time of the report. Both the investigator and the MAH assessed the AE as possibly related to the vaccine administration, based on the plausible temporal relationship (cross-referenced with Section 16.3.1.2.1 *Important Identified Risks-Myocarditis*).

- Time to event onset (n = 25), range: from 3 days to 258 days, median: 109 days.
  - 3-7 days: 3 events;
  - 15 days: 1 event;
  - 42-181 days: 19 events;
  - ≥ 182 days: 2 events.
- Duration of event (n = 16)[141], range: from < 1 to 89 days, median: 5 days.
  - <1 day: 2 events;
  - 1 day: 2 events;
  - 2-7 days: 6 events;
  - 8-14 days: 3 events;
  - 31-89 days: 3 events.
- Event outcome: resolved/resolving (20), not resolved (6).

Post-Authorisation Data

- Number of cases: 18,451 (2.8% of 657,528 cases, the total PM dataset), compared to 1445 cases (0.4%) retrieved in the PSUR #1.).
- MC cases (8344), NMC cases (10,107).
- Country of incidence (≥2%): US (2340), Netherlands (2057), UK (1901), Germany (1774), France (1711), Japan (1323), Italy (922), Australia (872), Taiwan (581), Austria (580), Denmark (567) and Spain (566).
- Subjects' gender: female (9900), male (8075) and unknown (476).

[141] This number does not include 10 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Subjects' age in years (n = 18,024), range: 12 - 17, mean: 14.8, median: 15.0.
- Medical history (n = 3786): the most frequently (≥2%) reported medical conditions included Asthma (554), Seasonal allergy (335), Food allergy (304), Hypersensitivity (195), Drug hypersensitivity (182), Suppressed lactation[19] (160), Attention deficit hyperactivity disorder (133), Epilepsy (112), Mite allergy (110), Rhinitis allergic (103), Anxiety (96), Migraine (93), Depression (88), Allergy to animal (90) and Autism spectrum disorder (82).
- COVID-19 Medical history (n = 966): COVID-19 (622), Suspected COVID-19 (319), COVID-19 immunisation (14), SARS-CoV-2 test positive (10), Asymptomatic COVID-19, Exposure to SARS-CoV-2, Post-acute COVID-19 syndrome (7 each), and SARS-CoV-2-antibody test positive (1).
- Co-suspects (n = 160): the most frequently (≥2%) reported co-suspect vaccines/medications included adalimumab (16), COVID-19 vaccine mRNA (mRNA-1273) (14), ethinylestradiol/levonorgestrel (11), influenza vaccine (9), sodium chloride (8), dupilumab, COVID-19 J&J vaccine (4 each), HPV vaccine, medroxyprogesterone acetate, mestranol/norethisterone (3 each).
- Number of events: 56,667.
- Relevant event seriousness:[20] serious (20,772), non-serious (35,915).
- Most frequently reported PTs (≥2%): Headache (3501), Pyrexia (3014), Fatigue (2154), Nausea (1933), Malaise (1757), Dizziness (1410), Chest pain (1332), Vaccination site pain (1319) and Myalgia (1237).
- Time to event onset: n = 45,137[142], range: from <1 to 366 days, median: 1 day.
  - <1 day: 18,123 events;
  - 1 day: 12,760 events;
  - 2-7 days: 8533 events;
  - 8-14 days: 2343 events;
  - 15-30 days: 2087 events;
  - 31-181 days: 1276 events;
  - ≥ 182 days: 15 events.
- Duration of event: n = 10,059[143], range: from <1 to 406 days, median: 1 day.
  - <1 day: 3499 events;
  - 1 day: 2211 events;
  - 2-7 days: 3322 events;
  - 8-14 days: 580 events;

[142] This number does not include 71 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.

[143] This number does not include 12,570 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- 15-30 days: 264 events;
- 31-180 days: 182 events;
- ≥ 182 days: 1 event.

- Relevant event outcome: fatal (196), resolved/resolving (27,010), not resolved (14,034), resolved with sequelae (458), unknown (15,126).

- Fatal cases (73)

- Age: 12 years (11), 13 years (12), 14 years (6), 15 years (11), 16 years (19), 17 years (11), unknown (3).
- MC cases (40), NMC cases (33).
- Gender: females (26), males (44), unknown (3).
- Country (≥ 2): US (12), Germany, Philippines (9 each), Vietnam (5), France, Italy, Japan, Malaysia, New Zealand (3 each), Brazil, Mexico, Romania, Spain, Thailand and UK (2 each).
- Fatal PTs (196): the most frequently (≥ 2) reported AEs included Death (24), Cardiac arrest (9), Dyspnoea, Myocarditis, Pyrexia, Sudden death (6 each), Vomiting (5), Dizziness, Headache, Respiratory failure (4 each), Cardio-respiratory arrest, Pulmonary embolism, Pulmonary oedema, Seizure, Septic shock (3 each), Abdominal pain, Acute myocardial infarction, Anaemia, Anaphylactic reaction, Anaphylactic shock, Arrhythmia, Asthenia, Cardiac disorder, Cardiomegaly, Circulatory collapse, Coagulopathy, Cyanosis, Decreased appetite, Drowning, Fatigue, Lung disorder, Respiratory arrest, Syncope, Thrombotic thrombocytopenic purpura, Unresponsive to stimuli (2 each).
- Relevant medical history (n = 23): Epilepsy (3), Asthma, Hospitalisation (2), Allergy to vaccine, Asymptomatic COVID-19, Bronchopulmonary dysplasia, Cardiac disorder, Cardiomyopathy, Cardiovascular disorder, Cerebral palsy, Congenital multiplex arthrogryposis, COVID-19, Drug hypersensitivity, Dyspnoea, Dyspnoea exertional, Familial risk factor, Glucose-6-phosphate dehydrogenase deficiency, Haemorrhage intracranial, Head injury, Hypoxic-ischaemic encephalopathy, Mitral valve prolapse, Obesity, Pleural effusion, Pneumonia bacterial, Polycythaemia, Posthaemorrhagic hydrocephalus, Pulmonary artery atresia, Raynaud's phenomenon, Respiratory failure, Respiratory tract infection, SARS-CoV-2 antibody test positive, Sinus bradycardia, Superficial vein thrombosis, Thalassaemia minor, Tobacco user and Ventricular extrasystoles (1 each).

  The 73 fatal cases are summarised below:

- In 21 cases (7 MC and 14 NMC) reporting only Death (17) or Sudden death (4) as fatal AEs and in one additional MC case reporting Death and Unresponsive to stimuli as AEs causing fatal outcome, neither cause of death nor information on autopsy was provided. The time to fatal event onset is available in 4 cases: 2 days (1), 3 days (2) and 4 days (1). The limited information provided prevented any meaningful causality assessment.

- In one case, the subject did not die due to illness, but due to an unfortunate accident:

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- NMC case; age years; gender: unknown; fatal PT: Accident occurred 3 days after the vaccination; autopsy: no data.

– In 2 cases, the co-suspect contraceptives could have contributed to the occurrence of the events:

  - MC case; age: 1 fatal PT: Pulmonary embolism 11 days after the first dose of BNT162b2 (lot No. FF2834); co-suspect: ethinylestradiol/levonorgestrel; autopsy: performed, but results were not provided.
  - NMC case; age: ; fatal PT: Cardiac arrest, occurred 9 days after the first dose of BNT162b2; co-suspect: unspecified combined oral contraceptives; autopsy: no data.

– In 7 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

  - MC case; age: ; fatal PT: Pulmonary embolism, occurred 24 days after 2nd dose of BNT162b2; medical history: pleuropneumonia on the left with slight pleural effusion and thrombotic superficial arm vein occlusion; autopsy: unknown if performed.
  - MC case; age: ; fatal PTs: Pulmonary oedema, Ventricular extrasystoles, Infarction, Cardiopulmonary failure, all occurred 16 days after the first dose of vaccine (lot No FD0168); medical history: ventricular extrasystoles; autopsy: revealed pulmonary oedema with foci of infarction suggesting an arterial or venous thromboembolic mechanism, thromboembolic cause.
  - MC case; age: ; fatal PTs: Cardiac arrest (developed 2 days after 1st dose of BNT162b2) and Brain hypoxia (unknown onset date); medical history: asthma, Marfan's syndrome and mitral valve prolapse; autopsy: not performed.
  - MC case; age: fatal PTs Disseminated intravascular coagulation, Pulmonary haemorrhage, Pyrexia, Multiple organ dysfunction syndrome, Septic shock (all occurred 2 days after 2nd dose of vaccine, lot No 10020A) and Thoracic haemorrhage (unspecified onset date); medical history: bronchopulmonary dysplasia, intracranial haemorrhage, hypoxic-ischaemic encephalopathy, post-haemorrhagic hydrocephalus, symptomatic epilepsy and respiratory insufficiency; autopsy: not performed.
  - MC case; age: subject; fatal PTs: Respiratory failure, Cardiac arrest, occurred the day after dose 2 of BNT162b2 (lot No FF2382); medical history: severe cardiopathy with congenital pulmonary atresia and left-right shunt prevailing the interventricular septal defect and failure, restrictive respiratory associated with secondary DLCO reduction; autopsy: not performed.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- MC case; age: [redacted]; fatal PTs Headache, Pyrexia, Decreased appetite (all developed the day after the 2nd dose of vaccine), Death, Myocarditis (both occurred 2 days after vaccination); medical history: cardiomyopathy and congenital multiplex arthrogryposis. Autopsy results: cardiac death in cardiomyopathy; mechanism of death was multi-factorial and the vaccine dose administered was not the sole trigger of the fatal event. In appreciation of the overall circumstances, the cardiac insufficiency with severe myocardial damage was aggravated by the vaccination, which led to decompensation of the cardiac function. The time of death was thus probably triggered by the physiological vaccination reaction with fever.

- NMC case; age: [redacted]; fatal PTs Rash, Dizziness, Anaphylactic shock (all occurred on the same date of vaccination, dose unknown), Coagulopathy (unspecified onset date); medical history: allergy to vaccine (unspecified); autopsy: not performed.

– In one case, the results of autopsy did not reveal any evidence of connection between the subject's death and administration of BNT162b2:

  - MC case; age [redacted]; fatal PTs: Pulmonary oedema, Arrhythmia, Cardiac failure acute (all occurred 20 days after the 1st dose of BNT162b2), Lung disorder, Cardiac disorder, Brain oedema (unknown onset date for these 3 events); medical history: epilepsy. Autopsy results: there was no evidence of an inflammation of the myocardium (myocarditis), therefore, based on the findings, no indications of a connection between the acute heart pump failure causing death and the vaccination against SARS-CoV-2 that was carried out almost three weeks before death. A morphologically detectable cause of the acute pump failure could not be found in any of the investigations carried out; therefore, it was likely to have been a functional cause, most likely a cardiac arrhythmia.

– In the remaining 40 cases (24 MC and 16 NMC) reporting the following fatal PTs Cardiac arrest, Dyspnoea (6 each), Death, Myocarditis, Vomiting (5 each), Pyrexia (4), Seizure, Respiratory failure, Headache, Cardio-respiratory arrest, Dizziness (3 each), Sudden death, Respiratory arrest, Cyanosis, Acute myocardial infarction, Anaemia, Circulatory collapse, Thrombotic thrombocytopenic purpura, Anaphylactic reaction, Cardiomegaly, Abdominal pain, Septic shock, Syncope, Asthenia, Drowning, Fatigue (2 each), Arrhythmia, Cardiac disorder, Coagulopathy, Anaphylactic shock, Postictal state, Completed suicide, Chest discomfort, COVID-19, Oxygen saturation immeasurable, Crepitations, Lung disorder, Pupils unequal, Critical illness, Subarachnoid haemorrhage, Anal sphincter atony, Vaccination site pain, Bladder sphincter atony, Off label use, Decreased appetite, Pericardial effusion, Defaecation disorder, Adverse event following immunisation, Diabetes mellitus, Cardiogenic shock, Diabetic ketoacidosis, Cerebellar haemorrhage, Diarrhoea, Sudden cardiac death, Bone marrow failure, Chest pain, Bradycardia, Ventricular fibrillation, Drug ineffective, Neurological decompensation, Dyskinesia, Ovarian enlargement, Palpitations, Pneumonia, Feeling abnormal, Pulmonary embolism, Breath sounds, Pulmonary sepsis, Hemiparesis, Interchange of vaccine products, Respiratory distress, Intestinal ischaemia, Aneurysm,

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Leukaemia, Shock, Loss of consciousness, Subdural haematoma, Bronchospasm, Cerebral venous sinus thrombosis, Malaise, Thrombocytopenia, Myocardial infarction, Unresponsive to stimuli, Abnormal faeces, Venous injury, Nausea, ADAMTS-13 activity decreased, Nerve injury, Pulmonary oedema, Nervous system disorder (1 each). No confounding factors have been identified; in most cases (27) the limited information available does not allow a medically meaningful causality assessment, in the remaining cases (13) a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results proved any causal relationship.

- **Analysis by presence of comorbidities**
- Number of subjects with comorbidities: 1181 (6.0% of 19,828 cases, the total paediatric dataset).
- Upon review, no significant differences in the occurrence of the most frequently reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

Literature

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

Conclusion

No new significant safety information was identified based on the review of the cases reported in the overall paediatric population. The most frequently reported AEs[144] events were consistent with the known reactogenicity of the vaccine and listed in Section 4.4 *Special warnings and precautions for use* and/or in Section 4.8 *Undesirable effects* of the CDS.

No relevant differences in the occurrence of the most frequently reported events, case seriousness and case outcomes were identified among the 3 paediatric age groups presented above.

16.3.5.3. Use in Pregnant/Lactating Women[145]

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.

[144] For the CT cases, the analysis was focused on AEs assessed as related to BNT162b2 or blinded therapy.

[145] EIU cases are included.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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)".

As per PRAC AR

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.*

Response

Please refer to Appendix 6A for details.

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

<u>*Cumulative review (Pregnancy Cases)*</u>

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

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Country of incidence: US (184), Japan (132), Argentina (33), Brazil (32), South Africa (30), Spain (16), UK (11), Germany (3) and Turkey (2).
- Of the 374 mother cases, 282 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The frequently reported pregnancy related events (>1 occurrence) were coded to the PTs Maternal exposure before pregnancy (183), Maternal exposure during pregnancy (52), Maternal exposure timing unspecified (19), Exposure during pregnancy (10), Drug exposure before pregnancy (7), Pregnancy (6), and Maternal exposure via partner during pregnancy (2).
- Ninety-two (92) mother cases, 90 serious and 2 non-serious, reported additional clinical events, which occurred in the vaccinated mothers.
  - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (40), Abortion spontaneous (34), Maternal exposure before pregnancy (7), Pre-eclampsia (6), Gestational hypertension, Premature separation of placenta (4 each), Cephalo-pelvic disproportion, Ectopic pregnancy, Postpartum haemorrhage, Premature delivery (3 each), Foetal death, Placental insufficiency, Uterine disorder (2 each).
  - Other reported clinical events were coded to the PTs Miscarriage of partner (2), Anaemia, Blood urine present, Cholelithiasis, Dysuria, Endometritis, Lower respiratory tract infection, Osteoarthritis, Pruritus, Pyelonephritis, Urinary tract procedural complication, Venous thrombosis limb (1 each). Of the 40 cases reporting spontaneous abortion or abortion related events in 17 cases, mother had a medical history of spontaneous abortion, alcohol/ tobacco use during pregnancy, ectopic pregnancy, obesity, diabetes mellitus, uterine disorder or hypertension which might have contributed to the event and in 23 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment. In 3 cases reporting ectopic pregnancy, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment. There were 2 cases reporting foetal death, in one of these 2 cases, mother had a medical history of spontaneous abortion and in the remaining case mother had a medical history of HIV infection which might have contributed to the event.
- Sixty-nine (69) baby/foetal cases, 68 serious and 1 non-serious. Cases are classified according to pregnancy outcome.
  - Pregnancy outcome: Live birth with congenital anomaly: Twenty (20) of these cases reported 42 congenital anomalies that coded to the PTs Atrial septal defect (4), Neonatal respiratory failure, Ankyloglossia congenital, Neonatal hypotension (2 each), Allergic colitis, Cardiac murmur, Coagulopathy, Coma neonatal, Congenital pneumonia, Congenital skin disorder, Craniosynostosis, Hypoperfusion, Hypoxic-ischaemic encephalopathy, Metabolic acidosis, Microcephaly, Neonatal intestinal perforation, Neonatal pneumothorax, Neonatal respiratory distress, Neonatal seizure, Nervous system disorder, Newborn persistent pulmonary hypertension, Patent ductus arteriosus, Pneumoperitoneum, Polydactyly, Pyelonephritis, Pyelonephritis acute, Renal failure neonatal, Renal tubular necrosis, Sepsis neonatal, Sex chromosome

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

abnormality, Shock, Small for dates baby, Thanatophoric dwarfism, Thrombocytopenia neonatal, Trisomy 21, Vesicoureteric reflux (1 each). Of these 20 cases, information regarding trimester of exposure was available in 14 cases. Of these 14 cases, in 11 cases foetus was exposed during 3rd trimester, in 2 cases foetus was exposed during 2nd trimester and in 1 case exposure occurred during 1st trimester. Of these 20 cases, in 1 case reporting atrial septal defect, mother of the baby had a medical history of tobacco use and in 1 case reporting neonatal respiratory failure, hypoxic-ischaemic encephalopathy, metabolic acidosis, renal failure neonatal, renal tubular necrosis, shock, newborn persistent pulmonary hypertension, thrombocytopenia neonatal, pneumoperitoneum, neonatal intestinal perforation, hypoperfusion, coma neonatal, coagulopathy, neonatal seizure, neonatal hypotension, and sepsis neonatal, mother had a medical history of premature separation of placenta which might have contributed to the development of the events. In the remaining 18 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

– Pregnancy outcome: Live birth without congenital anomaly: Forty-nine (49) cases reported live birth babies without congenital anomaly. Of these 49 cases, information regarding trimester of exposure was available in 32 cases. Of these 32 cases, in 22 cases, foetus was exposed during 3rd trimester, in 9 cases foetus was exposed during 2nd trimester and in 1 case exposure occurred during 1st trimester. The frequently reported events (>1 occurrence) in these 49 cases were coded to PTs Jaundice neonatal (8), Foetal distress syndrome (5), Neonatal respiratory distress syndrome (3), Foetal hypokinesia, Sepsis neonatal, Neonatal respiratory distress, Neonatal tachypnoea, Non-reassuring foetal heart rate pattern, Premature baby, Hyperbilirubinaemia neonatal (2 each). In all these 49 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Of the 443 cases, 378 cases provided pregnancy outcomes which are provided in Table 58 below. Pregnancy outcome was pending or not provided in the remaining 65 cases.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 58. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval

Pregnancy outcome	**Prospective cases 359 (81.0% of pregnancy cases)**					**Retrospective cases 19 (4.3% 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	2	0	0	0	0	1
Spontaneous abortion	0	17	0	0	16	0	4	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	1	0	0	0	0	0	0	0	1
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	1	0	1	0	0	0	0	0
Live birth with congenital anomaly	0	0	16	0	7	0	1	0	0	1
Live birth without congenital anomaly	0	72	61	0	165	0	2	3	0	5
Total	***0***	***90***	***78***	***0***	***191***	***0***	***7***	***3***	***0***	***9***

Cumulative review (Lactation cases)

- Number of lactation cases: 49 (2.8% of the total 1766 cases from the CT dataset). Of these 49 cases, 48 cases non-serious cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk, Maternal exposure during breast feeding) without the occurrence of any clinical events. In the remaining 1 serious case the clinical events were coded to PTs Hyperbilirubinaemia neonatal and Hypoglycaemia neonatal (1 each). In this case there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

Incremental review (CT cases)

- Number of pregnancy cases: 113 (15.7% of the total 721 cases from the CT dataset). These 113 cases represent 100 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 13 pregnancies). Cases originated from clinical studies C4591001 (20), C4591015 (89), C4591020 (1) and C4591031 (3) and study treatment was reported as blinded therapy (86), BNT162b2 (18), and placebo (9).

- Country of incidence: US (45), South Africa (24), Spain (16), Brazil (12), UK (11), Argentina (5).

- Fifty-one (51) serious maternal cases reported additional clinical events, which occurred in the vaccinated pregnant females.
  - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (33), Abortion spontaneous (10), Pre-eclampsia (5), Gestational hypertension (4), Cephalo-pelvic disproportion, Maternal exposure before pregnancy, Postpartum haemorrhage, Premature separation of placenta (3 each), Foetal death, Placental insufficiency, Uterine disorder (2 each).
  - Other reported clinical events coded to the PTs Anaemia, Blood urine present, Cholelithiasis, Dysuria, Endometritis, Lower respiratory tract infection, Miscarriage of partner, Osteoarthritis, Pyelonephritis, Urinary tract procedural complication, Venous thrombosis limb (1 each). Of the 12 cases reporting spontaneous abortion or abortion related events in 8 cases, mother had a medical history of spontaneous abortion, obesity, alcohol use, hypertension, tobacco use and/or were on multiple concomitant medications (i.e., mirtazapine, citalopram etc.) which might have contributed to the event and in the remaining 4 cases there was limited information regarding the mother's obstetric history which precluded meaningful causality assessment. There were 2 cases reporting foetal death, in one of these 2 cases, the mother had a medical history of spontaneous abortion and in the remaining case, the mother had a medical history of HIV infection which might have contributed to the event.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Sixty-two (62) serious baby/ foetal cases. Cases are classified according to pregnancy outcome.
  - Pregnancy outcome: Live birth with congenital anomaly: Twenty-nine (29) of these cases reported 38 congenital anomalies that coded to the PTs Atrial septal defect (4), Neonatal respiratory distress (3), Foetal growth restriction, Ankyloglossia congenital, Neonatal respiratory distress syndrome (2 each), Acute respiratory distress syndrome, Allergic colitis, Caput succedaneum, Cardiac murmur, Congenital pneumonia, Congenital skin dimples, Craniosynostosis, Encephalopathy neonatal, Grunting, Hyperbilirubinaemia neonatal, Injury to brachial plexus due to birth trauma, Microcephaly, Neonatal tachypnoea, Nervous system disorder, Patent ductus arteriosus, Polydactyly, Pyelonephritis acute, Sex chromosome abnormality, Small for dates baby, Subgaleal haemorrhage, Thanatophoric dwarfism, Traumatic intracranial haemorrhage, Trisomy 21, Ventricular septal defect, Vesicoureteric reflux (1 each). Of these 29 cases, information regarding trimester of exposure was available in 17 cases. Of these 17 cases, in 13 cases foetus was exposed during 3rd trimester and in 4 case exposure occurred during 2nd trimester. Of these 29 cases, in 1 case reporting neonatal respiratory distress syndrome, the mother of the baby had a medical history of alcohol use and in 1 case reporting microcephaly and small for dates baby, the mother of the baby had a medical history of gestational hypertension which might have contributed to the development of the events. In the remaining 27 cases, there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.
  - Pregnancy outcome: Live birth without congenital anomaly: Thirty-three (33) cases reported live birth babies without congenital anomaly. Of these 33 cases, information regarding trimester of exposure was available in 20 cases. Of these 20 cases, in 14 cases, foetal exposure occurred during 3rd trimester and in 6 cases, foetal exposure occurred during 2nd trimester. The frequently reported events (>1 occurrence) in these 33 cases were coded to PTs Jaundice neonatal (8), Foetal distress syndrome (5), Hypoglycaemia neonatal, Premature baby, Hyperbilirubinaemia neonatal, Sepsis neonatal (2 each). Of these 33 cases, in 6 cases reporting jaundice neonatal (2), foetal hypokinesia, premature baby, weight decrease neonatal, hypoglycaemia neonatal (1 each), the mother of the baby had a medical history of alcohol use, was on multiple concomitant medications or had a medical history of alloimmunisation. In 1 case reporting bronchiolitis, the event represents a coincidental viral infection as babies are more prone to develop viral infection during early stages of development after delivery. In the remaining 26 cases there was limited information regarding mother's obstetric history which precluded meaningful causality assessment.

The pregnancy outcomes for these 113 cases are provided in Table 59.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 59. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval

Pregnancy outcome	Prospective cases 109 (96.5% of pregnancy cases)					Retrospective cases 4 (3.5% 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	0	0	0	0
Spontaneous abortion	0	4	0	0	8	0	0	0	0	0
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	1	0	1	0	0	0	0	0
Live birth with congenital anomaly	0	1	25	0	13	0	0	0	0	2
Live birth without congenital anomaly	0	4	39	0	12	0	0	1	0	1
Total	***0***	***9***	***65***	***0***	***35***	***0***	***0***	***1***	***0***	***3***

Post-Authorisation Data

Incremental review (Pregnancy)

- Number of pregnancy cases: 5239 (0.8% of 657,528 cases, the total PM dataset), compared to 1661 cases (0.5%) retrieved in the PSUR #1. These 5239 cases represent 4896 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 343 pregnancies).

- Country of incidence (>100 occurrences): UK (1229), Netherlands (654), France (491), Germany (372), US (371), Japan (226), Canada (206), Estonia, Italy (143 each), Belgium (126), Australia (124), Sweden (103).

- Of the 4796 mother cases, 1056 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 (756), Maternal exposure timing unspecified (166), Exposure during pregnancy (88), Maternal exposure before pregnancy (39), Drug exposure before pregnancy, Pregnancy, Unintended pregnancy, Unwanted pregnancy (2 each), Paternal exposure during pregnancy (1).

- There were 3740 mother cases of which 2248 were serious and 1492 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. Pregnancy related events reported in these cases (>50 occurrences) were coded to the PTs Abortion spontaneous (1040), Vaginal haemorrhage (120), Foetal death (67), Abortion missed (54), Heavy menstrual bleeding (51)[146]. Other frequently reported (≥100 occurrences) clinical events coded to the PTs Headache (527), Fatigue (495), Vaccination site pain (394), Myalgia (298), Nausea (294), Pain in extremity (290), Pyrexia (289), Malaise (246), Chills (201), Pain (177), Arthralgia (157), Dizziness (141), Vomiting (136), Diarrhoea (100). The distribution of clinical events (≥100 occurrences) was similar in the pregnant mothers when compared with the general population.

- Four hundred -forty-three (443) baby/foetal cases, 389 serious and 54 non-serious. Cases are classified according to pregnancy outcome.

  - Pregnancy outcome: Live birth with congenital anomaly: Fifty three (53) of these cases reported 75 congenital anomalies that coded to the PTs Foetal growth restriction (5), Congenital anomaly, Heart disease congenital (4 each), Trisomy 21, Congenital hydrocephalus, Congenital central nervous system anomaly, Foetal cardiac disorder (3 each), Cerebral infarction, Spina bifida, Congenital hearing disorder, Foetal disorder, Foetal malformation, Hydrops foetalis (2 each), Coagulation disorder neonatal, Cardiogenic shock, Congenital cystic kidney disease, Mitral valve atresia, Cardiomyopathy neonatal, Porencephaly, Cataract congenital, Congenital inguinal hernia, Urinary tract malformation, Cytogenetic abnormality, Limb malformation, Encephalomalacia, Quadriparesis, Spinal meningioma benign, Fallot's tetralogy,

[146] Few additional events reported were coded to PTs Pre-eclampsia (3), Amniotic cavity infection (1).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Ureteric dilatation, Anophthalmos, Kidney malformation, Aplasia cutis congenita, Limb reduction defect, Microcephaly, Cleft lip and palate, Gastroschisis, Neonatal haemochromatosis, Gene mutation, Haemangioma, Cloacal exstrophy, Haemorrhage neonatal, Aberrant aortic arch, Spinal cord injury, Vena cava thrombosis, Supernumerary nipple, Ventricular hypoplasia, Coarctation of the aorta, Hypospadias, Urethral valves, Ventricular septal defect, Hepatic failure (1 each). Other frequently reported clinical events (>1 occurrence) reported in these cases coded to the PTs Foetal cardiac arrest (14), Hypoxic-ischaemic encephalopathy (4), Cerebral ventricle dilatation, Poor feeding infant (3 each), Adrenal haemorrhage, Apgar score low, Ascites, Blood glucose abnormal, Cardiac arrest, Cardiac disorder, Cerebral infarction, Clavicle fracture, Gastrointestinal obstruction, Hepatic failure, Lymphadenopathy, Neonatal pneumothorax, Perforation, Pyrexia, Testicular torsion, Thymus enlargement, Ureteric dilatation (2 each). Of these 53 cases, information regarding trimester of exposure was provided in 22 cases. Of these 22 cases, in 13 cases foetus was exposed during 1st trimester, in 4 cases foetus was exposed during 2nd trimester and in 5 cases exposure occurred during 3rd trimester. Of these 53 cases, 1 case reporting foetal growth restriction and foetal heart rate decreased, the mother of the baby was on multiple concomitant medications (i.e., diazepam and fluticasone etc.). In the remaining 52 cases there was limited information regarding obstetric history/ medical history of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Livebirth without congenital anomaly: Two hundred Eighteen (218) cases reported live birth babies without congenital anomaly. Of these 218 cases, 32 cases reported normal newborn and 9 cases reported abnormal newborn/ perinatal complication/post-perinatal complications. Of these 218 cases, information regarding trimester of exposure was provided in 61 cases. Of these 61 cases, in 7 cases, foetus was exposed during 1st trimester, in 22 cases, foetus was exposed during 2nd trimester and in 32 cases exposure occurred during 3rd trimester. The most frequently reported events (>5 occurrences) in these 218 cases other than exposure related events were coded to PTs Premature baby (78), Foetal hypokinesia (26), Foetal growth restriction (11), Tachycardia foetal (9), Premature delivery, Jaundice neonatal (7 each), Neonatal respiratory distress (6). Of these 218 cases, in 1 case, reporting hypoxic-ischaemic encephalopathy, hypotonia neonatal, poor sucking reflex, small for dates baby, the mother of the baby was on concomitant medication lamotrigine and in 1 case reporting premature baby and neonatal respiratory distress, the mother of the baby had a medical history of premature labour which might have led to development of the reported events. In the remaining 216 cases, there was limited information regarding obstetric history/ medical history and co-suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Stillbirth: Forty-one (41) cases reported foetal death/ neonatal death. Of these 41 cases, 17 cases reported stillbirth with foetal defects and remaining 24 cases reported stillbirth without foetal defect. Of these 41 cases, information regarding trimester of exposure was provided in 12 cases. Of these 12 cases, in 3 cases foetus was exposed during 1st trimester, in 6 cases, foetus was

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

exposed during 2nd trimester and in 3 cases exposure occurred during 3rd trimester. The most frequently reported events (>1 occurrence) in these 41 cases other than exposure related events were coded to PTs Foetal hypokinesia, Foetal death (10 each), Premature baby (6), Stillbirth, Congenital anomaly, Hypoxic-ischaemic encephalopathy (3 each), Foetal growth restriction, Neonatal anoxia, Hydrops foetalis, Death, Death neonatal, Umbilical cord abnormality (2 each). Of these 41 cases, in 11 cases mother had underlying medical history (i.e., spontaneous abortion, gestational diabetes, uterine anomaly etc.) which might have contributed to the reported events. In the remaining 30 cases there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

- Pregnancy outcome: Elective termination: Thirty (30) cases reported elective termination of pregnancy. Of these 30 cases, 29 cases reported elective termination due to foetal defects and 1 case reported elective termination without foetal defects or unknown. Of these 30 cases, information regarding trimester of exposure was provided in 13 cases. Of these 13 cases, in 10 cases foetus was exposed during 1st trimester, in 2 cases, foetus was exposed during 2nd trimester and in 1 case exposure occurred during 3rd trimester. The most frequently reported events (>1 occurrence) in these 30 cases other than exposure related events were coded to PTs Anencephaly (4), Foetal malformation, Foetal cardiac arrest, Foetal growth restriction (3 each), Abortion induced, Limb malformation, Trisomy 18, Foetal death, Cerebral ventricle dilatation, Foetal growth abnormality, Foetal heart rate abnormal (2 each). In these 30 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.
- Pregnancy outcome: Spontaneous abortion: One hundred one (101) cases reported spontaneous abortion. Of these 101 cases, information regarding trimester of exposure was provided in 44 cases. Of these 44 cases, in 37 cases, foetus was exposed during 1st trimester, in 5 cases foetus was exposed during 2nd trimester and in 2 cases exposure occurred during 3rd trimester. The most frequently reported events (≥5 occurrences) in these 101 cases other than exposure related events were coded to PTs Foetal growth restriction (36), Foetal heart rate abnormal (16), Congenital anomaly (15), Foetal death (12), Foetal cardiac arrest (8), Foetal growth abnormality (5). Of these 101 cases, in 14 cases mother had underlying medical history (i.e., spontaneous abortion, hypertension, polycystic ovaries, tobacco use, endometritis etc.) which might have contributed to the reported events. In the remaining 87 cases, there was limited information regarding obstetric history and co-suspect medications of mother which precluded meaningful causality assessment.

Of the 5239 cases, 2944 cases provided pregnancy outcomes which are provided in Table 60. Pregnancy outcome was pending or not provided in the remaining 2295 cases.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 60. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a]

Pregnancy outcome	Prospective cases 1877 (35.8% of pregnancy cases)					Retrospective cases 1067 (20.4% 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	2	0	0	3	0	1	0	0	4
Spontaneous abortion	0	45	6	0	66	0	251	30	0	350
Elective termination (foetal defects)	0	3	0	0	5	0	12	4	0	27
Elective termination (no foetal defects or unknown)	0	1	0	0	0	0	4	0	0	3
Stillbirth with foetal defects	0	1	0	0	1	0	3	6	0	10
Stillbirth without foetal defects	0	0	2	0	7	0	4	26	0	34
Live birth with congenital anomaly	0	14	2	0	17	0	7	10	0	19
Live birth without congenital anomaly	0	193	404	0	1105	0	12	103	0	147
Total	***0***	***259***	***414***	***0***	***1204***	***0***	***294***	***179***	***0***	***594***

a. 19 June 2021 through 18 December 2021.

Incremental review (Lactation)

- Number of lactation cases: 2670 (0.4% of 657,528 cases, the total PM dataset), compared to 966 cases (0.3%) retrieved in the PSUR #1.
  - Breast feeding baby cases: 1921, of which:
  - One thousand four hundred sixty-two (1462) 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.
  - Four hundred fifty nine (459) cases, 191 serious and 268 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 (>10 occurrences) were coded to the PTs Pyrexia (129), Diarrhoea (62), Rash (41), Infantile vomiting (35), Crying (33), Somnolence (32), Cough (23), Malaise (22), Fatigue, Irritability (21 each), Nasopharyngitis, Poor feeding infant (19 each), Vomiting (18), Infant irritability, Rhinorrhoea (16 each), Lethargy (15), Illness, Restlessness (13 each), Insomnia (12).
  - Breast feeding mother cases: 749, of which:
  - Eighty-nine (89) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
  - Six hundred sixty (660) cases, 242 serious and 418 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>20 occurrences) were coded to the PTs Headache (121), Fatigue (101), Pain in extremity (62), Pyrexia (60), Lymphadenopathy (55), Vaccination site pain (52), Myalgia (51), Nausea (50), Chills (41), Arthralgia (39), Pain (35), Malaise (33), Diarrhoea, Dizziness (25 each), Mastitis (21).

Literature

Review of the literature cumulatively through 30 December 2021 about the use of BNT162b2 in pregnant and lactating women was included in the response to the EMA email received on 17 December 2021 requesting a review of all available evidence on vaccination in pregnant or breastfeeding women, including a status update on relevant RMP measures and a discussion on the need to update the product information of Comirnaty. Conclusion provided in this response are noted below for convenience of review.

Accumulating data from literature on the epidemiology and outcomes of COVID-19 during pregnancy suggest that pregnant versus non-pregnant women with COVID-19 more frequently require hospitalisation, ICU admission, and invasive ventilation, compared with uninfected pregnant women. COVID-19 is also associated with increased risk of poor maternal/fetal outcomes, including preeclampsia, preterm birth, maternal/infant ICU admission, invasive ventilation, maternal death, and stillbirth.
The review of the safety information from literature reports of use of BNT162b2 in pregnant women did not reveal a new safety signal or concern. There is, however, limited information for long term post-natal outcomes, therefore no definite conclusions can be drawn.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 Comorbidities

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 SMQ Immune-mediated/autoimmune disorders (Narrow and Broad scope); HLGTs (Primary Path) Autoimmune disorders; Immune disorders NEC; HLT (Primary Path) Neuromuscular junction dysfunction.

Search criteria for frail patients with comorbidities (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.

Of the 67,108 cases, 9 cases were determined to be non-contributory and were not included in the discussion, since the subjects were exposed to the vaccine during pregnancy or breastfeeding.[61]

Clinical Trial Data

- Number of cases: 286 (blinded therapy [96], BNT162b2 [176] and placebo [14]) (39.7% of 721 cases, the total CT dataset), compared to 314 cases (44.7%) retrieved in the PSUR #1.
- Country of incidence: US (242), Argentina (29), Germany (5), China (3), Brazil, South Africa (2 each), [redacted] (1 each).
- Subjects' gender: female (157) and male (129).
- Subjects' age in years (n = 283), range: 4 - 91, mean: 60.2, median: 63.0.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Medical history (n = 286): the most frequently (> 20 occurrences) reported medical conditions included Hypertension (143), Type 2 diabetes mellitus (76), Gastrooesophageal reflux disease (55), Asthma (49), Obesity (47), Hypothyroidism (46), Depression, Hypercholesterolaemia (41 each), Seasonal allergy (40), Osteoarthritis (39), Hyperlipidaemia (36), Hysterectomy (35), Anxiety (33), Insomnia (32), Chronic obstructive pulmonary disease (22) and Benign prostatic hyperplasia (21).
- COVID-19 Medical history: COVID-19 (4) and COVID-19 immunisation (3).
- Co-suspects (n = 3): metamfetamine, naproxen and warfarin (1 each).
- Number of events: 347 reported in the relevant cases.
- Most frequently reported relevant PTs (≥4): Condition aggravated (7), Osteoarthritis, Pneumonia, Prostate cancer, Pulmonary embolism (6 each), Acute myocardial infarction, Death, Diverticulitis, Urinary tract infection (5 each), Acute kidney injury, Appendicitis, Atrial fibrillation, Breast cancer, Cerebrovascular accident, Chronic obstructive pulmonary disease, Maternal exposure during pregnancy, Sepsis and Syncope (4 each). All the most frequently reported serious adverse events were assessed as unrelated to BNT162b2 by the investigator and the Sponsor.
- Event outcome: fatal (25), resolved/resolving (241), resolved with sequelae (12), not resolved (67), and unknown (2).

Post-Authorisation Data

- Number of cases: 66,813 (10.2% of 657,528 cases, the total PM dataset), compared to 51,076 cases (15.6%) retrieved in the PSUR #1.
- MC cases (27,422), NMC cases (39,391).
- Country of incidence (≥ 200 occurrences): France (11,711), UK (10,469), US (9738), Japan (7011), Germany (4948), Italy (3440), Sweden (2118), Netherlands (1839), Czech Republic (1788), Denmark (1567), Canada (1507), Spain (1453), Austria (1070), Norway (1067), Ireland (744), Belgium (688), Finland (684), Portugal (497), Brazil (488), Greece (399), Switzerland (388), Croatia (349), Estonia (320) and Hungary (207).
- Subjects' gender: female (47,417), male (18,298) and unknown (1098).
- Subjects' age in years (n = 63,408), range: 0.5-121, mean: 53.6, median: 53.0.
- Medical history (n = 66,813): the most frequently (≥1100 occurrences) reported medical conditions included Asthma (14,450), Hypertension (11,357), Hypothyroidism (6309), Diabetes mellitus (6178), Drug hypersensitivity (4190), Type 2 diabetes mellitus (3565), Seasonal allergy (3149), Food allergy (2721), Rheumatoid arthritis (2605), Hypersensitivity (2525), Autoimmune thyroiditis (2457), Immunodeficiency (2434), Chronic obstructive pulmonary disease (2050), Breast cancer (1964), Suppressed lactation[19] (1931), Depression (1926), Obesity (1754), Atrial fibrillation (1669), Psoriasis (1487), Multiple sclerosis (1367), Chronic kidney disease (1352), Arthritis (1343), Gastrooesophageal reflux disease (1314), Migraine (1245), Dyslipidaemia (1207), Fibromyalgia (1131), Type 1 diabetes mellitus (1108), Thyroid disorder (1104), Crohn's disease (1101) and Colitis ulcerative (1100).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- COVID-19 Medical history: the most frequently (≥10 occurrences) reported COVID-19 (3061), Suspected COVID-19 (1394), COVID-19 pneumonia (72), Post-acute COVID-19 syndrome (45), SARS-CoV-2 test positive (31), Exposure to SARS-CoV-2 (27), Asymptomatic COVID-19 (26) and COVID-19 immunisation (16).
- Co-suspects (n = 559): the most frequently (≥3 occurrences) reported co-suspect vaccines/medications included apixaban (13), acenocoumarol (11), acetylsalicylate lysine (8), rivaroxaban (7), COVID-19 AstraZeneca vaccine (5), atorvastatin calcium, amoxicillin/clavulanate, clopidogrel, paracetamol, furosemide, fentanyl, morphine (4 each), oxycodone hydrochloride, haloperidol, fluindione, clozapine and acetylsalicylic acid (3 each).
- Number of events: 277,165.
- Event seriousness:[20] serious (121,617), non-serious (155,684).
- Most frequently reported relevant PTs (≥2%): Headache (11,206), Fatigue (9760), Pyrexia (9498), Pain in extremity (6018), Nausea (5698) and Vaccination site pain (5423).
- Reported event outcome:[47] fatal (5679), resolved/resolving (115,931), resolved with sequelae (5770), not resolved (72,515), unknown (78,528).

Conclusion

The reporting proportion of not resolved cases (37.1%), cases resolved with sequelae (2.3%), and fatal cases (3.1%) in subjects with comorbidities is slightly higher than the reporting proportion observed in the overall population (32.4% for outcome of not resolved, 1.1% for outcome of resolved with sequelae and 0.8% for fatal outcome). This is expected, considering that most of the cases reporting subjects 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 summarised 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 110 (BNT162b2 [68], blinded therapy [39], and placebo [3]) (15.3% of 721 cases, the total CT dataset), compared to 105 cases (15.0%) retrieved in the PSUR #1.
- Country of incidence: US (88), Argentina (15), Germany (4), South Africa (2), and [redacted] (1).
- Subjects' gender: female (70), and male (40).
- Subjects' age in years (n = 109), range: 13 – 86, mean: 62.8, median: 65.
- Medical history (n = 110): the most frequently (≥5 occurrences) reported relevant medical conditions included Hysterectomy (35), Breast cancer (9), Basal cell carcinoma, Cholecystectomy, Prostate cancer (8 each), Radiotherapy (7), Benign prostatic hyperplasia, Breast conserving surgery, Chemotherapy, Diverticulitis, Tonsillectomy (6 each), Gastrectomy, HIV infection, Nephrectomy (5 each).
- COVID-19 Medical history: COVID-19 (3).
- Co-suspects (n = 3): The reported co-suspect agents included ibuprofen, levothyroxine, and oxycodone (1 each).
- Number of events: 134.
- Most frequently reported clinical PTs (>2%): Diverticulitis (5, 4.5%), Prostate cancer (5, 4.5%), Cerebrovascular accident (3, 2.7%), Condition aggravated (3, 2.7%), Invasive ductal breast carcinoma (3, 2.7%), Small intestinal obstruction (3, 2.7%), Urinary tract infection (3, 2.7%).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.
- Time to event onset: (n = 79 events),[147] range: <24 hours to 181 days, median: 96 days.
  - <24 hours: 1 event;
  - 1 day: 0 event;
  - 2-7 days: 1 event;
  - 8-14 days: 4 events;
  - 15-30 days: 14 events;
  - 31-181 days: 59 events.

[147] This number does not include 42 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Duration of event: (n = 64 of 68 events with outcome of resolved/resolved with sequelae)[148]
  - < 24 hours: 2 events;
  - 1 day: 11 events;
  - 2-7 days: 24 events;
  - 8-14 days: 10 events;
  - 15-30 days: 7 events;
  - 31-181 days: 10 events.
- Reported event outcome: fatal (6), resolved/resolving (85), resolved with sequelae (3), not resolved (38), and unknown (2).

Post-Authorisation Data

- Number of cases: 14,657 (2.2% of 657,528 cases, the total PM dataset), compared to 11,995 cases (3.7%) retrieved in the PSUR #1.
- MC cases (6417), NMC cases (8240).
- Country of incidence: France (3429), UK (3178), US (1898), Japan (1106), Germany (937), Italy (707), Czech Republic (499), Sweden (318), Denmark (280), Spain (273), Netherlands (272); the remaining 1760 cases were distributed among 59 countries.
- Subjects' gender: female (9970), male (4381) and unknown (306).
- Subjects' age in years (n = 13,752), range: 7 – 121, mean: 59.0, median: 60.0.
- Medical history (n = 14,657). The most frequently (≥200 occurrences) reported relevant medical conditions included Immunodeficiency (2435), Breast cancer (1964), Thyroidectomy (858), Neoplasm malignant (729), Hysterectomy (688), Prostate cancer (663), Chemotherapy (477), Renal transplant (415), Neoplasm (409), Radiotherapy (405), Surgery (334), Colon cancer (313), Chronic lymphocytic leukaemia (310), Thyroid cancer (306), Lung neoplasm malignant (273), Malignant melanoma (272), Cholecystectomy (270), Appendicectomy (228), Splenectomy (221), Lymphoma (217), Mastectomy (201).
- COVID-19 Medical history (n = 1133): COVID-19 (662), Suspected COVID-19 (416), COVID-19 pneumonia (23), Post-acute COVID-19 syndrome (11), SARS-CoV-2 test positive (8), Exposure to SARS-CoV-2 (5), Asymptomatic COVID-19 (4), Coronavirus infection (3), SARS-CoV-2 antibody test positive (1).
- Co-suspects (n = 453): The most frequently (≥10 cases) reported co-suspect vaccines/medications included Influenza vaccine (44), COVID-19 Vaccine NRVV AD

[148] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

(22), Hepatitis A vaccine (15), pembrolizumab (14), Influenza vaccine (surface antigen, inactivated, adjuvanted) (13), adalimumab (12), nivolumab (11) and rituximab (10).

- Number of events: 62,595.
- Event seriousness:[20] serious (31,483), non-serious (31,142).
- Most frequently reported clinical PTs (≥3%): Headache (2273, 15.5%), Fatigue (1996, 13.6%), Pyrexia (1990, 13.6%), Immunisation[23] (1771, 12.1%), Pain in extremity (1353, 9.2%), Nausea (1160, 7.9%), Arthralgia (1142, 7.8%), Myalgia (1045, 7.1%), Vaccination site pain (1039, 7.1%), Pain (966, 6.6%), Interchange of vaccine products (955, 6.5%), Asthenia (939, 6.4%), Chills (911, 6.2%), Dyspnoea (906, 6.2%), Malaise (900, 6.1%), Dizziness (835, 5.7%), Lymphadenopathy (738, 5.0%), COVID-19 (638, 4.4%), Diarrhoea (600, 4.1%), Chest pain (538, 3.7%), Vomiting (501, 3.4%), Rash (491, 3.3%), Pruritus (480, 3.3%), Influenza like illness (460, 3.1%), Paraesthesia (433), 3.0%).
- Time to event onset (n = 44,061 events),[149] range: <24 hours to 181 days, median: 1 day.
  - < 24 hours: 15,738 events;
  - 1 day: 9409 events;
  - 2-7 days: 8976 events;
  - 8-14 days: 3072 events;
  - 15-30 days: 2853 events;
  - 31-181 days: 4013 events.
- Duration of event (n = 6361 of 6370 events with outcome of resolved/resolved with sequelae)[150]
  - < 24 hours: 449 events;
  - 1 day: 1534 events;
  - 2-7 days: 2970 events;
  - 8-14 days: 649 events;
  - 15-30 days: 450 events;
  - 31-181 days: 309 events.
- Event outcome:[47] fatal (1709), resolved/resolving (23,823), resolved with sequelae (1133), not resolved (15,030), unknown (21,245).

---

[149] This number does not include 455 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.

[150] This number does not include 9 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Analysis by age group

- CT Data: Paediatric (2), Adults (50), Elderly (57), and Unknown (1).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (119), Adults (7937), Elderly (5754) and Unknown (847).
  - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to PTs COVID-19, Lymphadenopathy and Paraesthesia. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (2.3% [179 cases] in adults vs 7.6% [435 cases] in elderly). In majority of the elderly cases (424 of 435 cases) that reported the event coded to PT COVID-19, the co-reported events was coded to the PTs Drug ineffective (161 cases) and Vaccination failure (263 cases). These cases are also summarized in Section 16.3.4.5 *Lack of Therapeutic Efficacy*).
  - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (7.1% [566 cases] in adults vs 2.0% [113 cases] in elderly) compared to the elderly population. And a higher reporting proportion of events coded to PT Paraesthesia was observed in the adult population (4.3% [339 cases] in adults vs 1.4% [80 cases] in elderly) compared to the elderly population.
  - No comparison was made to the paediatric population considering limited number of cases.

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.

Clinical Trial Data

- Number of cases: 101 (BNT162b2 [60], blinded therapy [33], placebo [7] and BNT162b2s01 [1]) (14.0% of 721 cases, the total CT dataset), compared to 123 cases (17.5%) retrieved in the PSUR #1.
- Of the 101 cases, the most frequently reported PTs (≥3%) included: Osteoarthritis (4, 4.0%), Pneumonia (4, 4.0%), Acute myocardial infarction (3, 3.0%), Appendicitis (3, 3.0%), Appendicitis perforated (3, 3.0%), and Atrial fibrillation (3, 3.0%).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Event outcome: fatal (6), resolved/resolving (103), resolved with sequelae (3), and not resolved (18).
- BNT162b2 related events coded to the PT: Hepatic enzyme increased (1). Time to onset of event is 4 days and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-Authorisation Data

- Number of cases: 35,514 (5.4% of 657,528, the total PM dataset), compared to 26,352 cases (8.1%) retrieved in the PSUR #1.
- MC cases (13,435), NMC cases (22,079).
- Of the 35,514 cases, the most frequently reported clinical PTs (>3%) included: Headache (6193, 17.4%), Fatigue (5492, 15.5%), Pyrexia (4926, 13.9%), Pain in extremity (3343, 9.4%), Arthralgia (3184, 9.0%), Nausea (3114, 8.8%), Myalgia (2979, 8.4%), Vaccination site pain (2895, 8.2%), Pain (2662, 7.5%), Immunisation[23] (2548, 7.2%), Chills (2543, 7.2%), Dizziness (2487, 7.0%), Malaise (2397, 6.7%), Dyspnoea (2176, 6.1%), Asthenia (2066, 5.8%), Lymphadenopathy (1597, 4.5%), Diarrhoea (1546, 4.4%), Paraesthesia (1527, 4.3%), Chest pain (1390, 3.9%), Interchange of vaccine products (1360, 3.8%), Pruritus (1323, 3.7%), Rash (1299, 3.7%), Vomiting (1169, 3.3%), Hypoaesthesia (1161, 3.3%).
- Event seriousness: serious (63,726), non-serious (86,866).
- Event outcome: fatal (2243), resolved/resolving (62,062), resolved with sequelae (3197), not resolved (41,644), unknown (42,062).
- The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

Exacerbation or Flare-up

- During the reporting interval, the focus of the analysis has been narrowed to include exacerbation or flare of PTs of interest (ie, condition aggravated, disease progression), rather than all events.
- Of the 1452 cases that reported PTs indicative of exacerbation or flare, 711 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (eg, abdominal distension, acute coronary syndrome, arrhythmia, deep vein thrombosis, kidney disease, migraine, trigeminal neuralgia). Of note, 12 of these 711 cases also reported events indicative of exacerbation or flare and are included in the relevant 751 cases below.

Therefore, 751 cases are included in the analysis below.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Clinical Trial Data

- Number of cases: 1 (BNT162b2) (0.1% of 721 cases, the total CT dataset), compared to 1 (0.1%) retrieved in the PSUR #1.
- A [redacted] case, involving a [redacted] subject with a history of interstitial lung disease, experienced an exacerbation of interstitial lung disease (PT Condition aggravated) approximately 107 days after receiving the third dose of the BNT162b2. The event resolved after 1 day and was considered unrelated to BNT162b2.

Post-Authorisation Data

- Number of cases: 750 (0.1% of 657,528 cases, the total PM dataset), compared to 371 (0.1%) retrieved in the PSUR #1.
- MC cases (355), NMC cases (395).
- Country of incidence (>30 occurrences): France (227), UK (96), Germany, US (80 each), Netherlands (40), Japan (38), and Italy (31).
- Subjects' gender: female (505), male (228) and unknown (17).
- Subjects' age in years (n = 704), range: 12 - 99, mean: 50.4, median: 50.0.
- Relevant medical history: the most frequently (>20 occurrences) reported medical conditions included: Pericarditis (73), Hypothyroidism (50), Myocarditis, Rheumatoid arthritis (46 each), Immune thrombocytopenia (41), Colitis ulcerative (39), Autoimmune thyroiditis, Diabetes mellitus (36 each), Ankylosing spondylitis, Psoriasis (34 each), Basedow's disease (32), Multiple sclerosis (31), Autoimmune disorder 27), Sjogren's syndrome (24), Arthritis, Systemic lupus erythematosus (23 each).
- COVID-19 Medical history (n = 48): COVID-19 (38), Suspected COVID-19 (8), Asymptomatic COVID-19, SARS-CoV-2 test positive (1 each).
- Co-suspect vaccines/medications: tofacitinib (3), COVID-19 Vaccine NRVV AD (2), acetylsalicylic acid, adalimumab, amitryptyline, apixaban, baclofen, colchicine, COVID-19 vaccine, dupilumab, eltrombopag, ibuprofen, influenza vaccine, insulin, COVID-19 J&J vaccine, melatonin, methotrexate, methylprednisolone, lidocaine, mycophenolate, ocrelizumab, pneumococcal vaccine, prednisolone, prednisone, ruxolitnib, tacrolimus, teriflunomide, and varicella zoster vaccine (1 each).
- Number of events: 3967 (of which 756 were events of interest ie, exacerbation/flare AEs).
- Relevant event seriousness:[20] serious (617), non-serious (145).
- Most frequently reported relevant PTs (≥2%): Condition aggravated (416), Disease recurrence (327).
- Time to event onset (n = 2536 events), range: 0 - 158 days, median: 3 days.
  - <24 hours: 555 events;
  - 1 day: 438 events;
  - 2-7 days: 842 events;

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

  - 8-14 days: 269 events;
  - 15-30 days: 246 events;
  - 31-181 days: 186 events.

- Duration of event (n = 285 events with outcome resolved/resolved with sequelae)[151], range: 0 - 126 days.

  - <24 hours: 10 events;
  - 1 day: 24 events;
  - 2-7 days: 134 events;
  - 8-14 days: 38 events;
  - 15-30 days: 43 events.
  - 31-181 days: 36 events

- Relevant event outcome: fatal (4), resolved/resolving (310), resolved with sequelae (14), not resolved (281), unknown (153).

Analysis by age group

- CT: Elderly (1).

- PM: Paediatric (15), Adults (534), Elderly (158) and Unknown (43).

  - Exacerbation and/or flare of underlying autoimmune or inflammatory disorders occurred more frequently in the adult population which is likely due to the fact that the largest group of vaccinated individuals reporting adverse events are in this age group. Also, the autoimmune or inflammatory disorders often occur during adulthood.

Analysis by dose

- Number of vaccine doses administered at the time of the event onset: 1 dose in 336 cases, 2 doses in 337 cases, 3 doses in 30 cases; in 108 cases the dose was either not specified or reported as other.

- There are no differences between the AEs reported after the 1st and 2nd dose. Due to the low number of cases who received 3 doses, a comparison of AEs was not made.

Conclusion

Overall, there were 751 cases (1 CT case and 750 PM cases [0.1% of the overall dataset]) that reported exacerbation/flares in subjects with autoimmune or inflammatory disorders following administration of BNT162b2. Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders occurred more frequently in the adult population which is

[151] This number does not include 394 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 Comorbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders, active Tuberculosis)

Search criteria - Patients with Medical history of PTs included in HLGTs (Primary Path) Bronchial disorders (excl neoplasms), Heart failures, Mental impairment disorders, Movement disorders (incl parkinsonism), Nephropathies, Pulmonary vascular disorders, Renal disorders (excl nephropathies); HLTs (Primary Path) Autonomic nervous system disorders, Diabetes mellitus (incl subtypes), Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis, Motor neurone diseases, Muscle tone abnormal, Neuromuscular disorders NEC, Pulmonary hypertensions, Respiratory failures (excl. neonatal); patients with Medical history of ongoing Tuberculosis.

Clinical Trial Data

- Number of cases: 176 (BNT162b2 [109], blinded therapy [57], and placebo [10]) (24.4% of 721 cases, the total CT dataset), compared to 193 cases (27.5%) retrieved in the PSUR #1.
- Country of incidence: US (144), Argentina (22), Germany (4), China (2), [redacted] (1 each).
- Subjects' gender: female (81), and male (95).
- Subjects' age in years (n = 174)[152], range: 5 – 88, mean: 60.8, median: 62.5.
- Medical history (n = 176): the most frequently (≥15 occurrences) reported relevant medical conditions included Hypertension (104), Type 2 diabetes mellitus (76), Asthma (49), Obesity (38), Gastrooesophageal reflux disease (31), Osteoarthritis (29), Hypercholesterolaemia, Seasonal allergy (28 each), Hyperlipidaemia (26), Depression (24), Anxiety, Chronic obstructive pulmonary disease (22 each), Hypothyroidism (21), Insomnia (20), Hysterectomy (16), and Benign prostatic hyperplasia (15).
- COVID-19 Medical history: COVID-19 (3).
- Co-suspects (n = 73): The reported co-suspect agents included ibuprofen (2), bamlanivimab, cocaine, diazepam, dulaglutide, etesevimab, fluoxetine, glipizide, ibuprofen, losartan, metformin, and oxycodone (1 each).
- Number of events: 225.

[152] Excluded 1 case with contradictory demographic information (physical characteristics not matching with the reported age value) from reported minimum age calculation.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Most frequently reported clinical PTs (>2%): Urinary tract infection (6, 3.4%), Pulmonary embolism (5, 2.8%), Chronic obstructive pulmonary disease (4, 2.3%), Condition aggravated (4, 2.3%), and Coronary artery disease (4, 2.3%).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.
- Time to event onset: (n = 144 events),[153] range: <24 hours to 181 days, median: 97 days.
  - <24 hours: 1 event;
  - 1 day: 0 event;
  - 2-7 days: 5 events;
  - 8-14 days: 6 events;
  - 15-30 days: 14 events;
  - 31-181 days: 118 events.
- Duration of event: (n = 117 of 119 events with outcome of resolved/resolved with sequelae)[154]
  - < 24 hours: 7 events;
  - 1 day: 11 events;
  - 2-7 days: 48 events;
  - 8-14 days: 18 events;
  - 15-30 days: 12 events;
  - 31-181 days: 20 events
  - 240-365 days: 1 event.
- Reported event outcome: fatal (19), resolved/resolving (153), resolved with sequelae (11), not resolved (41), and unknown (1).

Post-Authorisation Data

- Number of cases: 33,889 (5.2 % of 657,528, the total PM dataset), compared to 28,023 cases (8.6%) retrieved in the PSUR #1.
- MC cases (15,806), NMC cases (18,083).
- Country of incidence: France (5,753), Japan (4,905), US (4,648), UK (4,517), Germany (2,563), Italy (1,433), Sweden (1,102), Czech Republic (1,058), Denmark (955), Netherlands (821), Spain (774), Canada (636), Austria (532), Norway (496), Finland (391), Ireland (389), Belgium (357), Portugal (279), Estonia (222), Switzerland (218),

[153] This number does not include 59 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.

[154] This number does not include 2 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Brazil (215), Croatia (134), South Africa (124), Mexico (119), Greece (116), Hungary (110), Panama (107); the remaining 915 cases were distributed among 61 countries

- Subject's gender: female (21,955), male (11,471), and unknown (463).
- Subject's age in years (n = 32,484)[155], range: 5 - 109 years, mean: 55.2, median: 55.0.
- Medical history (n = 33,889): the most frequently reported (≥500 cases) included: Asthma (14450), Hypertension (7862), Diabetes mellitus (6178), Type 2 diabetes mellitus (3565), Drug hypersensitivity (2149), Seasonal allergy (2118), Chronic obstructive pulmonary disease (2050), Food allergy (1756), Hypersensitivity (1667), Chronic kidney disease (1352), Hypothyroidism (1306), Obesity (1280), Atrial fibrillation (1231), Depression (1131), Type 1 diabetes mellitus (1108), Cardiac failure (1018), Pulmonary embolism (928), Dyslipidaemia (878), Suppressed lactation[19] (785), Gastrooesophageal reflux disease (774), Dementia (697), Mite allergy (672), Hypercholesterolaemia (669), Allergy to animal (661), Migraine (637), Pain (622), Osteoarthritis (577), Steroid therapy (569), Anxiety, Hyperlipidaemia, Immunodeficiency , Renal failure (562 each), Cerebrovascular accident (535), Sleep apnoea syndrome (525), Osteoporosis (515).
- COVID-19 Medical history (n = 2382): COVID-19 (1617), Suspected COVID-19 (619), COVID-19 pneumonia (47), Post-acute COVID-19 syndrome (28), Exposure to SARS-CoV-2 (21), Asymptomatic COVID-19 (20), SARS-CoV-2 test positive (15), Coronavirus infection (12), SARS-CoV-2 antibody test positive (2), Occupational exposure to SARS-CoV-2 (1).
- Co-suspects (n = 636): The most frequently (>10 occurrences) reported co-suspect vaccines/medications included Influenza vaccine (88), COVID-19 Vaccine NRVV AD (45), Influenza vaccine (surface antigen, inactivated, adjuvanted) (26), adalimumab (23), COVID-19 Vaccine MRNA (MRNA 1273) (18), Hepatitis A vaccine (16), apixaban (12), Influenza vaccine INACT SPLIT 4V (11).
- Number of events: 140,825
- Relevant event seriousness:[20] serious (77,221), non-serious (63,658).
- Most frequently reported (≥3%) clinical PTs: Headache (5392, 15.9%), Pyrexia (5031, 14.8%), Fatigue (4655, 13.7%), Dyspnoea (3062, 9.0%), Pain in extremity (2871, 8.5%), Nausea (2861, 8.4%), Vaccination site pain (2855, 8.4%), Myalgia (2548, 7.5%), Arthralgia (2431, 7.2%), Malaise (2395, 7.1%), Pain (2369, 7.0%), Dizziness (2272, 6.7%), Chills (2237, 6.6%), Immunisation[23] (2225, 6.6%), Asthenia (1900, 5.6%), Pruritus (1376, 4.1%), Chest pain (1358, 4.0%), Diarrhoea (1352, 4.0%), COVID-19 (1319, 3.9%), Cough (1275, 3.8%), Lymphadenopathy (1274, 3.8%), Vomiting (1241, 3.7%), Interchange of vaccine products (1119, 3.3%), Rash (1106, 3.3%), and Paraesthesia (1074, 3.2%). All the clinical events are listed events per the current

[155] Excluded 3 cases with contradictory demographic information (physical characteristics not matching with the reported age value) from reported minimum age calculation.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

COVID-19 mRNA vaccine RSI and were consistent with the most frequent events observed in the overall population.

- Time to event onset (n = 105,814 events),[156] range: <24 hours to 181 days, median: 1 day.
  - < 24 hours: 41,331 events;
  - 1 day: 24,360 events;
  - 2-7 days: 20,464 events;
  - 8-14 days: 6331 events;
  - 15-30 days: 5863 events;
  - 31-181 days: 7465 events.

- Duration of event (n = 15,728 of 15,745 events with outcome of resolved/resolved with sequelae)[157]
  - < 24 hours: 1887 events;
  - 1 day: 3899 events;
  - 2-7 days: 6715 events;
  - 8-14 days: 1439 events;
  - 15-30 days: 1118 events;
  - 31-181 days: 670 events.

- Relevant event outcome:[47] fatal (4398), resolved/resolving (59,616), resolved with sequelae (3037), not resolved (34,030), unknown (40,290).

Analysis by age group

- CT Data: Paediatric (7), Adults (88), Elderly (80), and Unknown (1).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (804), Adults (20,163), Elderly (11,677) and Unknown (1245).
  - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to PTs COVID-19, Lymphadenopathy, and paraesthesia. A higher reporting proportion of events coded to PT COVID-19 was observed in the elderly population when compared to the adult population (1.7% [341 cases] in adults vs 8.1% [942 cases] in elderly). In majority of the elderly cases (906 of 942 cases) that reported the event coded to PT COVID-19, the co-reported events was coded to the

[156] This number does not include 1187 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.

[157] This number does not include 18 events for which partial administration and/or events with a not meaningful time to onset/cessation value as per reported information.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

PTs Drug ineffective (333 cases) and Vaccination failure (573 cases). These cases are also summarised 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 (5.4% [1082 cases] in adults vs 1.1% [126 cases] in elderly) compared to the elderly population. And a higher reporting proportion of events coded to PT Paraesthesia was observed in the adult population (4.4% [881 cases] in adults vs 1.4% [158 cases] in elderly) compared to the elderly population.
- No comparison was made to the paediatric population considering limited number of cases.

Conclusion

The reporting proportion of not resolved cases (33.5%) and cases resolved with sequelae (2.4%) in frail subjects is similar to the reporting proportion observed in the overall population (32.4% for outcome of not resolved, 1.1% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (4.8%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (0.8%). This is expected, considering that most of the cases reporting a fatal outcome (86%) among the frail subjects involved subjects over 75 years of age who, due to their advanced age and underlying comorbidities, are more likely to die than younger individuals. Underlying comorbidities are likely to be contributory to their deaths.

The vaccine has been studied in individuals with stable chronic diseases (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 227 cases, 209 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - in 7 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 22 cases, the drug possibly interacting with BNT162b2 was not specified;
  - in 9 cases, alcohol (5), food (3) or herbal (1) interaction occurred;
  - in 1 case BNT162b2 was not involved in the interaction;
  - in 170 cases (of which 83 were serious), the subjects experienced drug interactions with the following medications (≥2): rituximab (11), etonogestrel (5), bupropion, etanercept, sertraline hydrochloride, tramadol (4 each), amoxicillin, ibuprofen, immunoglobulin human normal, infliximab, lisdexamfetamine mesilate, naproxen, oxycodone, ustekinumab (3 each), acenocoumarol, adalimumab, antibiotics, apixaban, botulinum toxin type A, clozapine, dexamfetamine sulfate, estradiol, norethisterone

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

acetate, gabapentin, glatiramer acetate, hyaluronic acid, hydromorphone hydrochloride, lamotrigine, levothyroxine sodium, lorazepam, metformin, mycophenolate mofetil hydrochloride, ocrelizumab, pantoprazole, paracetamol, quetiapine fumarate, rivaroxaban, semaglutide, testosterone, tofacitinib citrate, valproate, warfarin (2 each).

- Eighteen of the 227 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, as in the PSUR #1.

Post-Authorisation Data

- Number of cases: 18 (0.003% of 657,528 cases, the total PM dataset), compared to 2 (0.001%) retrieved in the PSUR #1.
- MC case (11), NMC case (7).
- Country of incidence: Norway, US (5 each), Denmark, Germany (2 each), [redacted] (1 each).
- Subjects' gender: female (9), male (7), unknown (2).
- Subjects' age in years (n = 15): range: 16 - 75, mean: 48.5, median: 52.0.
- Medical history (n = 8): Asthma (3), Headache, Joint injury (2 each), Chronic obstructive pulmonary disease, Dizziness, Drug hypersensitivity, Gastrooesophageal reflux disease, Glaucoma, Herpes zoster, Hypersensitivity, Hypertension, Hypotension, Myalgia, Pain, Prophylaxis against gastrointestinal ulcer, Tension headache and Urticaria chronic (1 each).
- COVID-19 Medical history: COVID-19 (1).
- Co-suspect vaccines (n = 16): COVID-19 AstraZeneca vaccine (7), influenza vaccine (4), COVID-19 Moderna vaccine (2), BCG vaccine, diphtheria vaccine toxoid, tetanus vaccine toxoid and varicella zoster vaccine RGE (CHO) (1 each). In additional 2 cases interacting vaccines were reported as concomitant drugs: RSV vaccine and diphtheria vaccine toxoid/tetanus vaccine toxoid (1 each).
- Other co-suspects (n = 2): azelastine hydrochloride/fluticasone propionate, desloratadine, levonorgestrel and omalizumab (1 each).
- Number of events: 116 (of which 19 were events of interest).
- Relevant event seriousness: serious (7), non-serious (12).
- Relevant PT: Drug interaction (17), Drug-disease interaction and Potentiating drug interaction (1 each).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

- Co-reported AEs (≥ 2%): Headache (8), Off label use (5), Hypertension, Interchange of vaccine products, Product use issue (4 each), Pain, Pyrexia (3 each), COVID-19 immunisation, Crying, Diarrhoea, Discomfort, Dizziness, Fatigue, Herpes zoster, Hypoaesthesia, Immunisation,[23] Loss of personal independence in daily activities, Malaise, Muscle spasms, Muscular weakness, Nausea and Tinnitus (2 each).
- Time to event onset: n = 10, range: <1 - 94 days, median: <1 day.
  - >24 hours: 6 events;
  - 2-7 days: 2 events;
  - 30 days: 1 event;
  - 31-94 days: 1 event.
- Relevant event outcome: resolving/resolved (3), not resolved (6) and unknown (10).

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

Among the overall 227 cases, 209 were considered not relevant, as a drug interaction did not occur in 7 cases, the interacting agents was not specified in 22 cases, BNT162b2 was not involved in 1 case and in the remaining 179 cases, the interaction occurred with alcohol, food, herbal or concurrent medications rather than another vaccine.

There were 18 cases in the overall post-marketing dataset that involve a vaccine interaction. The most frequently co-reported events other than off label use and interchange of vaccines PTs were events or consequences of events consistent with the known reactogenicity of the vaccine and listed in Section 4.4. *Special warnings and precautions for use* and Section 4.8 *Undesirable effects* of the CDS or possibly attributable to the co-suspect vaccine (in one of the 2 cases reporting Herpes zoster, the subject received the varicella zoster vaccine, that is known to possibly caused this). Of note, one case also reported an interaction with the previous COVID-19 infection (PT Drug-disease interaction).

There is no indication of a safety signal of interference of immune response of vaccines noted based on the review of these cases.

16.4. Characterisation of Risks

During the reporting period, the MAH submitted to EMA the updated EU-RMP version 2.3 in support of the EU submission for the inclusion of the new important identified risk of myocarditis and pericarditis in the list of safety concerns.

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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

What constitutes an important risk depends upon several factors including the impact on the individual subject, the seriousness of the risk and its severity, and the impact on public health. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered. Risks may be related to nonclinical or clinical safety or quality issues. The intended purpose and impact of the product 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 61 characterises the important identified and potential risks of BNT162b2.

Table 61. Characterisation of Important Risks

Important Identified Risk: Anaphylaxis *Search criteria* *PTs: 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 61. Characterisation of Important Risks

	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 December 2021)	***Post-marketing sources:*** - No. of cases: 7444. - Relevant PTs: Anaphylactic reaction (6539), Anaphylactic shock (985), Anaphylactoid reaction (167), Anaphylactoid shock (8). - Frequently reported additional PTs (>200 occurrences): Dyspnoea (1653), Nausea (993), Pruritus (914), Dizziness (790), Erythema (784), Cough (718), Headache (686), Rash (686), Urticaria (669), Tachycardia (612), Throat tightness (551), Blood pressure increased (496), Malaise (476), Vomiting (426), Pyrexia (420), Oropharyngeal discomfort (417), Feeling abnormal (412), Blood pressure decreased (405), Hypoaesthesia (350), Palpitations (349), Chest discomfort (338), Paraesthesia (323), Fatigue (318), Wheezing (316), Hypersensitivity (295), Chills (291), Hypotension (285), Loss of consciousness (277), Heart rate increased (264), Pallor (257), Flushing (255), Pharyngeal swelling (255), Depressed level of consciousness (254), Oxygen saturation decreased (254), Swollen tongue (253), Tremor (249), Asthenia (248), Dysphonia (241), Abdominal pain (234), Angioedema (233), Hypertension (229), Throat irritation (225), Hyperhidrosis (223), Lip swelling (223), Cold sweat (219), Feeling hot (219), Presyncope (213), Diarrhoea (209), and Respiratory distress (206). - Subjects' gender: female (5946), male (1180), unknown (318) - Subjects' age in years (n = 6804), range: 8 – 104, mean: 44.7, median: 44. - Age group: Paediatric (203), Adults (5786), Elderly (828) and Unknown (627). - Case source: Spontaneous (7303), Literature (124), Non-interventional study (16), Solicited (1). - Event seriousness: serious (7695), non-serious (4) - Event outcome: Fatal (49), Not resolved (447), Resolved with sequelae (124), Resolved/resolving (5672), Unknown data (1416). ***Clinical trials:*** - No. of cases: 5 (of which 3 involved blinded therapy) - No. of SAEs: 5 - The most common PTs: Anaphylactic reaction (3), 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.
Important Identified Risk: Myocarditis and Pericarditis *Search criteria*	

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 61. Characterisation of Important Risks

Myocarditis - PTs: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis. *Pericarditis - PTs: Autoimmune pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.*	
Characterisation	*Potential mechanisms, evidence source and strength of evidence* A mechanism of action (MOA) by which the vaccine could cause myocarditis and pericarditis has not been established. Nonclinical studies, protein sequence analyses and animal studies in rats and non-human primates have not identified a MOA. Hypotheses for MOA include an immune stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response. *Risk factors and risk groups* Post-authorization reports have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the EU and US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine. *Preventability* Due to an unknown MOA, preventative measures cannot be indicated. *Impact on the risk benefit balance of the biologic product* The vaccine continues to have a favorable risk benefit balance. *Public health impact* Considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.
Cumulative Case Characterisation (through 18 December 2021)	***Post-marketing sources:*** Cumulatively, there were 12578 potentially relevant cases of Myocarditis and Pericarditis: 6879 cases reported myocarditis and 5699 cases reported pericarditis (in 890 of these 12578 cases, the subjects developed both myocarditis and pericarditis). Myocarditis - No. of cases: 6879 - Relevant PTs: Myocarditis (6869), Autoimmune myocarditis, Eosinophilic myocarditis (4 each), Hypersensitivity myocarditis (3), Immune-mediated myocarditis (1). - Frequently reported additional PTs (≥200 occurrences): Chest pain (2095), Dyspnoea (1217), Pyrexia (1020), Pericarditis (888), Fatigue (857), Palpitations (781), Chest discomfort (583), Troponin increased (529), Headache (514), Tachycardia (498), Immunisation[23] (359), Off label use (334), Malaise (288), Dizziness (279), Nausea (275), Inappropriate schedule of product administration (272), Asthenia (264), Myalgia (257), Interchange of vaccine products (249), Pain (238), Chills (237), Pain in extremity (235), and Pericardial effusion (206).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 61. Characterisation of Important Risks

Cumulative Case Characterisation (through 18 December 2021) *Cont'd*	- Subjects' gender: female (2183), male (4388), unknown (308) - Subjects' age in years (n = 6125), range: 6-102, mean: 34.6, median: 30.0. - Age group: Paediatric (1063), Adults (4628), Elderly (489) and Unknown (699). - Case source: Spontaneous (6736), Literature (128), Clinical study (12), Solicited (3) - Event seriousness: serious (6877), non-serious (4) - Event outcome: Fatal (93), Not resolved (2055), Resolved with sequelae (129), Resolved/resolving (2811), Unknown data (1804). *Pericarditis* - No. of cases: 5699. - Relevant PTs: Pericarditis (5651), Pleuropericarditis (47), Pericarditis constrictive (11), Pericarditis adhesive (1). - Frequently reported additional PTs (≥2%): Chest pain (2002), Dyspnoea (1132), Myocarditis (889), Fatigue (674), Palpitations (593), Pyrexia (585), Chest discomfort (468), Pericardial effusion (416), Headache (388), Tachycardia (384), Immunisation[23] (259), Dizziness (233), Malaise (219), Myalgia (216), Off label use (201), Arthralgia (192), Nausea (184), Pain (179), Pain in extremity (168), Asthenia (159), Inappropriate schedule of product administration (157), Interchange of vaccine products (153), Paraesthesia (131), and Chills (129). - Subjects' gender: female (2546), male (3021), unknown (132). - Subjects' age in years (n = 5303), range: 2 - 98, mean: 39.2, median: 36. - Age group: Paediatric (419: adolescent 414; children 5), Adults (4433), Elderly (542) and Unknown (305). - Case source: Spontaneous (5646), Literature (29), Solicited (1). - Event seriousness: serious (5699). - Event outcome:[47] Fatal (13), Not resolved (1996), Resolved with sequelae (62), Resolved/resolving (2304), Unknown data (1342). ***Clinical trials:*** *Myocarditis* - No. of cases: 3 of BNT162b2 - No. of SAEs: 3 - The most common PTs: Myocarditis (3). - Related SAEs: Myocarditis (3). Based on the cumulative post-marketing and clinical trials data, no new safety information was identified for BNT162b2 and myocarditis. *Pericarditis* - No. of cases: 3 (of which 1 involved blinded therapy) - No. of SAEs: 3 - Reported PT: Pericarditis (3). - Related SAEs: None. Based on the cumulative post-marketing and clinical trials data, no new safety information was identified for BNT162b2 myocarditis and pericarditis.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 61. Characterisation of Important Risks

<table>
<tr><td colspan="2">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.</td></tr>
<tr><td>Characterisation</td><td>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.[158,159] 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.[160] 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).[161]

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.[161]

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</td></tr>
</table>

[158] 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.

[159] Haynes BF, Corey L, Fernandes P, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med 2020;12(568):eabe0948.

[160] Openshaw PJ, Culley FJ, Olszewska W. Immunopathogenesis of vaccine-enhanced RSV disease. Vaccine 2001;20(Suppl 1):S27-31.

[161] Graham BS. Rapid COVID-19 vaccine development. Science 2020;368(6494):945-6.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 61. Characterisation of Important Risks

	expected to mitigate the risk of VAED/VAERD;[158,161] that immune profile is elicited by COVID-19 mRNA vaccine in clinical and preclinical studies.[162,163] *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 December 2021)	***Post-marketing sources:*** - No. of cases*: 2169.* - Relevant PTs most frequently reported (≥2%): Drug ineffective (1210), Vaccination failure (954), COVID-19 pneumonia (889), Dyspnoea (652), Diarrhoea (349), Vomiting (147), Respiratory failure (128), Hypoxia (92), Myocarditis (89), Pulmonary embolism (88), Abdominal pain (87), Cardiac failure (74), Acute respiratory distress syndrome (68), Acute kidney injury (66), and Tachypnoea (65). - Frequently reported additional PTs (≥100 occurrences): COVID-19 (1319), Pyrexia (438), Cough (362), Headache (244), Fatigue (237), Asthenia (233), Suspected Covid-19 (190), Oxygen saturation decreased (131), Nausea (120), Myalgia (111), Malaise (110), Chills, Pain (103 each). - Subjects' gender: female (1074), male (1047), unknown (48) - Subjects' age in years (n = 2078), range: 12 – 104, mean: 68.5, median: 74. - Age group: Paediatric (15), Adults (720), Elderly (1352) and Unknown (82). - Case source: Spontaneous (2126), Literature (9), Non-interventional study (34) - Relevant event seriousness: serious (4641), non-serious (597) -Relevant vent outcome: Fatal (972), Not resolved (891), Resolved with sequelae (46), Resolved/resolving (1707), Unknown data (1632). ***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.

---

[162] 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.

[163] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

16.4.2. Description of Missing Information

Table 62 describes missing information associated with the use of BNT162b2.

Table 62. 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 risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.3 *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 Comorbidities (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 summarised in Section 16.3.5.8 *Interactions with other Vaccines.*

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 62. Description of Missing Information

Topic	Description
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 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 5 years of age and older.

Study C4591001 is a multicenter, placebo controlled- efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[164] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[164] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment,[165] were included as were participants with known stable infection with HIV, HCV, or HBV.[164]

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.

[164] Ref #12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2

[165] Ref #21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 63. 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*,[166]			
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[167]			
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).

---

[166] 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.

[167] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 63. 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 Cl 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 64 and Table 65.

Table 64. 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[168]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo Na=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)

[168] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 64. 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[168]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo Na=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/m2. 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 65. 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)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 65. 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/m2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 66) 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 66. 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[169,170]			
	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[171,172]			
	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:[173]

---

[169] 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.

[170] 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.

[171] 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.

[172] 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.

[173] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 66. 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:[173]

- Hospitalisation;
- Admission to the ICU;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.[174]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.[174]
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 67.

[174] Ref #62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 67. 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*,[175]			
	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[176]			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1110 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Adolescents 12 to 15 Years of Age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In C4591001 an analysis of SARS-CoV-2 neutralising titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses comparing adolescents 12 to 15 years of age to participants 16 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

[175] 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.

[176] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

immune response in participants 16 to 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titers at 1 month after Dose 2. The GMT ratio of the adolescents 12 to 15 years of age group to the participants 16 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.[177]

Efficacy and immunogenicity in participants ≥ 16 years of age after booster dose

Neutralizing SARS-CoV-2 antibody titers and S1-binding IgG antibodies were evaluated at 6 months after Dose 2 for Study C4591001. The data noted the persistence of a robust immune response elicited by BNT162b2 30 µg vaccination in adults for up to 6 months; and also suggest, based on the modest decline in GMTs and GMCs from 1 month to 6 months after receiving Dose 2, that vaccinees may benefit from a booster dose at 6 months or thereafter. Study C4591031 was designed to assess a booster dose in this participant population.

Study C4591031 is a Phase 3 randomised, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who have completed a 2-dose primary series of BNT162b2 in Study C4591001, at least 6 months prior to randomisation, were enroled and participants were randomised at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomisation was stratified by age, such that approximately 60% of participants enroled were to be ≥16 to 55 years of age and approximately 40% of participants >55 years of age.

Considering the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards and those randomised to receive a booster dose of placebo were offered a dose of BNT162b2 30 µg to receive a booster of active vaccine. In Section 17.1 *Important Baseline Efficacy and Effectiveness Information,* the newly identified information on efficacy and effectiveness of the 2-month interim analysis of study C4591031 is presented.

17.2. Newly Identified Information on Efficacy and Effectiveness

Efficacy and effectiveness of the 2-month interim analysis of study C4591031

The protocol pre-specified interim analysis of efficacy was conducted when all participants reached 2 months post-booster, for a planned DMC review. The interim analysis for DMC review included COVID-19 cases that occurred from 7 days after booster vaccination up to 2 months after booster vaccination. The timing of interim analyses was prespecified in the protocol in order to assess whether those in the placebo group were potentially disadvantaged

[177] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

by not having received a BNT162b2 booster dose. Key 2-month post-booster interim analysis results are summarised below for the evaluable efficacy populations:

- Among participants without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥7 days after booster vaccination to <2 months after booster vaccination, the relative vaccine efficacy (RVE) was estimated as 95.6% (2-sided 95% CI: 89.3%, 98.6%), based on 5 cases in the BNT162b2 group and 109 cases in the placebo group.

- Among participants with or without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥7 days after booster vaccination to <2 months after booster vaccination, the estimated RVE was 94.7% (2-sided 95% CI: 88.2%, 98.1%), based on 6 cases in the BNT162b2 group and 110 cases in the placebo group.

Based on these results showing high RVE at 2 months post-booster, the DMC recommended unblinding the study and continuation of participants being unblinded to allow placebo recipients the opportunity to receive a BNT162b2 booster dose.

The relative vaccine efficacy (RVE) following booster vaccination was estimated from 7 days post-booster to the data cutoff date (05 October 2021) during the blinded placebo-controlled follow-up period. Notably, the cases in this RVE analyses accrued during a period of July to the October cutoff date, during a time that the highly transmissible B.1.617.2 (Delta) variant has been the predominant SARS-CoV-2 strain in circulation in the US and globally.[178,179] Based on COVID-19 cases accrued from booster vaccination to the data cutoff date, the observed RVE was as follows:

- The RVE in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 95.3% (2-sided 95% CI: 89.5%, 98.3%), based on 6 cases in the BNT162b2 group and 123 cases in the placebo group.

- The RVE in the evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 94.6% (2-sided 95% CI: 88.5%, 97.9%), based on 7 cases in the BNT162b2 group and 124 cases in the placebo group.

- The RVE in the all-available efficacy (mITT) population from booster vaccination onwards was 89.8% (2-sided 95% CI: 82.6%, 94.4%), based on 15 cases in the BNT162b2 group and 141 cases in the placebo group reported after booster vaccination.

[178] Centers for Disease Control and Prevention (CDC). COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 16 October 2021.

[179] Centers for Disease Control and Prevention (CDC). COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#global-variant-report-map. Accessed 16 October 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Efficacy against severe COVID-19

Based on cases up to the data cutoff date (05 October 2021), in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster, 1 case meeting severe criteria per the FDA definition was observed in the placebo group. This case occurred 22 days post-Dose 3 (placebo) and met the severe criterion of 'clinical signs at rest indicative of severe systemic illness' (SpO_2 ≤93% on room air at sea level).

In the all-available efficacy (mITT) population, 2 cases meeting severe criteria per the FDA definition were observed, both in the placebo group, which included the case in the evaluable efficacy population described above. This additional case occurred 31 days post-Dose 3 (placebo) and also met the severe criterion of 'clinical signs at rest indicative of severe systemic illness' (SpO_2 ≤93% on room air at sea level).

Both severe cases (per FDA definition) occurred in participants who were baseline SARS-CoV-2 negative.

No cases were reported that were based on CDC criteria for severe COVID-19.

Efficacy and immunogenicity in children 5 through <12 years of age – after 2 doses

Study C4591007 (Study 3) is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enroled participants 5 through <12 years of age.

A descriptive efficacy analysis of Study 3 has been performed in 1968 children 5 through 11 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of 08 October 2021.[180]

The descriptive vaccine efficacy results in children 5 through 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 68. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. [180]

[180] Ref #82 of the CDS. Clinical Information Amendment - COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 68. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through 11 Years of Age Evaluable Efficacy Population

First COVID-19 occurrence from 7 days after Dose 2 in children 5 through 11 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME± 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

± Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA).

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.

In Study 3, an analysis of SARS-CoV-2 50% neutralising titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 69.[181]

[181] Ref #73 of the CDS. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 69. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through Less Than 12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n[a]=264	30 mcg/Dose 16 Through 25 Years n[a]=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through less than 12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children − young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 70.[181]

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 70. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID-19 Vaccine			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Efficacy and effectiveness against SARS-CoV-2 infection between 1 and 6 months after full vaccination and after booster dose

Knowing whether and to what extent COVID-19 vaccine effectiveness wanes is critical. The MAH performs systematic and regular reviews keeping track of new publications, studies with vaccine efficacy or effectiveness (VE) estimates for any WHO Emergency-Use-Listed COVID-19 vaccine at discrete time intervals after full vaccination and booster strategies underwent full-text review. On average, VE against SARS-CoV-2 infection decreased

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

between 1 and 6 months after full vaccination by 18·5 percentage points (95% CI 8·4-33·4, p=0·0006) among persons of all ages and 19·9 percentage points (95% CI 9·2-36·7, p=0·0007) among older persons; for symptomatic COVID-19 disease, VE decreased by 25·4 (95% CI 13·7-42·5) and 32·0 percentage points (95% CI 11·0-69·0), respectively; and for severe COVID-19 disease, VE decreased by 8·0 (95% CI 3·6-15·2) and 9·7 percentage points (95% CI 5·9-14·7), respectively. The majority of VE estimates against severe disease remained over 70% for all time points.

COVID-19 vaccine efficacy or effectiveness against COVID-19 severe disease remained high in most studies in the six months after full vaccination; >70% in general and >80% for Pfizer/BioNTech vaccine and within the mRNA platforms class, although it did decrease some (on average, 8-10 percentage points) between one and six months after full vaccination. In contrast, VE against SARS-CoV-2 infection and symptomatic COVID-19 disease decreased approximately 20-30 percentage points during the six months after vaccination. The decrease in VE is likely due, at least in part, to waning immunity. Continued follow-up of VE beyond six months is critical.[182]

Booster strategies have been implemented because of waning immunity and recently the UK evaluated booster vaccination with mRNA starting on 14 September 2021. A test-negative case-control design was used to estimate the relative effectiveness of a booster dose of BNT162b2 (Pfizer-BioNTech) compared to only a 2-dose primary course (at least 175 days after the second dose) as well as compared to unvaccinated individuals from 13 September 2021 to 05 December 2021, when Delta variant was dominant in circulation. Outcomes were symptomatic COVID-19 and hospitalization. The relative effectiveness against symptomatic disease 14-34 days after a BNT162b2 or mRNA-1273 (Moderna) booster after a ChAdOx1-S (AstraZeneca) and BNT162b2 as a primary course ranged from around 85 to 95%. Absolute VE ranged from 94-97% and was similar in all age groups. Limited waning was seen 10+ weeks after the booster. Against hospitalisation or death absolute effectiveness of a BNT162b2 booster ranged from around 97% to 99% in all age groups irrespective of the primary course with no evidence of waning up to 10 weeks. This study provides real world evidence of significant increased protection from the booster vaccine dose against mild and severe disease irrespective of the primary course.[183]

However, since the end of 2021, a new variant of concern (VOC) is overgrowing the previous predominant Delta variant, therefore we assessed the VE against this new variant.

The identification and emergence of the Omicron variant (B.1.1.529) the 26 of November 2021, with more than 30 mutations in the spike protein in comparison with the original wild type Wuhan-hu-1 strain, triggered a dramatic shift in the pandemic burden with a wide and

---

[182] Faikin et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: Results of a systematic review and meta-regression Lancet preprint 18 November 2021 SSRN-id3961378.pdf.

[183] Andrews et al. Effectiveness of BNT162b2 COVID-19 booster vaccine against COVID-19 related symptoms and hospitalization in England. Nature 2022 doi: https://doi.org/10.1038/d41591-022-00013-3.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

rapid spread of the virus showing a high degree of neutralizing antibody escape.[184] Preliminary studies have shown that two doses of BNT162b2 mRNA vaccine (Pfizer-BioNTech) do not sufficiently neutralise Omicron. In addition, although three doses of BNT162b2 increase neutralisation efficiency, levels of Omicron neutralisation after a booster dose are less than that observed for Delta.[185,186,187,188] Early data suggest that T-cell responses induced by prior infection and by BNT162b2, however, seem to remain intact against Omicron.[189,190,191,192,193]

Estimates of real-world effectiveness of BNT162b2 (and other COVID-19 vaccines) against Omicron outcomes are limited to preliminary data from South Africa[194] and preprint reports

[184] Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. medRxiv 2021:2021.12.19.21268028. DOI: 10.1101/2021.12.19.21268028.

[185] Schmidt F, Muecksch F, Weisblum Y, et al. Plasma Neutralization of the SARS-CoV-2 Omicron Variant. New England Journal of Medicine 2021. DOI: 10.1056/NEJMc2119641.,

[186] Cele S, Jackson L, Khan K, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. medRxiv 2021:2021.12.08.21267417. DOI: 10.1101/2021.12.08.21267417.

[187] Pfizer. Pfizer and BioNTech Provide Update on Omicron Variant. (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant).

[188] Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. N Engl J Med 2021. DOI: 10.1056/NEJMc2119358.

[189] De Marco L, D'Orso S, Pirronello M, et al. Preserved T cell reactivity to the SARS-CoV-2 Omicron variant indicates continued protection in vaccinated individuals. bioRxiv 2021:2021.12.30.474453. DOI: 10.1101/2021.12.30.474453.

[190] GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS CoV-2 Omicron-specific T- and B-cell responses in COVID-19 vaccine recipients. medRxiv 2021:2021.12.27.21268416. DOI: 10.1101/2021.12.27.21268416.

[191] Tarke A, Coelho CH, Zhang Z, et al. SARS-CoV-2 vaccination induces immunological memory able to cross-recognize variants from Alpha to Omicron. bioRxiv 2021:2021.12.28.474333. DOI: 10.1101/2021.12.28.474333.

[192] Liu J, Chandrashekar A, Sellers D, et al. Vaccines Elicit Highly Cross-Reactive Cellular Immunity to the SARS-CoV-2 Omicron Variant. medRxiv 2022:2022.01.02.22268634. DOI: 10.1101/2022.01.02.22268634.

[193] Keeton R, Tincho MB, Ngomti A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. medRxiv 2021:2021.12.26.21268380. DOI: 10.1101/2021.12.26.21268380.

[194] Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. New England Journal of Medicine 2021. DOI: 10.1056/NEJMc2119270.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

from the UK[195], Canada,[196] and Denmark[197]. Generally speaking, these data showed that two doses of mRNA vaccine likely provides either very short-lived protection (effectiveness of roughly 50% seen only in the first month after receiving the second dose)[198] or no[199] protection against omicron infection. Protection against symptomatic COVID-19 also appears short-lived for omicron, with VE falling below 40% at ≥3 months after the receipt of the second dose (or sooner for older adults).[200] Two doses likely provide roughly 50–70%[195] effectiveness against hospitalisation depending on time since receipt of the second dose.[194,200] Effectiveness of a third (booster) dose against omicron infection or symptomatic COVID-19 has been estimated to be roughly 35–70%[195,196,200] with waning observed after only one month.[195,200] Only one non-peer-reviewed report has estimated effectiveness of mRNA boosters dose against Omicron-related hospitalisation, showing VE of approximately 90%.[195,200] These limited effectiveness estimates, however, need additional confirmation and further follow up.

Nevertheless, considering recent publications, data reaffirms the overall benefit of vaccines.

17.3. Characterisation of Benefits

Data in Section 17.1 demonstrates a high degree of efficacy against symptomatic and severe COVID-19 in non-immunocompromised people over 12 years of age, during the period at least 7 days following the second dose of vaccine. 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

---

[195] UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England -- Technical Briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529). (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044481/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf).

[196] Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta infection. medRxiv 2022:2021.12.30.21268565. DOI: 10.1101/2021.12.30.21268565.

[197] Hansen CH, Schelde AB, Moustsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study. medRxiv 2021:2021.12.20.21267966. DOI: 10.1101/2021.12.20.21267966.

[198] Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. New England Journal of Medicine 2021. DOI: 10.1056/NEJMc2119270.

[199] Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta infection. medRxiv 2022:2021.12.30.21268565. DOI: 10.1101/2021.12.30.21268565.

[200] UK Health Security Agency. Effectiveness of 3 doses of COVID-19 vaccines against symptomatic COVID-19 and hospitalisation in adults aged 65 years and older. (https://khub.net/documents/135939561/338928724/Effectiveness+of+3+doses+of+COVID-19+vaccines+against+symptomatic+COVID-19+and+hospitalisation+in+adults+aged+65+years+and+older.pdf/ab8f3558-1e16-465c-4b92-56334b6a832a).

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

reduced hospitalisation, severe morbidity and death from COVID-19. Section 17.2 describes the newly identified information on efficacy and effectiveness of the 2-month interim analysis of study C4591031 and on efficacy in children 5 through < 12 years of age. Additionally, the variation of VE against SARS-CoV-2 infection between 1 and 6 months after full vaccination and after booster dose and data concerning VE against Delta and Omicron variants are presented.

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.

Incidence

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.[201] 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.[202]

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[203].

As of 16 January 2022, the overall number of people who had been infected with SARS-CoV-2 was over 327 million worldwide[204]. Table 71 shows the incidence and prevalence as of 16 January 2022 for the US, UK, and EU-27 countries. In the EU and the UK, by 16 January 2022 the total number of confirmed cases had accumulated to 83.5 million people, or 16,232 per 100,000 people. Across countries in the EU, the number of confirmed cases ranged from 6,682 to 25,649 cases per 100,000 people. Finland, Germany and Romania reported the lowest incidence rates while Czech Republic and Slovenia reported the highest.[204]

---

[201] 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.

[202] World Health Organization. 2020. Coronavirus Disease 2019 (COVID-19) Situation Report – 11.

[203] Worldometers.info 2022a. Worldometer COVID-19 Data. https://www.worldometers.info/about/. Accessed January 14, 2022

[204] Worldometers.info 2022b. Reported Cases and Deaths by Country or Territory. https://www.worldometers.info/coronavirus/#countrieshttps://www.worldometers.info/coronavirus/#countries. Accessed 16 January 2022.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

In the US, the number of confirmed cases had reached over 66 million (19,960 per 100,000 people) by 16 January 2022.[204]

Table 71. Incidence, Prevalence, and Mortality of COVID-19 as of 16 January 2022

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	327,199,527	4,131	55,000,506	694	5,555,306	70	7,920,696,515
EU-27	68,298,486	15,326	15,384,982	3,452	929,572	209	445,651,462
UK	15,147,120	22,134	3,695,847	5,401	151,899	222	68,434,456
EU-27 + UK	83,445,606	16,232	19,080,829	3,712	1,081,471	210	514,085,918
US	66,664,283	19,960	22,732,045	6,806	873,149	261	333,987,717
EU-27 Countries							
Austria	1,443,589	15,889	133,931	1,474	13,920	153	9,085,430
Belgium	2,410,731	20,662	430,611	3,691	28,612	245	11,667,199
Bulgaria	818,229	11,914	150,381	2,190	32,042	467	6,867,969
Croatia	817,435	20,103	55,499	1,365	13,118	323	4,066,317
Cyprus	223,767	13,859	98,724	3,617	673	52	1,220,875
Czech Republic	2,596,439	24,176	127,160	1,184	36,853	343	10,739,541
Denmark	1,093,978	18,785	279,211	4,794	3,494	60	5,823,575
Estonia	267,095	20,114	29,200	2,199	1,979	149	1,327,907
Finland	371,135	6,682	323,411	5,823	1,724	31	5,553,960
France	13,894,255	21,214	4,778,187	7,295	126,869	194	65,495,677
Germany	7,968,472	9,464	888,520	1,055	116,252	138	84,196,003
Greece	1,650,088	15,951	355,212	3,434	21,888	212	10,344,727
Hungary	1,327,014	13,791	128,268	1,333	40,237	418	9,622,615
Ireland	1,103,489	21,971	459,346	9,146	6,035	120	5,022,584
Italy	8,549,450	14,172	2,470,847	4,096	140,856	233	60,325,058
Latvia	303,794	16,385	26,622	1,436	4,730	255	1,854,112
Lithuania	567,921	21,320	43,708	1,641	7,654	287	2,663,844
Luxembourg	123,340	19,223	20,843	3,248	934	146	641,629
Malta	63,710	14,370	10,332	2,330	506	114	443,352
Netherlands	3,568,999	20,758	616,864	3,588	21,155	123	17,193,189
Poland	4,313,036	11,415	420,354	1,113	102,305	271	37,782,845
Portugal	1,852,703	18,251	309,633	3,050	19,270	190	10,150,971
Romania	1,903,428	9,997	68,066	357	59,240	311	19,040,249
Slovakia	879,656	16,100	34,999	641	17,300	317	5,463,710
Slovenia	533,334	25,649	66,791	3,212	5,697	274	2,079,378
Spain	8,093,036	17,299	2,752,905	5,884	90,759	194	46,782,635
Sweden	1,560,363	15,304	305,357	2,995	15,470	152	10,196,111

Estimated as the sum of the measurable population of countries available at Worldometer (https://www.worldometers.info/coronavirus/#countrieshttps://www.worldometers.info/coronavirus/#countries)

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested, as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

underreported. Further, as at-home rapid testing kits have become more readily available[205] and formal testing resources reach capacity due to the B.1.1.529 (Omicron) variant, the true estimate of cases may be larger than formally reported counts. The numbers should therefore be interpreted with caution. While there is limited information on number of cases attributable to specific variants, recent case counts are likely to reflect the B.1.1.529 (Omicron) variant, which is currently the predominant strain in many countries, including the US.[206]

The main existing treatment options:

Through 18 December 2021, other COVID-19 vaccines were authorised[207] 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- 45 % of patients, across age groups[208,209,210,211] to critical illness and death. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities.[211] One meta-analysis has estimated that 46.7% of infections in children are asymptomatic.[211] The most common symptoms of COVID-19 are

---

[205] Thomas E, Delabat S, Carattini YL, Andrews DM. SARS-CoV-2 and Variant Diagnostic Testing Approaches in the United States. Viruses. 2021;13(12):2492. Published 2021 Dec 13. doi:10.3390/v13122492

[206] CDC (2022). Variant Proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 15 January 2022.

[207] According to the Union Register of Medicinal Products https://ec.europa.eu/health/documents/community-register/html/ Accessed on 18 December 2021.

[208] Pollock A M, Lancaster J. Asymptomatic transmission of COVID-19. BMJ 2020; 371:m4851 doi:10.1136/bmj.m4851.

[209] 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.

[210] Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic Review. Ann Intern Med. 2021 May;174(5):655-662. doi: 10.7326/M20-6976. Epub 2021 Jan 22. PMID: 33481642; PMCID: PMC7839426.

[211] Sah P, Fitzpatrick MC, Zimmer CF, Abdollahi E, Juden-Kelly L, Moghadas SM, Singer BH, Galvani AP. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proc Natl Acad Sci U S A. 2021 Aug 24;118(34):e2109229118. doi: 10.1073/pnas.2109229118. PMID: 34376550.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

fever, cough, and shortness of breath for both children and adults.[212,213] Confirming these observations in a recent systematic review, researchers examined 1,140 cases of COVID-19 in children from 23 published studies. They reported that 11% of cases were asymptomatic. Among symptoms, fever was reported in 48%, cough in 37%, and any nasopharyngeal symptom in 22%.[214] In another study among unhospitalised children < 18 years of age, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three.

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.[215,216] 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.[216] Data on rates of re-infection are limited but variants that are not neutralised by immune antisera, such as the beta (South African), Delta, and Omicron variants, may lead to increased risk of re-infection in the future.[216,217]

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 11 January 2022, there were 3,919,141 new hospital admissions for patients with confirmed COVID-19 in the US.[218] For the week ending on 9 January 2022, 15.4 patients per 100,000 population were hospitalised due to COVID-19 in 17 countries of the EU/EEA with available

---

[212] CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020 Apr 10;69(14):422-426. doi: 10.15585/mmwr.mm6914e4. PMID: 32271728; PMCID: PMC7147903.

[213] Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021 May;56(5):837-848. doi: 10.1002/ppul.25245. Epub 2021 Jan 11. PMID: 33428826; PMCID: PMC8013394.

[214] Kumar B, Scheffler P. Ear, Nose, and Throat Manifestations of COVID-19 in Children. Pediatr Ann. 2021;50(7):e277-e281. doi:10.3928/19382359-20210613-01

[215] 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.

[216] 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.

[217] Khan K, Karim F, Cele S, et al. Omicron infection enhances neutralizing immunity against the Delta variant. Preprint. medRxiv. 2021;2021.12.27.21268439. Published 2021 Dec 27. doi:10.1101/2021.12.27.21268439

[218] CDC 2021i. COVID Data Tracker New Hospital Admissions. https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions. Accessed 13 January 2022.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

data.[219] Based on data from 24 states and New York City, as of 6 January 2022, 0.1%-1.6% of children with COVID-19 have been hospitalised and, based on data from 46 states, New York City, Puerto Rico, and Guam, 0.00%-0.02% of children with COVID-19 have died.[220]

Early in the pandemic, 17% to 40% of adults hospitalised with COVID-19 experienced severe symptoms necessitating intensive care,[221,222] with 31% of hospitalised children experiencing severe COVID-19 that necessitates intensive care or invasive ventilation or ends in death.[223] Risk factors for severe COVID-19 in hospitalised children include presence of a comorbid condition, younger age, and male sex. More than 75% of adult patients hospitalised with COVID-19 require supplemental oxygen.[224]

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.[215] In 14 countries of the EU/EEA with available data, 0.9 patients per 100,000 population were in the ICU due to COVID-19 for the week ending 04 November 2021.[225] One 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.[209] A recent study of 82 cases in three paediatric hospitals noted that older children and those with higher BMI or multiple comorbidities were more likely to receive respiratory support.[226]

---

[219] ECDC 2021e. Country Overview Report: Week 01, 2022. https://www.ecdc.europa.eu/en/covid-19/country-overviews. Accessed 13 January 2022.

[220] American Academy of Pediatrics 2022. Children and COVID-19: State-Level Data Report. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/. Accessed 13 January 2022.

[221] 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.

[222] 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.

[223] Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA Netw Open. 2021;4(4):e215298. Published 2021 Apr 1. doi:10.1001/jamanetworkopen.2021.5298.

[224] 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.

[225] ECDC. (2021). COVID-19 Surveillance report. Week 43, 2021. 04 November 2021. "4 TESSy data quality. 4.2 Variable completeness". Available from: https://COVID19-surveillance-report.ecdc.europa.eu. Accessed on: 31 December 2021.

[226] Rubenstein S, Grew E, Clouser K, et al. COVID-19 in Pediatric Inpatients: A Multi-Center Observational Study of Factors Associated with Negative Short-Term Outcomes. Children (Basel). 2021 Oct 22;8(11):951. doi: 10.3390/children8110951. PMID: 34828664.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Mortality

As of 13 January 2022, there were 840,286 deaths reported in the US for all age groups among 62,538,796 cases (1.3% of cases). [227] In the EU/EEA, as of 13 January 2022, there were 917,983 deaths reported for all age groups among 65,756,908 cases (1.4% of cases).[228] In the UK, as of 13 January 2022, there were 151,831 deaths from COVID-19 in all age groups among 15,064,185 cases (1.0% of cases).[229] According to a meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients is 0.1-2%.[209] In a study from January through June 2020 using the National Child Mortality Database (NCMD) in England, 5.7% of 437 children 0-17 years of age who died were SARS-CoV-2 PCR positive and those who died of COVID-19 were older and were more likely to be non-White ethnicity. [230]

Mortality data are also presented from Worldometers, an independent organisation that publishes current, reliable COVID-19 statistics online.[203] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases. As of 16 January 2022, the overall SARS-CoV-2 mortality for the EU + UK was 1,081,471 deaths, or 222 per 100,000 people.[204] Reported mortality among EU countries ranged from 31 to 467 deaths per 100,000.[204] Finland and Cyprus reported the lowest mortality rate; Czech Republic, Hungary, and Bulgaria reported the highest.[204] In the US, as of 16 January 2022, 873,149 COVID-19-related deaths (261 per 100,000 people) had been reported on Worldometers.[204]

A study using 2020 hospital surveillance data from the US, UK, and Spain reported a "U-Shaped" distribution of COVID-19 mortality from infancy to adulthood, with the lowest rate observed in children 3-10 years of age. [231]

Mortality rates are declining over time.[232]

---

[227] CDC 2021f. COVID Data Tracker as of 13Jan2022. https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed on 13 January 2022.

[228] ECDC 2021d. Situation Report. https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea. Accessed on 13 January 2022.

[229] JHU COVID Map 2022. https://coronavirus.jhu.edu/map.html.

Accessed on 13 January 2022.

[230] Odd D, Stoianova S, Williams T, et al. Child mortality in England during the COVID-19 pandemic. Archives of Disease in Childhood Published Online First: 21 June 2021. doi: 10.1136/archdischild-2020-320899.

[231] Khera N, Santesmasses D, Kerepesi C, et al. COVID-19 mortality rate in children is U-shaped. Aging (Albany NY). 2021 Aug 18;13(16):19954-19962. doi: 10.18632/aging.203442. Epub 2021 Aug 18. PMID: 34411000; PMCID: PMC8436910.

[232] 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[221,233,234] Based on a meta-analysis of 42 studies, the risk of thromboembolism was 21% overall and 31% in the ICU, with the pooled odds of mortality being 74% higher among those who experienced thromboembolism compared to those who did not.[235]

COVID-19 symptoms can persist weeks or months beyond the acute infection.[236,237] The NICE guideline scope published on 30 October 2020 defined "Long COVID" signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more and for which signs and symptoms are not explained by an alternative diagnosis).[238]

A meta-analysis of 31 studies published until 17 September 2020 (prior to the emergence of the omicron variant) among patients between 18 to 49 years of age found that COVID-19 symptoms were experienced for 14 days to 3 months post-infection, including persistent fatigue (39–73%), breathlessness (39–74%), decrease in quality of life (44–69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%), evidence of peri-/perimyo-/myocarditis (3–26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33–36%).[239] Post-acute COVID symptoms in children with asymptomatic or mild disease appear to be less severe than in adults, with the most common

[233] Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369:m1996.

[234] Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A Review. JAMA 2020;324(8):782-93.

[235] Malas MB, Naazie IN, Elsayed N, et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine 2020;29:100639. doi: 10.1016/j.eclinm.2020.100639. Epub 2020 Nov 20. PMID: 33251499; PMCID: PMC7679115.

[236] Carfì A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020;324(6):603-5. doi: 10.1001/jama.2020.12603. PMID: 32644129; PMCID: PMC7349096.

[237] Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute COVID-19 in primary care. BMJ 2020;370:m3026. doi: 10.1136/bmj.m3026. PMID: 32784198.

[238] NICE (National Institute for Health and Care Excellence). https://www.nice.org.uk/guidance/ng188/chapter/context#post-covid-19-syndrome. Accessed on 04 April 2021.

[239] Willi S, Lüthold R, Hunt A, e al. COVID-19 sequelae in adults aged less than 50 years: A systematic review. Travel Med Infect Dis 2021;40:101995. doi: 10.1016/j.tmaid.2021.101995. Epub ahead of print. PMID: 33631340; PMCID: PMC7898978.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

symptoms being a post-viral cough (4%), fatigue (2%), or both symptoms (1%) with the duration of symptoms lasting 3 to 8 weeks.[240]

Children who are infected with COVID-19 are at risk of subsequent multisystem inflammatory syndrome (MIS-C) and often develop a rash following resolution of COVID-19.[209,241,242] Additional symptoms of MIS-C include abdominal pain, bloodshot eyes, chest tightness or pain, diarrhoea, lethargy, headache, low blood pressure, neck pain, and vomiting.[243] As of 3 January 2022, there were 6,431 cases of MIS-C reported to health departments in the US, with 55 deaths.[244]

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

---

[240] Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. Lancet Child Adolesc Health. 2021;5(6):e22-e23. doi:10.1016/S2352-4642(21)00124-3.

[241] Feldstein LR, Tenforde MW, Friedman KG, et al. Overcoming COVID-19 Investigators. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021; 325(11):1074-1087. doi: 10.1001/jama.2021.2091. PMID: 33625505; PMCID: PMC7905703.

[242] Kelly MS, Fernandes ND, Carr AV, et al. Distinguishing features of patients evaluated for multisystem inflammatory syndrome in children. Pediatr Emerg Care 2021;37(3):179-184. doi: 10.1097/PEC.0000000000002344. PMID: 33651762.

[243] CDC 2021h. For Parents: Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19. https://www.cdc.gov/mis/mis-c.html. Accessed 24 August 2021.

[244] https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

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 summarised in Table 72.

Based on pharmacovigilance monitoring activities, there has been no new safety information contributing importantly to the risk of BNT162b2.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)

Table 72. 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.
Myocarditis and Pericarditis	No new data from clinical studies were identified during the reporting interval.	Based on the review of post-marketing data, no new safety information was identified for BNT162b2 and myocarditis and pericarditis.	No new significant data received from literature sources.	Myocarditis and pericarditis is an adverse reaction in Section 4.8 of the EU SmPC and in other 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 minimised through provision of relevant product information in the RSI to support safe use of the product. Risks have been evaluated in the context of the enumerated benefits of the product. Based on the available safety and efficacy data for BNT162b2, the overall benefit-risk profile of BNT162b2 remains favourable.

Table 73. Overall Benefit-Risk for BNT162b2

Consideration	Favourable Benefit-Risk	Non Contributory	Unfavourable Benefit-Risk
Severity of condition	The severity of the condition being treated, as well as comorbidities and outcomes in the population to be treated were considered. (See Section 18.1)	NA	NA
Unmet medical need	BNT162b2 meets an unmet medical need because there is - lack of alternative therapies, or - although alternative products are available in this class, this product may be the preferred therapeutic option or preferred in a select group of patients. (See Section 18.1)	NA	NA
Clinical benefit	The nature, clinical importance, duration, and generalizability of benefits were considered. (See Section 18.1)	NA	NA
Risk associated with treatment	The nature, seriousness, frequency, predictability, reversibility, impact on patients and public health of the product's risks were considered. (See Section 18.2.2)	NA	NA
Risk management	Risk minimisation measures currently in place for this product support a favourable benefit-risk balance. (See Section 18.2.2)	NA	NA

Table was adapted from European Medicines Agency. Benefit-risk Methodology Project – Working package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010.

19. CONCLUSION AND ACTIONS

Risks have been evaluated in the context of the benefits of the vaccine. Based on the available safety and efficacy/effectiveness data from the reporting interval for BNT162b2, 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.

090177e19965eea8\Approved\Approved On: 18-Feb-2022 16:08 (GMT)