PERIODIC SAFETY UPDATE REPORT #3
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (nucleoside modified) (BNT162b2)[1]

ATC CODE: J07BX03[2]

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD)[3]: 19 DECEMBER 2020

EUROPEAN UNION REFERENCE DATE (EURD): 19 DECEMBER 2020

INTERVAL COVERED BY THIS REPORT:

19 DECEMBER 2021 through 18 JUNE 2022

DATE OF THIS REPORT: 18 AUGUST 2022

SIGNATURE: [redacted] **Date: 18 August 2022**

NAME AND CONTACT DETAILS OF THE QPPV:	
EU Qualified Person Barbara De Bernardi, MD [redacted]	telephone: [redacted] fax number: [redacted] email: [redacted]
EU Qualified Person Deputy [redacted]	telephone: [redacted] fax number: [redacted] email: [redacted]

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

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

[1] Change of the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran in EU (EMEA/H/C/005735/X/0044/G).
[2] Implementation as new ATC code starting from 01 January 2022.
[3] Earliest conditional approval date.

EXECUTIVE SUMMARY

This is the 3rd 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)[4], covering the reporting interval 19 December 2021 through 18 June 2022.

A product description is provided in Table 1.

Table 1. Product Description[a]

Therapeutic class	The active substance of the COVID-19 mRNA vaccine is a highly purified single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA template, encoding the viral spike (S) protein of SARS-CoV-2.		
Mechanism of action	The nucleoside-modified mRNA is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralising antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.		
Indications	Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.		
Formulation and route of administration	The vaccine is a white to off-white frozen solution, is administered intramuscularly in the deltoid muscle and is available in 3 presentations.		
	Purple cap (for 12 years of age and older)	*Grey cap (for 12 years of age and older)*	*Orange cap (for age 5 years to <12 years)*
	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
	30 micrograms/dose	30 micrograms/dose	10 micrograms/dose
	Requires dilution	Do not dilute	Requires dilution
	PBS/Sucrose presentation	Tris/Sucrose presentation	Tris/Sucrose presentation
Posology	Individuals aged 12 years and older The 2 formulations (purple cap and grey cap) are administered as 30 µg/dose as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose (third dose) may be administered approximately 6 months after the second dose in individuals 16 years of age and older. Individuals aged 5 through 11 years The Tris/Sucrose formulation (orange cap) is administered after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart. A booster dose may be administered at least 6 months after the second dose.		

a. As per information reported in the Core Data Sheet version 13.0 dated 10 May 2022, in effect at the end of the reporting period. Since 17 June 2022, BNT162b2 is approved in individuals 6 months of age and older, as the paediatric Tris/Sucrose presentation - maroon cap was approved in the United States. Please refer below for details on this new formulation.

Abbreviations: COVID-19 = coronavirus disease 2019; DNA = deoxyribonucleic acid; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; PBS = phosphate buffered saline; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

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

Cumulatively, it is estimated that 66,656[5] participants have received BNT162b2 in sponsor initiated clinical trials worldwide, with 59,260 participants exposed to BNT162b2, 1836 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 7044 participants exposed to blinded therapy and 5871 to placebo.

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

From the receipt of the first temporary authorisation for emergency supply on 01 December 2020[6] through 18 June 2022, approximately 3,555,998,805 doses of BNT162b2 were shipped from BioNTech and Pfizer worldwide, corresponding to 2,693,922,584 estimated administered doses.

During the current reporting interval (19 December 2021 through 18 June 2022), approximately 1,115,282,160 doses of BNT162b2 were shipped from BioNTech and Pfizer worldwide, corresponding to 843,724,061 estimated administered doses.[7]

Overall, through 18 June 2022, a total of 143,844,450 adult Tris/Sucrose doses and a total of 229,269,400 paediatric Tris/Sucrose doses were shipped worldwide.

Additionally, as per data provided by license partner (LP) in Hong Kong, Macau, and Taiwan, 27,314,884 doses of BNT162b2 were administered cumulatively through 21 June 2022 and 12,126,713 dose were administered from 19 December 2021 through 21 June 2022.

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

[6] BNT162b2 received first temporary authorisation for emergency supply under Regulation 174 in the UK on this date.

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

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

- The PBS/Sucrose 30 µg formulation for individuals aged 16 years and older has received approvals in 103 countries[8] including full (5), conditional (49), emergency use authorisation (EUA) and other type of approvals (52).
- The PBS/Sucrose 30 µg formulation for individuals aged between 12 and 15 years has received approvals in 81 countries[9] including full (2), conditional (46), EUA and other type of approvals (34).
- The Tris/Sucrose 30 µg formulation for individuals aged 12 years and older has received approvals in 73 countries[10] including full (3), conditional (44), EUA and other type of approvals (28).
- The Tris/Sucrose 10 µg formulation for individuals aged between 5 and 11 years has received approvals in 79 countries[9] including full (2), conditional (43), EUA and other type of approvals (35).
- The Tris/Sucrose 3 µg formulation for individuals aged between 6 months and 4 years has received EUA approval in the US.
- The booster dose has received approvals in 83 countries[11] including full (3), conditional (46), EUA and other type of approvals (36).

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

The marketing authorisation holders (MAHs) of BNT162b2 are the following: BioNTech (56 countries); Pfizer (40 countries), the local Ministry of Health (MoH) and local Government (3 countries each), the LP Fosun Pharma (2 countries), and the LP Hemas (1 country).

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

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

[8] For this population, both conditional and EUA approvals were granted in the United Kingdom (UK), full and EUA approvals in Singapore and the US.

[9] Both conditional and EUA approvals for this population were granted in the UK.

[10] For this population, both conditional and EUA approvals were granted in the UK, full and EUA approvals in the US.

[11] For this population, both conditional and EUA approvals were granted in the UK, full and EUA approvals in Singapore.

During the reporting period, no actions have been taken with respect to BNT162b2 for safety reasons, either by a Health Authority (HA) or by the MAH. Although not considered by definition a regulatory action taken for safety reasons because it does not significantly impact the benefit risk balance of use of the product in authorised populations, due to the receipt of spontaneous reports of Guillain-Barré syndrome (GBS) after vaccination with mRNA COVID-19 vaccines including BNT162b2, Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has required class changes to include GBS in the important precautions section of the Japan package insert[12] and inclusion of GBS as an important potential risk in the Japan Risk Management Plan (RMP)[13]. It should be noted that based on PMDA assessment, the frequency of reported cases of GBS was not significantly higher than the background incidence in any gender or age group and a mechanism is not known.

The reference safety information (RSI) for this PSUR is the COVID 19 mRNA vaccine Core Data Sheet (CDS) version 13.0 dated 10 May 2022, in effect at the end of the reporting period.

Four (4) previous CDS versions (version 9.0 dated 02 December 2021[14], version 10.0 dated 21 December 2021, version 11.0 dated 14 January 2022 and version 12.0 dated 23 March 2022[14]) were also in effect during the reporting period.

Safety-related changes included updates of the following sections: 4.2 *Posology and method of administration* (CDS version 13.0), 4.8 *Undesirable effects* (CDS versions 10.0, 11.0 and 13.0), 5.1 *Pharmacodynamic properties* (CDS versions 10.0 and 11.0), Appendix A, Appendix B (CDS version 10.0).

During the reporting period, the following signals were addressed:

- Signals determined not to be risks: Appendicitis, Hemolytic anemia, Uveitis, Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders, Capillary leak syndrome (CLS), Corneal graft rejection, Vasculitis, Cerebral venous sinus thrombosis (CVST), Lymphocytic colitis, Chronic urticaria, Polymyalgia rheumatica (PMR), Subacute thyroiditis (SAT), Cerebrovascular accident (CVA)/stroke, Amenorrhea, Heavy menstrual bleeding, Loss of/altered taste and smell.
- Signal determined to be an identified risk (not important): Irritability.

[12] The Japan package insert was updated by the MAH during the current reporting period, on 10 June 2022.

[13] Guillain-Barré syndrome was added as important potential risk to the safety concerns in the Japan RMP after Data Lock Point (DLP) of this PSUR, on 22 June 2022.

[14] This version of the CDS did not include any safety-related changes.

- Signal determined to be an important identified risk: Myocarditis and pericarditis[15].
- Ongoing signal: Hearing loss.

Commitments to be addressed in this PSUR were received from European Medicines Agency (EMA), World Health Organization (WHO) and Health Canada. The Pharmacovigilance Risk Assessment Committee (PRAC) requests were included in the Assessment Reports (ARs) of the Summary Safety Reports (SSRs), in the Final AR of PSUR #2 and in signals' AR. The WHO requests were included in the EUL Procedure. Topics covered in these commitments are summarised in the table below.

HA	Commitment(s)
PRAC	Closely monitoring multisystem inflammatory syndrome in children and in adults (MIS-C/A) and reporting of new cases of MIS.
	Observed vs Expected (O/E) analyses using at least no risk window, 14-day risk window and 21-day risk window and sensitivity O/E analyses which include the processed cases plus the backlog cases.
	Assessment of the used study methods in not (yet) peer-reviewed retrieved relevant literature to determine if the study results are valid or not.
	More effort in presenting/evaluating the cases considered to be confounded and present the risk factors for developing the respective conditions.
	Use of follow-up questionnaires anaphylaxis and vaccine associated enhanced disease/vaccine associated enhanced respiratory disease (VAED/VAERD).
	Presentation of all relevant literature concerning the safety of Comirnaty (also besides the database Medline and Embase) during the reporting period.
	Safety evaluation of sudden sensorineural hearing loss, tinnitus, glomerulonephritis and nephrotic syndrome, autoimmune hepatitis, dizziness, acquired haemophilia, IgA nephropathy.
	Continue to report on the number of processed cases downloaded from EudraVigilance.
	Estimate of the exposure of "third doses" in European economic area (EEA) countries, per country and by age group.
	Handling and dosing errors as result of different BNT162b2 formulations on the market.
WHO	Pregnancy outcome in clinical trials.
	Data on low- and middle-income countries (LMICs) populations with HIV, malnutrition and tuberculosis and other infectious diseases.
Health Canada	Review on the new variant "Omicron" and other variants.
	Safety evaluation of tinnitus and hearing loss.

According to the European Risk Management Plan (EU-RMP) version 4.0 adopted on 26 November 2021, in effect at the beginning of the reporting period, safety concerns for BNT162b2 are:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: 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 (eg, chronic

[15] This refers to the company core list of safety concerns. Myocarditis and pericarditis were already important identified risks in the EU-RMP, US-PVP and many country-level RMP addendums.

obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders); Use in patients with autoimmune or inflammatory disorders; Interaction with other vaccines; Long term safety data.

A summary of the EU-RMP versions and associated procedures, submitted during the reporting period and immediately after the PSUR DLP, are summarised in the table below. Version number of the EU-RMPs was agreed with EMA.

Procedure description	Procedure number	Submitted EU-RMP	Approval date
Reporting period			
Consolidation of RMPs version 2.6 and 4.0.	EMEA/H/C/005735/II/0087 and EMEA/H/C/005735/X/0077	Version 5.0, submitted on 10 March 2022	10 March 2022
After the PSUR DLP			
Line extension for COMIRNATY® 3 µg Concentrate for dispersion for injection for infants and children between 6 months to 4 years of age. Removal of the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received on 10 March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087).	EMEA/H/C/005735/X/0138	Version 5.1, submitted on 08 July 2022	Ongoing procedure with pending approval.
Variation 0140- To support the extension of the indication to ≥12 years of age to receive an additional booster (fourth) dose of bivalent Omicron-(BA.1) modified vaccine.	EMEA/H/C/005735/II/0140	Version 6.0, submitted on 19 July 2022	Ongoing procedure, with pending assessment.
To support the extension of the indication to introduce a first or second booster dose of a bivalent Omicron variant-modified vaccine, (BNT162b2 15 µg + BNT162b2 OMI BA.4/5 15 µg, total 30 µg), given ≥3 months after the primary series or ≥4 months after the third dose in individuals ≥12 years of age.	EMEA/H/C/005735/II/0143	Version 7.0, submitted on 15 August 2022	Ongoing procedure, with pending assessment.

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

After the DLP, an updated CDS (version 14.0) was made effective on 26 July 2022:

- to extend the indication to individuals 6 months of age and older in section 4.1 *Therapeutic indications*;
- to add the posology and method of administration for the Tris/Sucrose presentation 3 micrograms/dose in section 4.2 *Posology and method of administration*;
- to add a statement regarding the reporting rates of myocarditis and pericarditis after primary series and booster doses, based on accumulating data, in section 4.4 *Special warnings and precautions for use*;
- to add clinical data after 3 doses for children 2 through 4 years of age and for children 6 through 23 months of age, irritability and injection site tenderness as adverse drug reactions (ADRs), and myocarditis and pericarditis as ADRs post-authorisation experience in section 4.8 *Undesirable effects*;
- to add efficacy and immunogenicity data in individuals 6 months through 5 years of age in section 5.1 *Pharmacodynamic properties*;
- to add myocarditis and pericarditis as ADRs in Appendices A and B.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADEM	acute disseminated encephalomyelitis
ADR	adverse drug reaction
AE	adverse event
AERP	adverse event reporting proportion
AESI	adverse event of special interest
AIHI	autoimmune haemolytic anaemia
ALC-0315	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
AR	assessment report
ARDS	acute respiratory distress syndrome
AT	Austria
ATC	anatomical therapeutic chemical
BC	Brighton Collaboration
BE	Belgium
BG	Bulgaria
BLA	biologics license application
BMI	body mass index
BoH	Board of Health
BT	blinded therapy
CDC	Centres for Disease Control and Prevention
CDS	core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLS	capillary leak syndrome
CMI	Charlson comorbidity index
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 Vaccines Global Access
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
CVA	cerebrovascular accident
CVST	cerebral venous sinus thrombosis
CY	Cyprus
CZ	Czechia
DE	Germany
DK	Denmark
DLP	data lock point

Abbreviation	Term
DNA	deoxyribonucleic acid
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCTD	electronic common technical document
EE	Estonia
EEA	European economic area
EL	Greece
EMA	European Medicines Agency
EPITT	European pharmacovigilance issues tracking tool
ER	estrogen receptor
ES	Spain
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	emergency use authorization
EUL	emergency use listing
EURD	European Union reference dates
F	female
FDA	Food and Drug Administration
FFRNT	fluorescent focus reduction neutralization test
FI	Finland
FR	France
GBS	Guillain-Barrè syndrome
GI	gastrointestinal
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
GVP	Good pharmacovigilance practices
HA	Health Authority
HCP	healthcare professional
HBV	hepatitis B virus
HCV	hepatitis C virus
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HLGT	high level group term
HLT	high level term
HMB	heavy menstrual bleeding
HPV	human papilloma virus
HR	Croatia
HU	Hungary

Abbreviation	Term
IBD	International Birth Date
IC	immunocompromising condition
ICH	International Council for Harmonisation; intracerebral haemorrhage
ICU	Intensive care unit
IE	Ireland
Ig	immunoglobulin
INR	international normalised ratio
IR	incident rate
IS	Iceland
IT	Italy
IV	intravenous
JNJ	Johnson & Johnson
JST	Japan Standard Time
LI	Liechtenstein
LLOQ	lower limit of quantitation
LLT	lower level term
LMIC	low- and middle-income country
LNP	lipid nanoparticles
LOE	lack of efficacy
LP	license partner
LT	Lithuania
LU	Luxembourg
LV	Latvia
M	male
MAA	marketing authorisation application
MAH	marketing authorisation holder
MC	medically confirmed
ME	myalgic encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	middle East respiratory syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
MIS	multisystem inflammatory syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
mod	modified
MoH	ministry of health
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSSR/SMSR	summary monthly safety report
MT	Malta
N/A	not applicable
NAAT	nucleic acid amplification test
NCMD	National Child Mortality Database

Abbreviation	Term
NEC	not elsewhere classified
NHBA	Neisserial heparin binding antigen
NL	Netherlands
NMC	non-medically confirmed
NO	Norway
NOS	not otherwise specified
NT50	50% neutralising titer
O/E	observed versus expected
OMI	Omicron
OMV	outer membrane vesicles
OR	odds ratio
PASS	post-authorisation safety study
PBRER	periodic benefit-risk evaluation report
PBS	phosphate buffered saline
PC	product complaint
PCR	polymerase chain reaction
PI	product information
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
PSUSA	periodic safety update report single assessment
PT	Preferred Term, Portugal
PVFS	post viral fatigue syndrome
PVP	pharmacovigilance plan
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
RO	Romania
ROW	rest of world
RNA	ribonucleic acid
RSI	reference safety information
RT-PCR	reverse transcription-polymerase chain reaction
RVE	relative vaccine efficacy
RWE	real world evidence
S	spike
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAT	subacute thyroiditis
SBSR	summary bimonthly safety report
SCLS	systemic capillary leak syndrome

Abbreviation	Term
SE	Sweden
SFDA	Saudi Food and Drug Authority
SI	Slovenia
SIIV	seasonal inactivated influenza vaccine
SK	Slovakia
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA Query
SOC	system organ class
SPEAC	Safety Platform for Emergency vACcines
SSNHL	sudden sensorineural hearing loss
SSR	summary safety report
TGA	Therapeutic Goods Administration
TME	targeted medical event
Tris	tromethamine
U	unknown
UK	United Kingdom
UMC	Uppsala Monitoring Centre
Unk	Unknown
US	United States
USG	United States Government
VACTERL	vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities
VAED	vaccine associated enhanced disease
VAERD	vaccine associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VLP	virus-like particle
VOC	variant of concern
WHO	World Health Organization

1. INTRODUCTION

This is the 3rd PSUR for the COVID-19 mRNA vaccine (nucleoside modified), COMIRNATY®, also referred to as BNT162b2,[4] covering the reporting interval 19 December 2021 through 18 June 2022.

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]), corePSUR19 guidance (EMA/362988/2021 [08 July 2021]), and Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance v. 3.0 (EMA/PRAC/73244/2022 [08 February 2022]).

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

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

The PBS/Sucrose presentation includes additionally potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, as excipients. The Tris/Sucrose presentation 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 presentations (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 presentation – 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. A booster dose may be administered intramuscularly at least 6 months after the second dose.

On 17 June 2022, an additional formulation was approved first in the US: the paediatric Tris/Sucrose presentation - maroon cap (3 micrograms/dose) for individuals aged between 6

months and 4 years. This is a concentrate for dispersion for injection, to be administered after dilution intramuscularly in the anterolateral aspect of the thigh (or in the deltoid muscle in individuals 1 year of age and older) as a primary series of 3 doses (0.2 mL). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.

The list of the PSURs prepared for BNT162b2 is presented in Table 2.

Table 2. List of PSURs

PSUR Number	Reporting Period
1	19 December 2020 through 18 June 2021
2	19 June 2021 through 18 December 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[16] on 01 December 2020.

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

BNT162b2 is authorised for the following formulations:

PBS/Sucrose – Purple cap 30 µg formulation:

- in individuals aged 16 years and older in 103 countries[8] including full (5), conditional[17] (49), EUA and other type of approvals[18] (52).

- in individuals aged between 12 and 15 years in 81 countries[9] including full (2), conditional (46), EUA and other type of approvals (34).

Tris/Sucrose formulation:

[16] On 01 January 2021, conditional marketing authorisation approval was also granted in the UK and the approval is currently active.

[17] Including temporary authorisations.

[18] Including special import licenses.

- Grey cap: at the dosage of 30 µg formulation in individuals aged 12 years and older in 73 countries[10] including full (3), conditional (44), EUA and other type of approvals (28).
- Orange cap: at the dosage of 10 µg formulation in individuals aged between 5 and 11 years in 79 countries[9] including full (2), conditional (43), EUA and other type of approvals (35).
- Maroon cap: at the dosage of 3 µg formulation in individuals aged between 6 months and 4 years in the US with EUA[19].
- The booster dose has received approvals in 83 countries[11] including full (3), conditional (46), EUA and other type of approvals (36).

Overall BNT162b2 is authorised in 104 countries/regions; in Table 3 the MAHs and the number of countries where the different MAHs hold the authorisation are presented.

Table 3. Marketing Authorisation Holders of BNT162b2

Marketing Authorisation Holder	Number of Countries/Regions Where the Marketing Authorisation is Held
BioNTech	56
Pfizer	40
Fosun Pharma	2
Local MoH	3
Local Government	3
Hemas (LP)	1
Countries Where BNT162b2 is Authorised	104[a]

a. The sum of the number of the countries where the authorisation is held does not coincide with the total number of countries where BNT162b2 is authorised, because in the UK there are 2 different authorisations: the UK Government is the MAH of the EUA and BioNTech is the MAH of the conditional authorisation.

In addition, WHO had approved the EUL of BNT162b2.

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

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

[19] On 17 June 2022, the paediatric Tris/Sucrose formulation for age 6 months through 4 years was approved first in the US.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

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

Although not considered by definition a regulatory action taken for safety reasons because it does not significantly impact the benefit risk balance of use of the product in authorised populations, due to the receipt of spontaneous reports of Guillain-Barré syndrome (GBS) after vaccination with mRNA COVID-19 vaccines including BNT162b2, PMDA in Japan has required class changes to include GBS in the important precautions section of the Japan package insert[20] and inclusion of GBS as an important potential risk in the Japan RMP[21]. It should be noted that based on PMDA assessment, the frequency of reported cases of GBS was not significantly higher than the background incidence in any gender or age group and a mechanism is not known.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The RSI for this PSUR is the COVID 19 mRNA vaccine CDS version 13.0 dated 10 May 2022, in effect at the end of the reporting period and included in Appendix 1.

The 4 previous CDS versions (version 9.0 dated 02 December 2021[22], version 10.0 dated 21 December 2021, version 11.0 dated 14 January 2022 and version 12.0 dated 23 March 2022[22]), which were also in effect during the reporting period, are included in Appendix 1.2 through Appendix 1.5.

Safety-related changes included updates of the following sections:

- 4.2 *Posology and method of administration* (version 13.0),
- 4.8 *Undesirable effects* (versions 10.0, 11.0 and 13.0),
- 5.1 *Pharmacodynamic properties* (versions 10.0 and 11.0),
- Appendix A and Appendix B (version 10.0).

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

After the DLP, an updated CDS (version 14.0) was made effective on 26 July 2022; the safety-related changes are summarised in Table 4.

[20] The Japan package insert was updated by the MAH during the current reporting period, on 10 June 2022.

[21] Guillain-Barré syndrome was added as important potential risk to the safety concerns in the Japan RMP after DLP of this report on 22 June 2022.

[22] This version of the CDS did not include any safety-related changes.

Table 4. Safety-Related Changes Made to the RSI After the DLP

Version 14.0 dated 26 July 2022		
Section	**Revision Type**	**Revision**
4.1 *Therapeutic indications*	Update	Indication was updated to individuals 6 months of age and older.
4.2 *Posology and method of administration*	Addition	Posology and method of administration for the Tris/Sucrose presentation 3 micrograms/dose.
4.4 *Special warnings and precautions for use*	Addition	Statement regarding the reporting rates of myocarditis and pericarditis after primary series and booster doses, based on accumulating data.
4.8 *Undesirable effects*	Addition	• Clinical data after 3 doses for children 2 through 4 years of age and for children 6 through 23 months of age • Irritability and injection site tenderness as ADRs • Myocarditis and pericarditis as ADRs post-authorisation experience.
5.1 *Pharmacodynamic properties*	Addition	Efficacy and immunogenicity data in individuals 6 months through 5 years of age.
Appendices A and B	Addition	Myocarditis and pericarditis as ADRs.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 66,656[5] participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

BNT162b2: 59,260 participants of which

- 33,096 had received BNT162b2;
- 25,205 had received BNT162b2 post-unblinding and had received placebo before;
- 959 had received BNT162b2/placebo.

Variant vaccines based on BNT162b2: 1836 participants of which

- 747 had received BNT162b2 (B.1.351)[23];
- 372[24] had received BNT162b2 (B.1.617.2);
- 697 had received BNT162b2 (B.1.1.7 + B.1.617.2);
- 20 had received BNT162b2 (B.1.1.7).

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

[24] The number of participants exposed to variant vaccine B.1.617.2 is lower compared to the number reported in the 2nd PSUR, since the participants, who were administered an incorrect dose according to trial specific protocol, are not included.

Early development candidates: 633 participants of which

- 30 had received BNT162a1;
- 411 had received BNT162b1;
- 96 had received BNT162b3;
- 96 had received BNT162c2.

Blinded therapy: 7044 participants.

Placebo: 5871 participants.

Participant demographics data (e.g., age, gender, race) for 'C459' CTs is presented by treatment group in Appendix 2.3. Cumulative CT exposures with demographic data from BioNTech and Fosun CTs is presented in Appendix 2.3B and Appendix 2.3C.

Of note, BNT162b2 is also being utilised in another Pfizer clinical development program (B747): 372 participants received BNT162b2 as a study vaccine or as a comparator in the clinical study B7471026[25]. Participant demographics data (e.g., age, gender, race) by treatment groups are presented in Appendix 2.3.1.

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

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

EMEA/H/C/005735/MEA/002.8 (9th 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 9 through Table 13. Details for the cumulative number of third doses administered by age group and during the interval period in the EU/EEA countries are shown in Table 9 and in Table 13.

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

Cumulative exposure – MAH and LP Data

The worldwide number of shipped doses may serve as a reasonable indicator of subject exposure, considering that approximately 76% of the shipped doses were administered. This ratio represents the proportion of doses cumulatively administered (as per public available data for the EEA[26] countries, the US[27], and Japan[28]) out of those cumulatively shipped (based on MAH data, according to the shipment tracker [Order Book][29]).

With these caveats in mind, it is estimated that:

Approximately 3,555,998,805 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 18 June 2022, corresponding to 2,693,922,584 estimated administered doses.[30]

Overall, through 18 June 2022, a total of 143,844,450 adult Tris/Sucrose doses were shipped worldwide.

Overall, through 18 June 2022, a total of 229,269,400 paediatric Tris/Sucrose doses were shipped worldwide.[31]

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

[26] Approximately 73% 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 16 June 2022.

[27] Approximately 77% 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 17 June 2022.

[28] Approximately 81% of the doses shipped in Japan were administered; this proportion 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://www.kantei.go.jp/jp/headline/kansensho/vaccine.html, as of 20 June 2022.

[29] 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 Taiwan were provided by BioNTech.

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

[31] This total does not include 285,800 doses shipped to US at the DLP of 18 June 2022; on 17 June 2022, FDA approved the Tris/Sucrose presentation - maroon cap (3 micrograms/dose) for individuals aged between 6 months and 4 years.

Table 5. 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	**33.3**	**1184790735**	**873840606**
European Union (27)	24.6	874223640	638183257
European Economic Area Countries (3)	0.4	12454785	9091993
Switzerland	0.3	10501650	7981254
UK	3.4	121752585	92531965
Other Countries[a]	3.6	126651915	96255455
Commonwealth of Independent States	1.1	39206160	29796682
North America	**14.7**	**523868135**	**402657330**
US	12.7	451754755	347851161
Canada	2.0	72113380	54806169
Central and South America[b]	**14.4**	**510365375**	**387877685**
Asia	**29.6**	**1051292420**	**812428536**
Japan	7.6	268925940	217830011
Other Countries[c]	22.0	782366480	594598525
Oceania	**2.3**	**81140220**	**61666567**
Australia/New Zealand	2.3	80243250	60984870
Other Countries[d]	0.0	896970	681697
Africa[e]	**5.8**	**204541920**	**155451859**
Total	**100.0**	**3555998805[f]**	**2693922584**

a. Includes the non-EU countries (Albania, Andorra, Bosnia, Kosovo, Montenegro, North Macedonia, Serbia, Turkey and Vatican City) and the Commonwealth of Independent States (Armenia, 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, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St Kitts & Nevis, Saint. Lucia, Saint Vincent & the Grenadine, Suriname, Trinidad & Tobago and Uruguay.
c. Includes Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, 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 Fiji, Nauru, Samoa, Solomon Islands, Tuvalu.
e. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Central Africa Republic, Chad, Comoros, Congo, Djibouti, Democratic Republic of Congo, Egypt, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Kiribati, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda and Zambia.
f. Out of these shipped doses, 35,240,400 doses were shipped for COVAX, 377,151,030 doses were shipped for USG Donation program and 41,807,550 doses were shipped for EC Donation program.

Out of the cumulative estimated shipped and administered doses, 1,948,639,685 and 1,480,966,161 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 6.

Table 6. Cumulative Administered Doses of BNT162b2 – License Partner Data

Region/Country	Total Number of Administered Doses
Asia	**27314884**
Hong Kong[a,b]	10314451
Macau[c,d]	256403
Taiwan[c,d]	16744030

a. Cumulative through 18 June 2022.
b. Conditional Authorisation under legislation 599K.
c. Special Import Permit.
d. Cumulative through 21 June 2022

Interval exposure – MAH and LP Data

Approximately 1,115,282,160 doses of BNT162b2 were shipped worldwide during the current reporting interval from 19 December 2021 through 18 June 2022, corresponding to 843,724,061 estimated administered doses.[30,32]

During the current reporting interval, a total of 143,844,450 adult Tris/Sucrose doses were shipped worldwide (this number coincides with the total doses shipped worldwide in the cumulative period). [33]

During the current reporting interval, a total of 182,231,200 paediatric Tris/Sucrose doses were shipped worldwide.

Interval worldwide estimated exposure by dose, and region based on or extrapolated from internal data (number of shipped doses) is displayed in Table 7.

[32] The same assumptions done for the ratio between the number of the doses shipped and the administered ones for cumulative data are applied also for interval data.

[33] First shipment of Adult Tris/Sucrose was in the US on 27 December 2021.

Table 7. 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	**30.0**	**334826010**	**246162526**
European Union (27)	24.5	273061770	199335092
European Economic Area Countries (3)	0.3	3779610	2759115
Switzerland	0.4	4978080	3783341
UK	2.2	24785520	18836995
Other Countries[a]	1.5	16756740	12735122
Commonwealth of Independent States	1.0	11464290	8712860
North America	**9.7**	**108011360**	**82997986**
US	8.2	90935210	70020112
Canada	1.5	17076150	12977874
Central and South America[b]	**13.5**	**150188600**	**114143336**
Asia	**36.0**	**401417480**	**308582794**
Japan	6.3	70110180	56789246
Other Countries[c]	29.7	331307300	251793548
Oceania	**3.0**	**32918880**	25018349
Australia/New Zealand	2.9	32122530	24413123
Other Countries[d]	0.1	796350	605226
Africa[e]	**7.9**	**87919830**	**66819071**
Total	**100.0**	**1115282160[f]**	**843724061**

a. Includes the non-EU countries (Albania, Bosnia, Kosovo, North Macedonia, Turkey and Vatican City) and the Commonwealth of Independent States (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Ukraine and Uzbekistan).
b. Includes Antigua & Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Jamaica, Mexico, Panama, Paraguay, Peru, Saint Kitts & Nevis, Saint. Lucia, Saint Vincent & Grenadine, Suriname, Trinidad & Tobago and Uruguay.
c. Includes Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, 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 Fiji, Nauru, Samoa, Tonga, Tuvalu.
e. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Central Africa Republic, Chad, Comoros, Congo, Djibouti, Democratic Republic of Congo, Egypt, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Kiribati, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda and Zambia.
f. Out of these shipped doses, 8,168,940 doses were shipped for COVAX, 186,024,630 doses were shipped for USG Donation program and 34,387,410 doses were shipped for EC Donation program.

During the reporting interval, out of the estimated shipped and administered doses, 677,395,390 and 514,820,496 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 8 below.

Table 8. Interval Administered Doses of BNT162b2 – License Partner Data

Region/Country	Total Number of Administered Doses (30 µg for 12 years and older)	Total Number of Administered Doses (10 µg for 5-11 years)
Asia	**11259174**	867539
Hong Kong[a,b]	4202582	N/A
Macau [c,d]	88514	
Taiwan [c,e]	6968078	867539

a. 19 December 2021 through 18 June 2022.
b. Conditional Authorisation under legislation 599K.
c. Special Import Permit. Only sum of COMIRNATY™ COVID-19 mRNA Vaccine (BNT162b2) 30 mcg and 10 mcg was announced by Macau Government.
d. 22 December 2021 through 21 June 2022
e. 15 December 2021 through 20 June 2022

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 9 through Table 12.

Table 9 displays the EEA published data with number of doses administered for each age group and by dose number.

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

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

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

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

Table 10 provides, as per EMEA/H/C/005735/MEA/002.8 (9th SMSR) and EMEA/H/C/005735/MEA/002.10 (11th SMSR) commitments, the cumulative total number of administered Comirnaty dose 3 (Dose additional 1 in the ECDC webpage) in EU/EEA, per country, and by age group. The table contains also data about Dose 4 (reported as Dose Additional 2).

.

Table 10. EU/EEA – Cumulative Number of BNT162b2 Administered 3rd and 4th Doses by Age Group and Country

Age Group by Dose → Countries ↓	<18 years		18 - 24 years		25 – 49 years		50 – 59 years		60 – 69 years		70 – 79 years		≥80 years		Age Unknown		ALL	
	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4	Dose 3	Dose 4
AT	149818	0	383699	0	1824532	0	1019240	0	850592	0	623022	0	444947	0			5146032	0
BE	217445	1397	555191	5714	2488143	43055	1306086	48807	1195270	65338	851861	78443	545700	159222	0	0	6942251	400579
BG	829	0	17099	0	178925	0	131340	0	194564	0	179688	0	55025	0	0	0	756641	0
CY			31491	7	197248	249	80079	280	79136	4576	61714	10237	29782	7704	0	0	479447	23053
CZ	64536	0	161043	0	1291474	0	717228	0	847562	0	806828	0	332451	0			4156586	0
DE																	49731767	5235439
DK			307330	0	1167386	0	699366	0	625579	0	556738	0	283294	0			3639689	0
EE	4138	93	24080	888	150508	5234	78706	2627	88436	2604	70437	1617	44183	1240	29	0	456349	14210
EL	3553	3	340741	121	1965277	3965	1068942	7582	1021888	74550	825051	124918	569454	103558	0	0	5791353	314694
ES	32057	462	1023148	4138	7624682	42758	5275741	43739	4926491	44635	3728992	32368	2629889	13964	0	0	25208943	181602
FI	14406	0	138920	0	879444	0	526986	0	593869	0	529840	0	293322	0	0	0	2962381	0
FR	843623	2588	3552493	22873	13638089	102484	7004761	168825	6646559	448796	5174638	707112	3173427	888811	0	0	39185859	2338345
HR	989	0	18115	6	184374	72	153973	80	245689	220	202042	375	93999	740	17	0	898192	1493
HU	53637	32	192630	1757	1233409	24567	626328	20945	806512	82280	650482	118480	282857	51769	0	0	3791047	299799
IE	94888	67	225371	307	1121029	3452	529084	4380	453880	88757	339642	146411	180834	80664	7	0	2849840	323971
IS			27048	3	108751	87	39375	119	35091	316	23288	581	11973	3159	0	0	245303	4265
IT	1311889	0	2718431	0	12156326	0	7477957	0	6376845	0	5332414	0	4474910	0			38536883	0
LI			1189	0	5678	0	3767	0	3388	0	2800	0	1338	0			18160	0
LT	1508	0	55113	0	289113	0	154543	0	178306	0	136029	0	76310	0	3	0	889414	0
LU			25976	906	142820	2056	69656	1456	51839	1009	32283	375	22084	10006			344658	15808
LV	2346	1	30415	6	189279	20	90226	10	100272	20	75486	15	41919	9	0	0	527597	80
MT	226	11	26118	30	159816	463	52197	367	56607	7033	37911	17200	17796	11487	3	0	349450	36582
NL	27940	0															9266117	2081682
NO	0	0	215907	0	1000979	0	574971	0	523458	0	425389	0	213127	0			2953831	0
PL			496732	0	3735728	0	1923529	0	2824743	0	2008675	0	850156	0	19605	0	11839563	0
PT			377941	225	2093355	2150	1257166	2171	1237816	4028	994533	9632	657389	299802	36	165	6618200	318008
RO	13719	2	97364	66	618683	1098	346623	800	371174	1900	223183	2148	73778	927			1730805	6939
SE			309765	1126	1726197	15753	985476	18848	940600	373461	934431	706835	520569	428102			5417038	1544125
SI	1198	0	25237	0	157671	0	119298	0	152731	0	122890	0	69999	0			647826	0
SK			76362	366	532569	1694	261509	560	391338	692	278826	404	104807	150	0	0	1645411	3866

Table 11 below shows the cumulative number of BNT162b2 dose administered in Japan.

Table 11. Japan - Cumulative Number of BNT162b2 Administered Doses

	Dose Number			
	1st Dose	**2nd Dose**	**3rd Dose**	**4th Dose**
General population[a]	80859379	80268661	45024154	78384
Elderly	32248732	32160764	20349603	53808
Child[c] (5 to < 12 years)	1334886	1185593	N/A	N/A
Medical workers[b]	6378205	5709228	N/A	N/A
All	**87237584**	**85977889**	**45024154**	**78384**

a. Including elderly and children for all doses. Starting from the 3rd dose, also includes medical workers.
b. Vaccinations for medical workers (1st and 2nd dose) was completed as of 30 July 2021. From the 3rd dose, medical workers are included in the general population.
c. Booster dose in children 5 to < 12 years is not approved in Japan.
Source: Government's website where this data was downloaded:
https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html Download Date: June 20, 2022, 05:00 p.m. [JST]

Table 12 shows the cumulative number of BNT162b2 doses administered in the US.

Table 12. US - Cumulative Number of BNT162b2 Administered Doses

Population	No. of Doses
All	349460399
Fully vaccinated (2 doses)	127603112
With a 1st booster dose	58521335
– 1st Booster dose with BNT162b2 after primary series with BNT162b2 (Homologous Dose Schedule)	49297112
– 1st Booster dose with BNT162b2 after primary series with Moderna (Heterologous Dose Schedule)	3156484
– 1st Booster dose with BNT162b2 after primary series with J&J (Heterologous Dose Schedule)	2024045
– 1st Booster dose with BNT162b2 after primary series with other COVID-19 vaccines (Heterologous Dose Schedule)[a]	51232
– 1st Booster dose with BNT162b2 after primary series with unknown COVID-19 vaccines (Heterologous Dose Schedule)	3992462
With a 2nd booster dose	8756788

a. Not BNT162b2, Moderna or J&J vaccine.

Source https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of 18 June 2022.

Interval exposure – Health Authority Public Data

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

Table 13 displays, as per EMEA/H/C/005735/MEA/002.8 (9th SMSR) and EMEA/H/C/005735/MEA/002.10 (11th SMSR) commitments, the interval data with number of doses administered for each age group and by dose number in the EEA countries.

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

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

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

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

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 25.0 has been used to code adverse events/reactions in summary tabulations.

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

Appendix 2.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in Pfizer clinical trial cases received by the MAH. This appendix is organised according to MedDRA SOC. This appendix includes SAEs originated from the following studies: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020, C4591024, C4591030 and C4591031.

Appendix 2.1.1 provides a cumulative summary tabulation, from the MAH's safety database, of SAEs reported in BioNTech and Fosun clinical trial cases. This appendix includes SAEs

originated from the following studies: BNT162-01, BNT162-03, BNT162-04, BNT162-06, BNT162-14 and BNT162-17.

6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 provides a cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. This tabulation includes serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources. The cumulative data include all data up to 18 June 2022 and the interval data are from 19 December 2021 to 18 June 2022. This appendix is organised according to SOC and presents data for spontaneous cases (including regulatory authority and literature cases) separately from non-interventional sources.

Please note that adverse event totals presented for safety topic evaluations in Section 16 *Signal and Risk Evaluation*, may differ from Appendix 2.2 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 (included in the PRAC ARs on PSURs, SMSRs/SBSRs or signal assessments), WHO and Health Canada to be addressed in the PSUR is detailed below.

Responses are provided in Appendix 6A and in the relevant sections/appendices cross-referenced below, apart from the response to request 5 of the AR of the 2nd PSUR (EMEA/H/C/PSUSA/00010898/202112) that is included in the eCTD sequence with the submission of the current PSUR.

As part of the PSURs AR, the PRAC requested the MAH to address the following requests:

- EMEA/H/C/PSUSA/00010898/202112 (2nd PSUR -reporting period 19 June 2021 through 18 December 2021)

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

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

  3. *The MAH is requested to provide a cumulative review of cases reporting dizziness after Comirnaty exposure outside the context of anxiety/stress-related reactions (as already labelled in the Comirnaty SmPC section 4.4) and a discussion on the need to*

add dizziness (including a proposal for the frequency of occurrence) to the ADR table of the Comirnaty SmPC section 4.8, as applicable. (Appendix 6A.1)

4. *The MAH is requested to provide a cumulative review of cases reporting acquired haemophilia, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccination. The MAH should also provide a comprehensive discussion of the literature, mechanism of action and a discussion on the need to update the product information of Comirnaty, if applicable.* (Appendix 6A.2)

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

- EMEA/H/C/PSUSA/00010898/202106 (1st PSUR - reporting period 19 December 2020 through 18 June 2021)

  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. (Appendix 6B)

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

- 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. (Section 5.2 *Cumulative and Interval Patient Exposure from Marketing Experience*)

- 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.* (Section 9.2 *Medication Errors*)

  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.* (Section 5.2 *Cumulative and Interval Patient Exposure from Marketing Experience*)

- EMA/PRAC/202255/2022 (13th SSR-2nd SBSR)

1. *The MAH is requested to discuss the following publications regarding sudden sensorineural hearing loss (SSNHL) in association with COVID-19 vaccination:*

   Yanir Y, Doweck I, Shibli R, Najjar-Debbiny R, Saliba W. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss [published online ahead of print, 2022 Feb 24]. JAMA Otolaryngol Head Neck Surg. 2022;e214278

   Formeister EJ Wu MJ, Chari DA, et al. Assessment of Sudden Sensorineural Hearing Loss After COVID-19 Vaccination [published online ahead of print, 2022 Feb 24]. JAMA Otolaryngol Head Neck Surg. 2022;e214414. doi:10.1001/jamaoto.2021.4414 (Section 11 *Literature* and Appendix 6A.3)

Furthermore, the MAH is requested to conduct age-stratified O/E analyses for the AESI of sudden hearing loss using the age-specific background incidence rates of SSNHL reported in the following publication: Alexander T and Harris J. Incidence of Sudden Sensorineural Hearing Loss. Otol Neurotol. 2013 Dec;34(9):1586-9. doi:10.1097/MAO.0000000000000222. (Appendix 6A.3)

3. *The MAH is requested in future SSRs and PSURs to present all relevant literature concerning the safety of Comirnaty (also besides the database Medline and Embase) that is published during the reporting period.*

4. *The MAH should continue to closely monitor MIS-C/A as outlined in PRAC's signal recommendation (EPITT 19732). All new cases of MIS should be reported in the SSRs and PSURs.* (Appendix 6A.4)

- EMA/PRAC/577594/2022 (14th SSR – 3rd SBSR)

1. *In not (yet) peer-reviewed retrieved relevant literature, the MAH is requested to assess the used study methods to determine if the study results are valid or not, for further characterisation of a particular safety issue (e.g., myocarditis and pericarditis).* (Appendix 6A.3)

2. *The MAH is requested to perform a cumulative review on the association between sudden sensorineural hearing loss and Comirnaty exposure, including a review of the relevant new literature published after the reporting period of the 14th SSR, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.* (Appendix 6A.3)

3. *In general the MAH should perform more effort in presenting/evaluating the cases that they have considered to be confounded and should present the risk factors for developing the respective conditions. If patient groups/patients with underlying disease have a higher risk of developing the condition this information is important to communicate. (NO)* (Section 16.3.1 *Evaluation of Important Identified Risks,*

Section 16.3.2 *Evaluation of Important Potential Risks*, Section 16.3.4.1 *Death* and Section 16.3.5.2 *Use in Paediatric Patients*)

As per signal assessment reports, the PRAC requested:

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

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

- Signal assessment report on multisystem inflammatory syndrome in children for COVID-19 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, A dedicated questionnaire should be implemented to retrieve an appropriate level of information to facilitate the assessment of the cases. The MAH should focus on the well described index case(s) and less on quantity and numbers. A few well described cases may be sufficient in our opinion to indicate a causal association for a very rare serious event. (Appendix 6A.4)

- Signal assessment on Autoimmune hepatitis with tozinameran EMA/PRAC/632042/2021 - EPITT 19749

  The MAH should provide in the next PSUR (submission date 27 August 2022) a cumulative review of all cases of autoimmune hepatitis, including any relevant new data, from all available sources.
  The cumulative review should include, but not be limited to, data from clinical trials, post-marketing cases and any relevant articles from literature, using a data lock-point as recent as possible. (Appendix 6A.5)

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. (Section 16.3.3.1.21 *AESIs in subjects with Malnutrition; HIV infection*)

The MAH was requested to present the outcome of the cases of pregnancy observed in the clinical studies. (Section 16.3.5.3 *Use in Pregnant/Lactating Women*)

Health Canada (29 November 2021)

Future updates of the Cumulative Review on the new variant "Omicron" and other variants should be included in the Monthly Summary Safety Report (MSSRs) and the Periodic Benefit-Risk Evaluation Reports (PBRER) for Comirnaty Pfizer-BioNTech COVID-19 Vaccine (tozinameran). (Section 16.3.4.5 *Lack of Therapeutic Efficacy* and Section 17.2 *Newly Identified Information on Efficacy and Effectiveness*)

Health Canada (31 May 2022 – 2nd SBSR AR)

Tinnitus and hearing loss: The WHO recently published an update regarding COVID-19 vaccines and hearing loss. Signal detection activities at the UMC up to 22 Feb 2022 retrieved 164 cases with HLT Hearing losses (142 cases for Comirnaty) and 367 cases with the PT Tinnitus (293 for Comirnaty) with COVID-19 vaccines. Based on well documented cases, alternative causes were not identified for most of the patients and a plausible mechanism of action has been suggested. As such, provide a cumulative review of all cases of tinnitus and hearing loss. This cumulative review should include analyses of all cases, stratified by age, gender, doses administered, time to onset, and any other relevant information. An observed-to-expected analysis should be provided including the appropriate risk window. An appropriate case definition including a causality assessment should also be provided. (Appendix 6A.3)

6.3.1.1. General Overview of the Safety Database – All Cases

As per PRAC assessment report of the 2nd PSUR (procedure EMEA/H/C/PSUSA/00010898/202112):

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

Response

Please refer to Appendix 6A.

General Overview – All Cases

A total of 508,351 case reports (668 from CT[34] and 507,683 from PM) containing 1,597,673 events fulfilled criteria for inclusion in this PSUR reporting period, compared to 658,249 case

[34] Clinical Trials cases include:

- 630 cases originated from 6 interventional trials (C4591001, C4591001-OPENLABEL, C4591007, C4591007-OPENLABEL, C4591015, C4591024, C4591030, C4591031, C4591031-OPENLABEL) for which BioNTech is the Sponsor and Pfizer acts as lead development party.
- 17 cases from 2 BioNTech interventional trials (BNT162-14 and BNT162-17), and

reports retrieved in the PSUR #2. Refer to Appendix 2.1 and Appendix 2.1.1 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.

Demographic information of all cases included in the safety database and received during the reporting interval are shown in Table 14.

Table 14. Demographic Information - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=508,351[g]	CT No. of Cases (%[a]) N=668	PM No. of Cases (%[a]) N=507,683 [g]
EudraVigilance Cases		309,455	0	309,455
MC	Yes	204,582 (40.2)	668 (100)	203,914 (40.2)
	No	303,769 (59.8)	0 (0)	303,769 (59.8)
Country of occurrence (*: ≥2% of all cases)	Germany*	114,573 (22.5)	27 (4.0)	114,546 (22.6)
	Austria*	55,474 (10.9)	0 (0)	55,474 (10.9)
	Netherlands*	38,790 (7.6)	0 (0)	38,790 (7.6)
	France*	38,418 (7.6)	0 (0)	38,418 (7.6)
	UK*	36,833 (7.2)	1 (0.1)	36,832 (7.3)
	Australia*	23,189 (4.6)	0 (0)	23,189 (4.6)
	US*	22,605 (4.4)	425 (63.6)	22,180 (4.4)
	Philippines*	17,981 (3.5)	0 (0)	17,981 (3.5)
	Sweden*	16,862 (3.3)	0 (0)	16,862 (3.3)
	Italy*	12,201 (2.4)	0 (0)	12,201 (2.4)
	Japan*	12,080 (2.4)	0 (0)	12,080 (2.4)
	Norway*	10,868 (2.1)	0 (0)	10,868 (2.1)
	Malaysia*	10,009 (2.0)	0 (0)	10,009 (2.0)
	Other countries	98,468 (19.4)	215 (32.2)	98,253 (19.4)
Gender	Female	324,059 (63.7)	304 (45.5)	323,755 (63.8)
	Male	149,371 (29.4)	360 (53.9)	149,011 (29.4)
	Unknown/No Data	34,921 (6.9)	4 (0.6)	34,917 (6.9)
Age (years)	N	447,034	649	446,385
	Min-Max	0.01-120	0.58-87	0.01-120
	Mean	42.5	49.8	42.5
	Median	41	57	41
Age Range	≤ 17 years	33,236[c,f] (6.5) [31,927] [e]	117 (17.5) [102] [e]	33,119 [c,f] (6.5) [31,825] [e]
	0 to 27 days	145 (0.03) [3] [e]	9 (1.3) [0] [e]	136 (0.03) [3] [e]

- 21 cases from 1 Fosun (BioNTech License Partner) interventional trial (BNT162-06) with BioNTech third party acting as lead development party.
- After DLP, an additional case originated from the BioNTech interventional trial BNT162-14 was identified, but it is not included among the CT cases, because the Case Report Type was erroneously reported as non-MAH sponsored interventional study. This case is from [redacted] and involved a 66-year-old male participant, who developed atrial fibrillation 175 days after vaccination with BNT162b2s01. The SAE resolved and was assessed as unrelated to the vaccine by the investigator and the Sponsor.

Table 14. Demographic Information - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=508,351[g]	CT No. of Cases (%[a]) N=668	PM No. of Cases (%[a]) N=507,683 [g]
	28 days to 23 months	1071 (0.2) [102] [c]	28 (4.2) [22] [c]	1043 (0.2) [80] [c]
	2-11 years	10,044 (2.0) [9864] [c]	65 (9.7) [65] [c]	9979 (2.0) [9799] [c]
	12-17 years	21,976 (4.3) [21,958] [e]	15 (2.2) [15] [e]	21,961 (4.3) [21,943] [e]
	18-30 years	91,380 (18.0)	37 (5.5)	91,343 (18.0)
	31-50 years	183,209 (36.0)	128 (19.2)	183,081 (36.1)
	51-64 years	86,885 (17.1)	171 (25.6)	86,714 (17.1)
	65-74 years	35,201 (6.9)	132 (19.8)	35,069 (6.9)
	≥ 75 years	21,598 (4.2)	79 (11.8)	21,519 (4.2)
	Unknown	56,648 (11.1)	1 (0.1)	56,647 (11.2)
	N/A [d]	194 (<0.1)	3 (0.4)	191 (<0.1)
Case Seriousness	Serious	152,093 (29.9)	668 (100)	151,425 (29.8)
	Non-serious	356,258 (70.1)	0 (0)	356,258 (70.2)
Case Outcome	Fatal	3,280 (0.6)	35 (5.2)	3,245 (0.6)
	Not recovered	160,905 (31.7)	93 (13.9)	160,812 (31.7)
	Recovered/ Recovering	178,812 (35.2)	499 (74.7)	178,313 (35.1)
	Recovered with sequelae	9,451 (1.9)	39 (5.8)	9,412 (1.9)
	Unknown	155,903 (30.7)	2 (0.3)	155,901 (30.7)
Presence of comorbidities [b]	Yes	38,787 (7.6)	259 (38.8)	38,528 (7.6)
	No	469,564 (92.4)	409 (61.2)	469,155 (92.4)

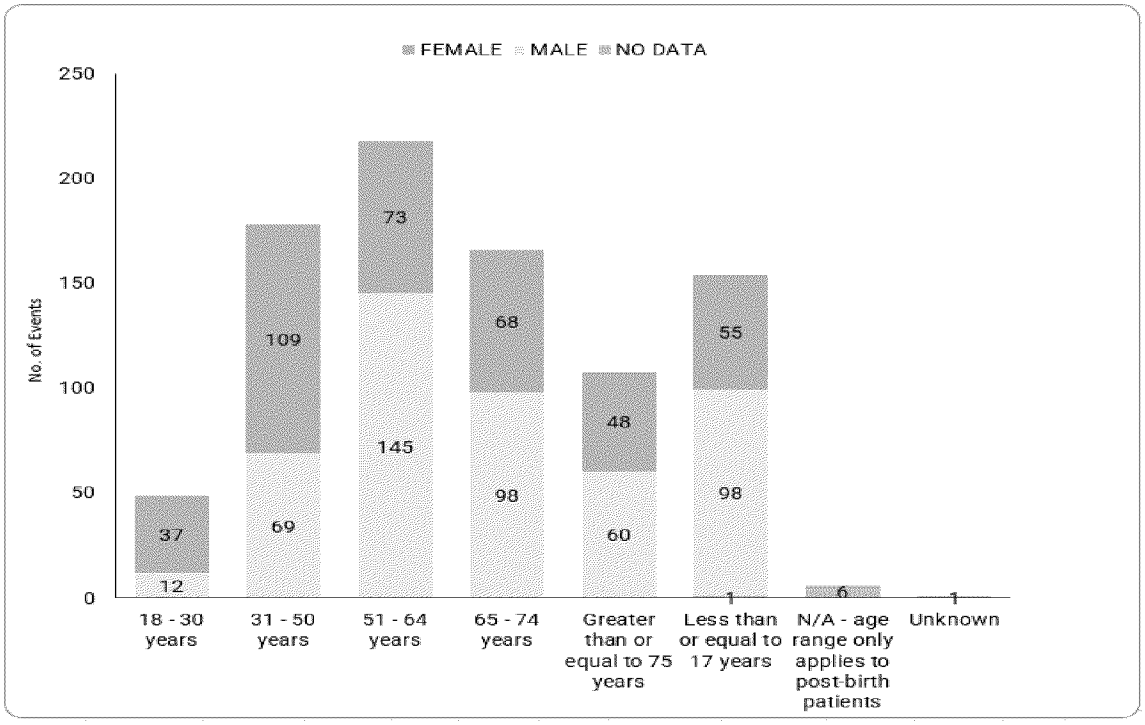
a. The sum of percentages may not exactly match 100% due to rounding in calculations.
b. Cases retrieved applying the criteria in place to identify the reports involving the special populations of Immunocompromised patients, Patients with autoimmune or inflammatory disorders, Frail patients with comorbidities (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.
c. It includes 2 pregnant female subjects aged 16 and 17 years.
d. Foetus cases-Age range only applies to post-birth subjects.
e. 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.
f. It includes 284 cases where the age is reported as "Adolescent".
g. There were 4 cases involving pregnant subjects, whose ages were erroneously reported under the elderly age group. These 4 cases are excluded in the Section 16.3.5.1 *Use in Elderly Patients*.
MC = Medically confirmed; N: Number of cases; N/A=Not applicable; CT=Clinical trial; PM=Post-marketing

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 male participants was slightly higher than female (53.9% vs 45.5%); the number of SAEs experienced by male participants

is slightly higher than female (482 vs 391); in the 18 - 30 years and the 31 - 50 years age groups, the number of SAEs reported in females was higher than in males, while in the paediatric population, in 51-64 years and in the elderly (≥ 65 years) age groups, the SAEs reported in male participants was higher than in females (Figure 1).

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



Case outcomes by presence/absence of comorbidities[35], 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 (7 cases, 1.0% of the total CT dataset) than female participants (6 cases, 0.9% of the total CT dataset) experienced a fatal outcome in the presence of comorbidities (Figure 3), and more male (18 cases, 2.7% of the total CT dataset) than female participants (4 cases, 0.6% of the total CT dataset) 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 the case outcomes of recovered/recovering (55), recovered with sequelae (5), and not recovered (16). Among the cases with a fatal outcome, most cases were presented in the age group ≥ 75 years (5); furthermore, the same number of occurrences was reported in the age groups 31-50 years and 51-64 years, as shown in Figure 4. In cases without comorbidities (Figure 5), most of the

[35] 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.

cases had a favourable outcome across all age groups at the time of reporting with the paediatric participants as more represented group, whose recovered case outcome involved 68 cases; the highest number of fatal outcomes occurred in the 31-50 years and 65-74 years followed by the 51-64 years.

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

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

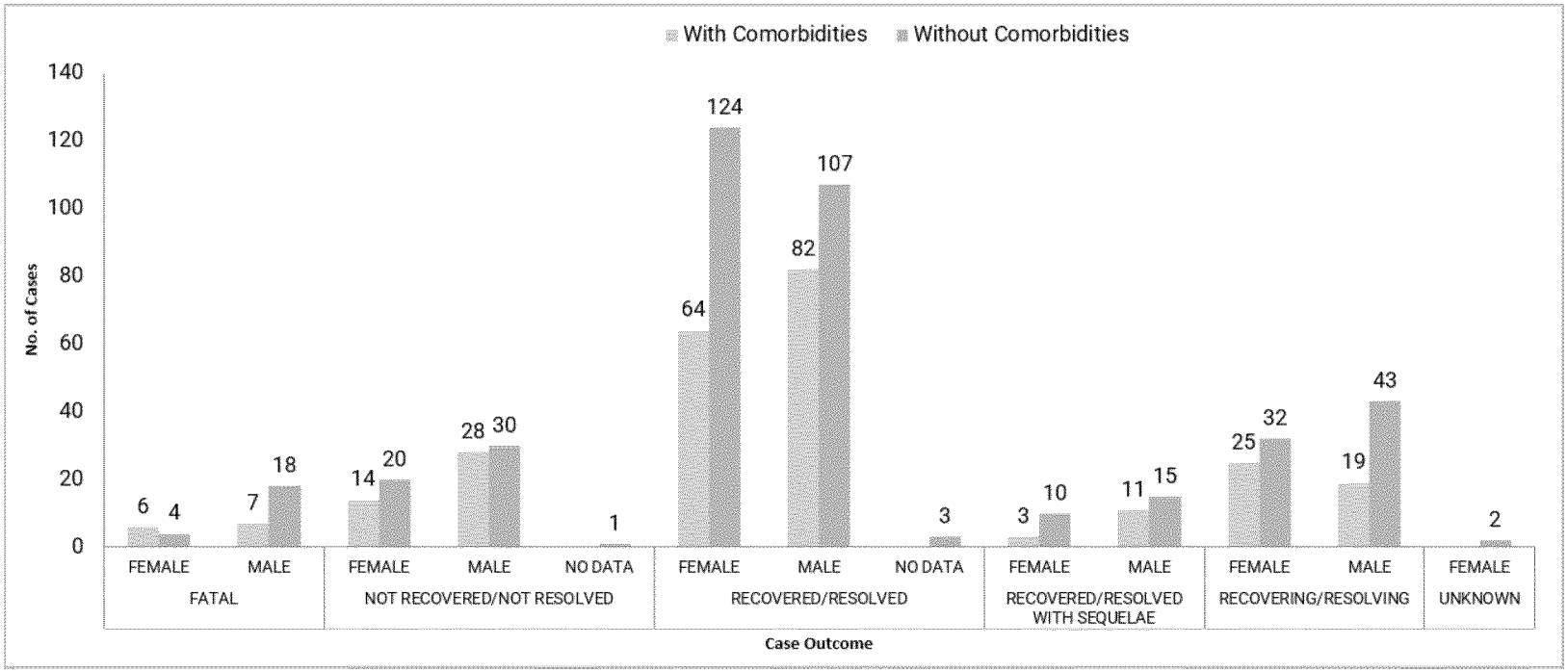


Figure 4. Clinical Trial Data: Case Outcome by Age Group in Presence of Comorbidities

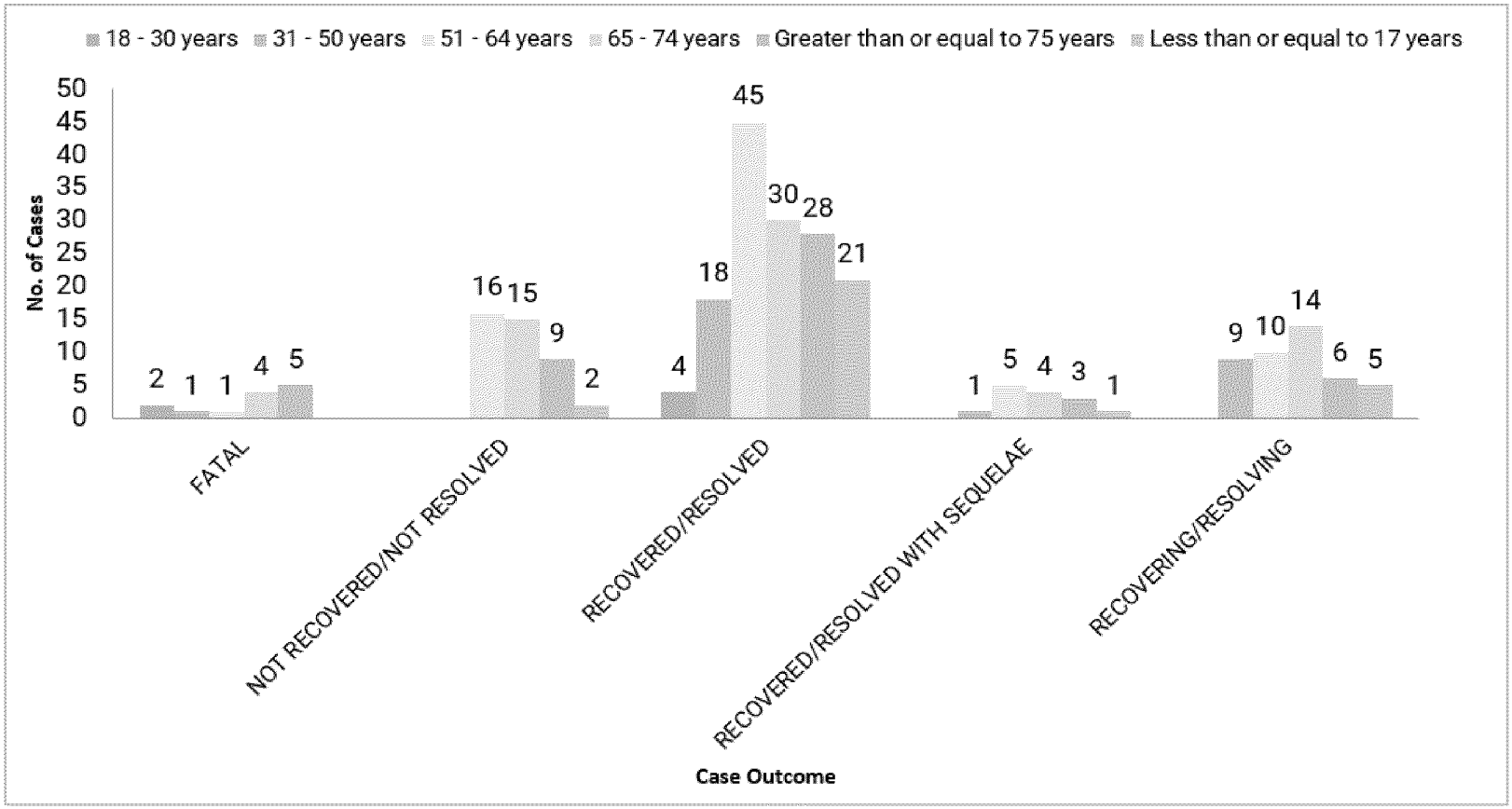
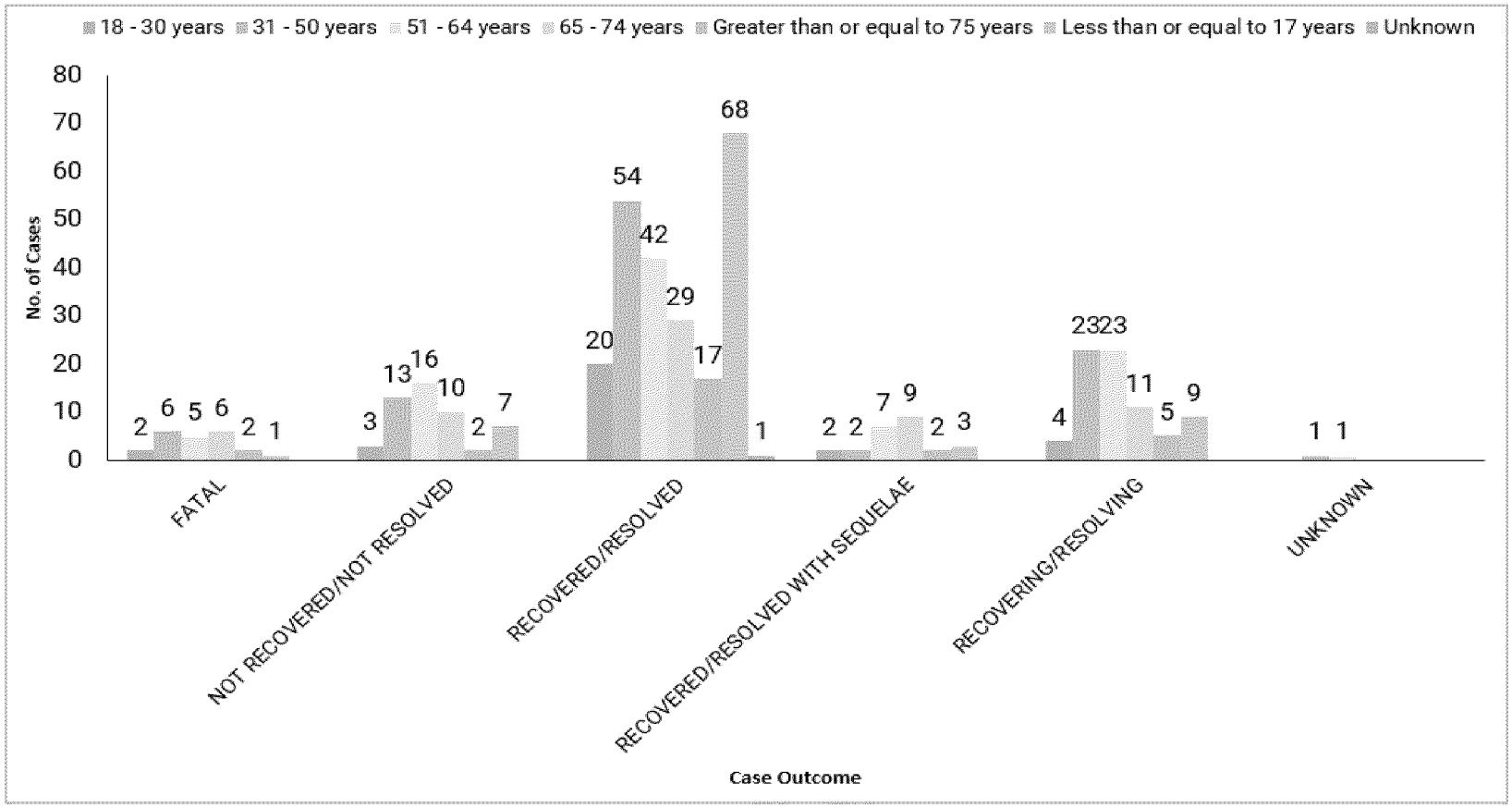


Figure 5. Clinical Trial Data: Case Outcome by Age Group in Absence of Comorbidities



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

Table 15. Clinical Trial Data: Medical History and Co-Suspects

Most frequently reported (≥2%) medical history (HLGT): Vascular hypertensive disorders (192), Lipid metabolism disorders (131), Appetite and general nutritional disorders, Glucose metabolism disorders (incl diabetes mellitus) (90 each), Allergic conditions (87), Joint disorders (86), Lifestyle issues (83), Gastrointestinal motility and defaecation conditions (76), Depressed mood disorders and disturbances (70), Anxiety disorders and symptoms (68), Bronchial disorders (excl neoplasms) (62), Gastrointestinal therapeutic procedures (57), Sleep disorders and disturbances (48), Thyroid gland disorders (46), Infections - pathogen unspecified (44), Cardiac arrhythmias, Coronary artery disorders (41 each), Obstetric and gynaecological therapeutic procedures (39), Bone and joint therapeutic procedures (35), Respiratory disorders NEC (34), Viral infectious disorders, Therapeutic procedures and supportive care NEC (31 each), Musculoskeletal and connective tissue disorders NEC, Headaches, Peripheral neuropathies, Vascular therapeutic procedures (27 each), Pregnancy, labour, delivery and postpartum conditions, Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders) (25 each), Epidermal and dermal conditions, Male genital tract therapeutic procedures (24 each), Age related factors (23), Vision disorders, Injuries NEC, Bone disorders (excl congenital and fractures), Prostatic disorders (excl infections and inflammations) (22 each), Upper respiratory tract disorders (excl infections), Bone and joint injuries (21 each), General system disorders NEC, Hepatobiliary therapeutic procedures (20 each), Gallbladder disorders, Renal and urinary tract therapeutic procedures (19 each), Abdominal hernias and other abdominal wall conditions, Muscle disorders (18 each), Lipid analyses, Central nervous system vascular disorders, Nervous system, skull and spine therapeutic procedures (16 each), Anterior eye structural change, deposit and degeneration, Renal disorders (excl nephropathies) (15 each), Anaemias nonhaemolytic and marrow depression, Purine and pyrimidine metabolism disorders, Urinary tract signs and symptoms, and Cardiac therapeutic procedures (14 each), Breast therapeutic procedures, and Gastrointestinal signs and symptoms (13 each).

The medical conditions (PTs History) reported in more than 2% of the cases included Hypertension (186), Obesity (77), Type 2 diabetes mellitus (71), Depression (63), Osteoarthritis, Seasonal allergy (62 each), Gastrooesophageal reflux disease (60), Anxiety (56), Hypercholesterolaemia (51), Hyperlipidaemia (48), Insomnia (45), Hypothyroidism (43), Asthma (34), Non-tobacco user, Dyslipidaemia (29 each), Coronary artery disease (28), Pregnancy, Atrial fibrillation (25 each), Ex-tobacco user (24), Chronic obstructive pulmonary disease (23), Back pain (22), Benign prostatic hyperplasia (20), Cholecystectomy (19), Appendicectomy, Migraine, Postmenopause (18 each), Tobacco user (16), Rhinitis allergic, Cholelithiasis, Neuropathy peripheral, Osteoporosis (15 each), Blood cholesterol increased, Cataract, Diabetes mellitus, Drug hypersensitivity, Hysterectomy, and Vasectomy (14 each), Sleep apnoea syndrome, Ex-alcohol user, Live birth, and Caesarean section (13 each).

COVID-19 medical history (n=8): COVID-19.

Most frequently reported (≥ 2 cases) co-suspect medications: amlodipine besilate and metformin (2 each).

Adverse Event Data

A total of 879 SAEs were reported in 668 cases.

The MedDRA SOCs containing the greatest number of reported events[36] (≥2%) from clinical trial data were Infections and infestations (158), Injury, poisoning and procedural complications (100), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (99), Cardiac disorders (66), Nervous system disorders (64), Gastrointestinal disorders (61), General disorders and administration site conditions (54), Respiratory, thoracic and mediastinal disorders (42), Musculoskeletal and connective tissue disorders (40), Hepatobiliary disorders (30), Psychiatric disorders (28), Vascular disorders (25), Pregnancy, puerperium and perinatal conditions (24), Metabolism and nutrition disorders, Renal and urinary disorders (22 each).

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

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

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

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

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

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

During the reporting period, 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 except Appendicitis. Among these most frequently reported serious adverse events, the reporting proportion of the PT Gastroenteritis during the reporting interval was higher (2.3%) compared to its proportion in the cumulative dataset (0.9%). Upon review, all SAEs of Gastroenteritis during the reporting interval are assessed as unrelated by the investigator and the Sponsor. Event outcomes were resolved (14) and resolved with sequelae (1).

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

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

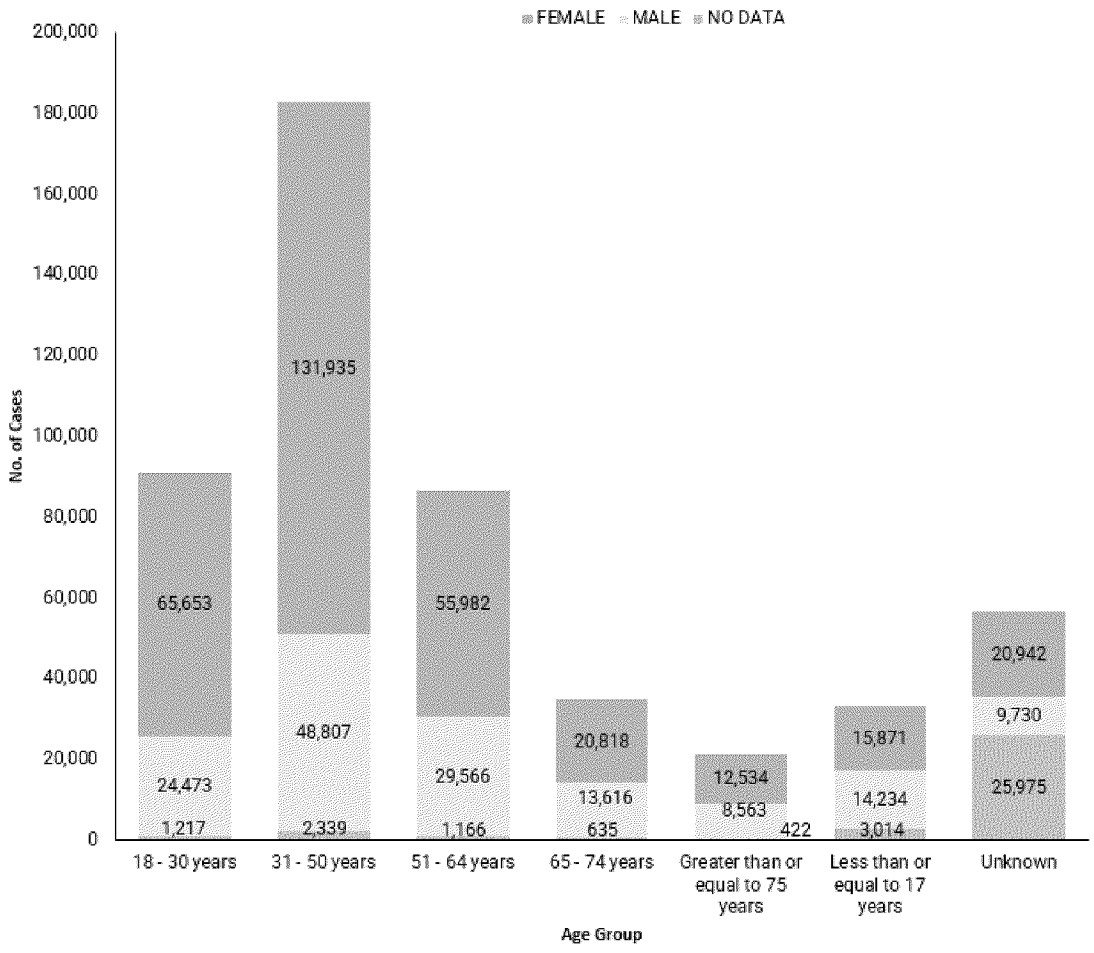
Conclusion

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 2.2 times the number of male subjects (63.8% vs 29.4%); across the different age groups the ratio of female/male cases ranged between 1.1 in the less than or equal to 17 years to 2.7 in the 31-50 years group (Figure 6).

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

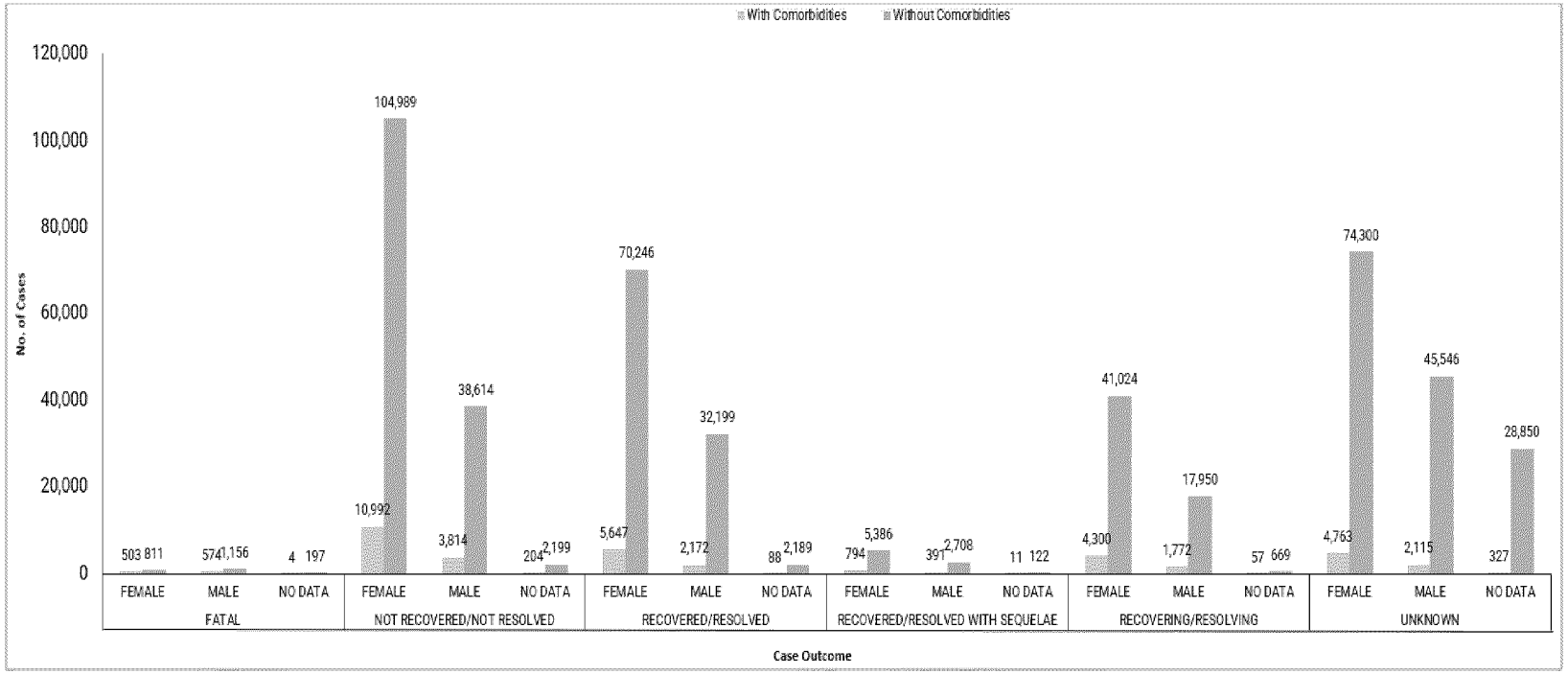


Case outcomes by presence/absence of comorbidities[35], by gender and age group in PM cases are presented in Figure 7 through Figure 10. Overall, the proportion of cases with comorbidities was 7.6% of the total PM dataset; Figure 7 shows the case outcome by presence/absence of comorbidities.

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).

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



The age group 31-50 years represents 36.1% 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.

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

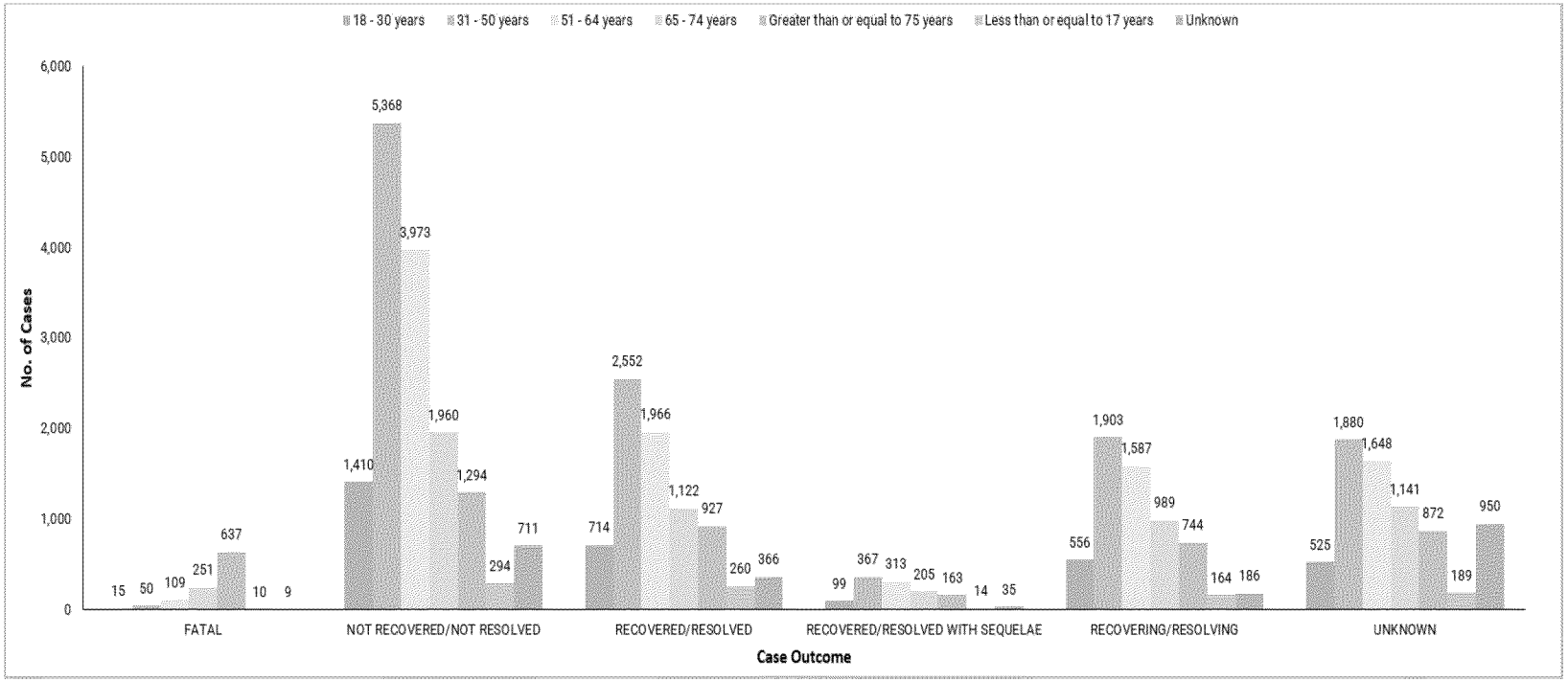
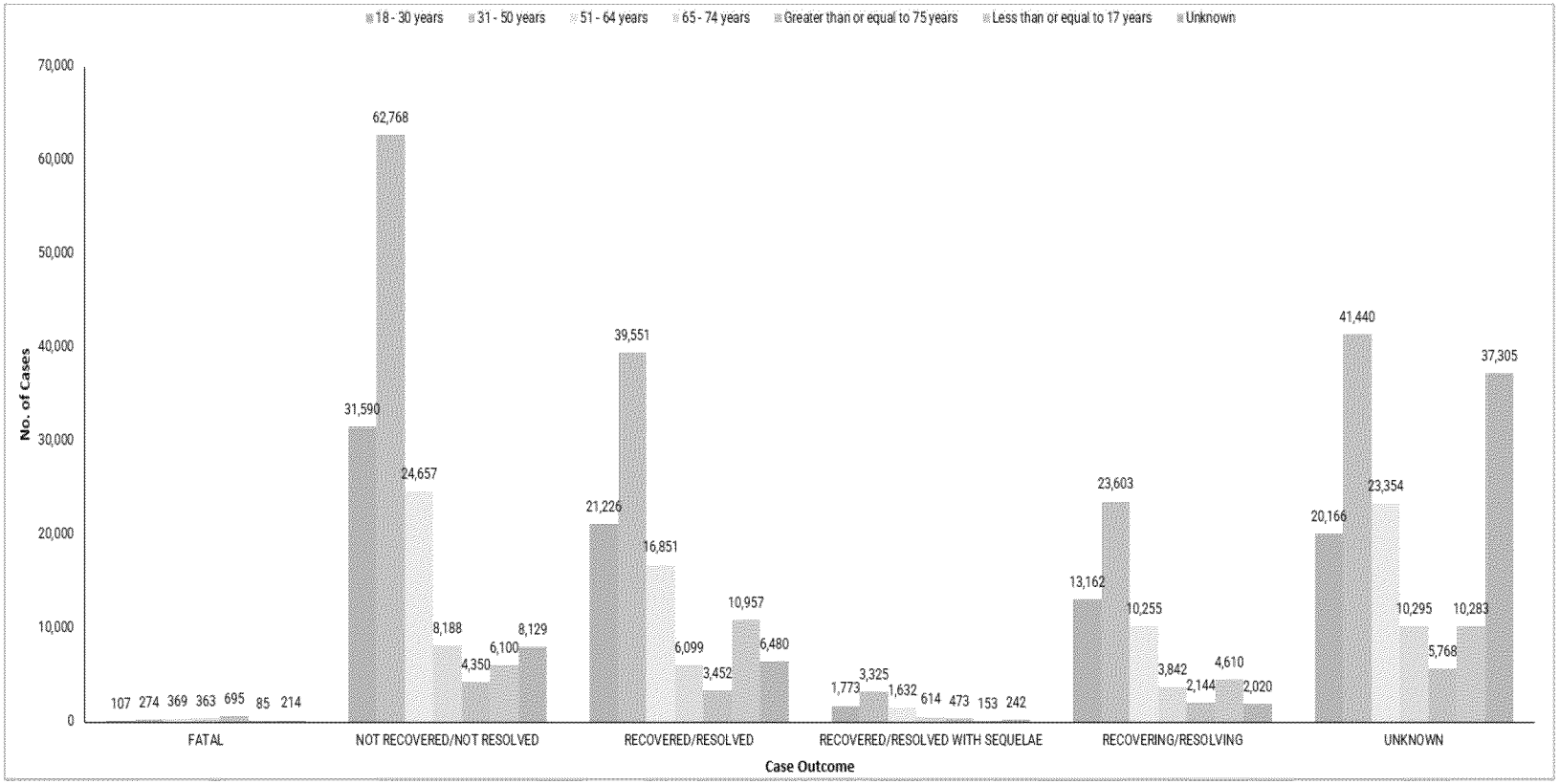


Figure 10. Post-Authorisation Data: Case Outcome by Age Group in Absence of Comorbidities



The summary of medical history and co-suspects reported in the PM cases is provided in Table 17

Table 17. Post-Authorisation Data: Medical History and Co-Suspects

Most frequently reported (≥2%) medical history (HLGT): Viral infectious disorders (22,612), Allergic conditions (19,947), Vascular hypertensive disorders (13,073), and Lifestyle issues (11,228). The medical conditions (PTs History) reported in more than 2% of the cases included PT Hypertension (12,888). **COVID-19 medical history:** COVID-19 (14,526), Suspected COVID-19 (5971), Post-acute COVID-19 syndrome (254), COVID-19 pneumonia (111), SARS-CoV-2 test positive (90), Coronavirus infection (77), Exposure to SARS-CoV-2 (71), Asymptomatic COVID-19 (52), SARS-CoV-2 antibody test positive (6), Coronavirus test positive, Occupational exposure to SARS-CoV-2 (3 each), Breakthrough COVID-19 (2), and COVID-19 treatment (1). **Most frequently reported (≥40) co-suspect vaccines/medications (other than COVID-19 vaccines):** adalimumab (626), influenza vaccine (465), influenza vaccine inact SAG 4V (149), influenza vaccine inact SPLIT 4V (143), ocrelizumab (92), upadacitinib (80), influenza vaccine inact SPLIT 3V (44), Risankizumab (42), pneumococcal vaccine polysacch 23V (41), apixaban, and ethinylestradiol/levonorgestrel (40 each). **Most frequently reported (≥42) co-suspect COVID-19 vaccines:** COVID-19 vaccine (1929), COVID-19 vaccine mRNA (mRNA 1273) (1608), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (1040), JNJ 78436735 (144), and COVID-19 vaccine inact (vero) CZ02 (42).

Adverse Event Data

A total of 1,596,793 AEs (of which 439,443 were serious and 1,158,240 non-serious[37]) were reported in 507,683 PM cases.

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

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

[37] 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.

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

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)
Nervous system disorders				
Headache [b]	77,974 (15.4)	9451 (6.2)	297,293 (20.0)	41,338 (9.7)
Dizziness [b]	30,880 (6.1)	5418 (3.6)	93,304 (6.3)	20,903 (4.9)
Paraesthesia [g]	14,993 (3.0)	3018 (2.0)	44,666 (3.0)	10,640 (2.5)
General disorders and administration site conditions				
Fatigue [b]	67,879 (13.4)	8675 (5.7)	235,562 (15.9)	34,742 (8.2)
Pyrexia [b]	57,746 (11.4)	6642 (4.4)	228,574 (15.4)	29,973 (7.0)
Vaccination site pain [b]	49,263 (9.7)	2199 (1.5)	190,875 (12.9)	9,703 (2.3)
Chills [b]	33,542 (6.6)	2895 (1.9)	128,602 (8.7)	14,687 (3.5)
Malaise [b]	32,701 (6.4)	3337 (2.2)	142,545 (9.6)	15,085 (3.5)
Drug ineffective [h]	26,688 (5.3)	26,664 (17.6)	41,566 (2.8)	41,515 (9.8)
Vaccination failure [d]	24,419 (4.8)	24,415 (16.1)	37,933 (2.6)	37,926 (8.9)
Chest pain [i]	17,945 (3.5)	5694 (3.8)	40,839 (2.8)	15,623 (3.7)
Pain [b]	16,529 (3.3)	3618 (2.4)	80,302 (5.4)	14,660 (3.4)
Asthenia [b]	13,703 (2.7)	2793 (1.8)	59,692 (4.0)	11,424 (2.7)
Vaccination site swelling [b]	10,670 (2.1)	446 (0.3)	40,218 (2.7)	1,954 (0.5)
Infections and infestations				
COVID-19 [c]	47,988 (9.5)	47,449 (31.3)	76,044 (5.1)	72,718 (17.1)
Musculoskeletal and connective tissue disorders				
Myalgia [b]	43,916 (8.7)	4451 (2.9)	178,198 (12.0)	18,937 (4.5)
Arthralgia [b]	29,430 (5.8)	4702 (3.1)	121,898 (8.2)	18,152 (4.3)
Pain in extremity [b]	25,090 (4.9)	4584 (3.0)	93,467 (6.3)	18,828 (4.4)
Limb discomfort [b]	11,578 (2.3)	670 (0.4)	23,939 (1.6)	2,558 (0.6)
Injury, poisoning and procedural complications				
Inappropriate schedule of product administration [d]	35,318 (7.0)	466 (0.3)	57,719 (3.9)	1,020 (0.2)
Off label use [d]	29,927 (5.9)	10,293 (6.8)	54,754 (3.7)	16,400 (3.9)
Poor quality product administered [j]	17,859 (3.5)	4 (0.003)	30,830 (2.1)	14 (0.004)

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

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)
Blood and lymphatic system disorders				
Lymphadenopathy [b]	31,132 (6.1)	2794 (1.9)	79,285 (5.3)	10,712 (2.5)
Gastrointestinal disorders				
Nausea [b]	30,670 (6.0)	4338 (2.9)	124,557 (8.4)	22,152 (5.2)
Vomiting [b]	11,424 (2.3)	2454 (1.6)	38,996 (2.6)	10,498 (2.5)
Diarrhoea [b]	10,211 (2.0)	1644 (1.1)	44,491 (3.0)	8,409 (2.0)
Surgical and medical procedures				
Immunisation [e]	25776 (5.1)	11,063 (7.3)	46,775 (9.6)	19,305 (4.5)
Interchange of vaccine products [e]	25,233 (5.0)	9397 (6.2)	38,522 (2.6)	14,276 (3.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea [b]	21,736 (4.3)	6947 (4.6)	56,998 (3.8)	22,516 (5.3)
Skin and subcutaneous tissue disorders				
Rash [b]	13,640 (2.7)	1802 (1.2)	41,937 (2.8)	7,742 (1.8)
Cardiac disorders				
Palpitations [b]	13,071 (2.6)	4231 (2.8)	30,535 (2.1)	10,716 (2.5)
Tachycardia [i]	10,914 (2.2)	3028 (2.0)	25,602 (1.7)	7,887 (1.9)
Reproductive system and breast disorders				
Heavy menstrual bleeding [i]	12,905 (2.5)	1711 (1.1)	30,498 (2.1)	6,381 (1.5)
Menstrual disorder [i]	12,579 (2.5)	871 (0.6)	24,442 (1.6)	2,370 (0.6)

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

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)

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

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

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

Out of the 1,596,793 AEs in the PM dataset, 72.5% 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, Drug ineffective, and Vaccination failure.

Figure 12 provides information about the age breakdown in the clinical AEs reported in more than 2% of the cases by SOC; the age group 31-50 years is the one reporting higher proportion of events than other age groups 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

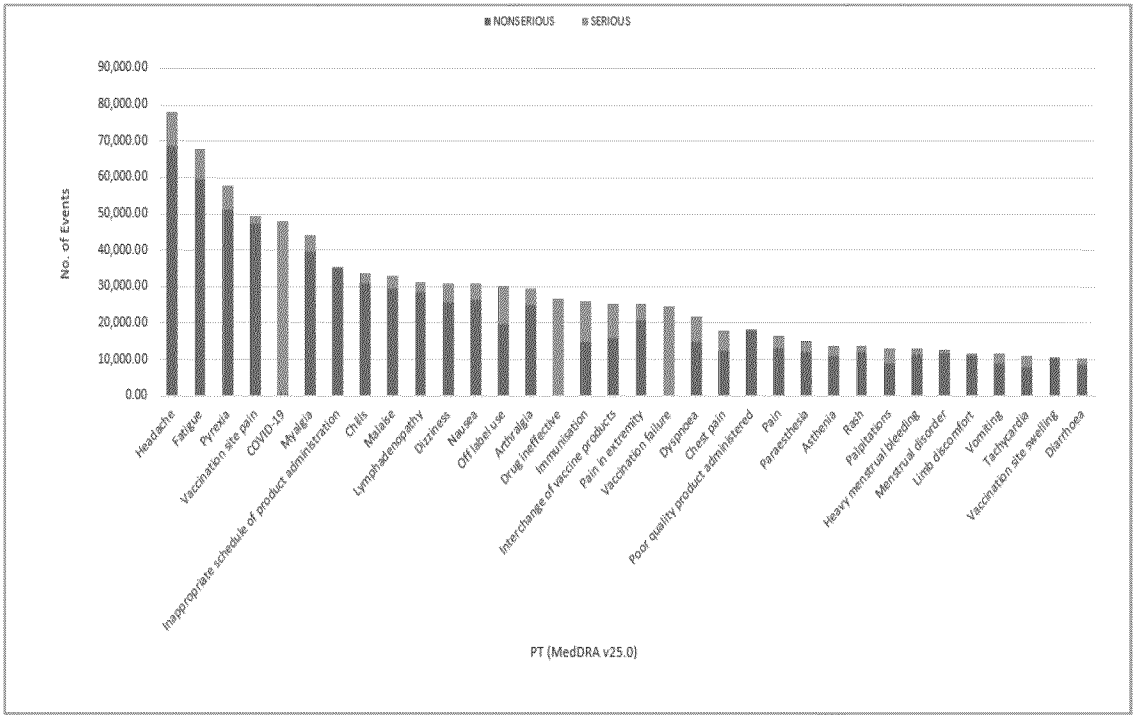
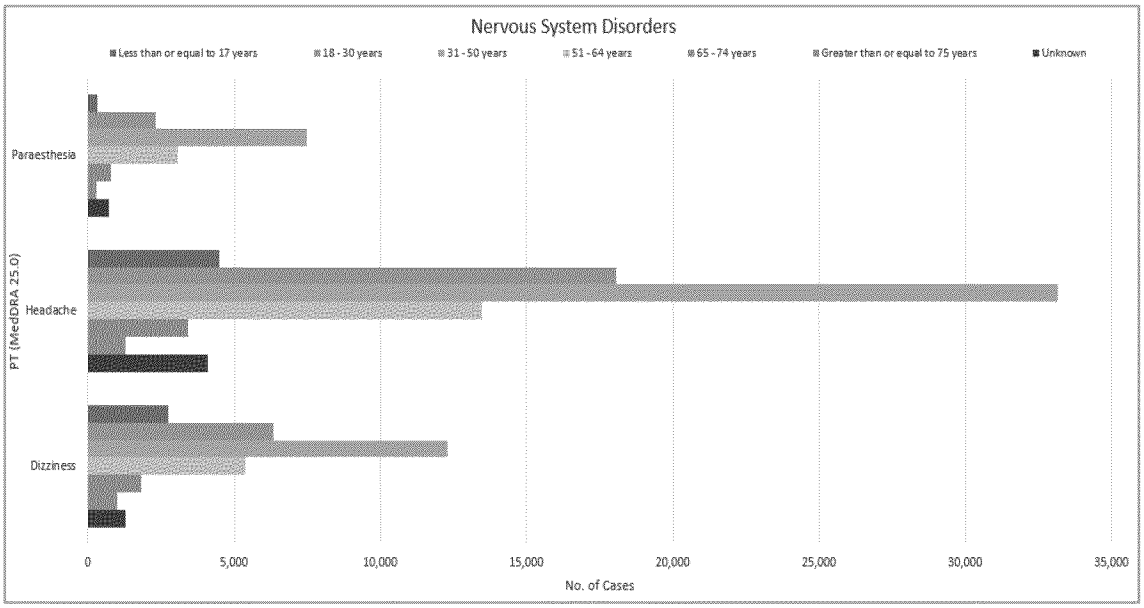
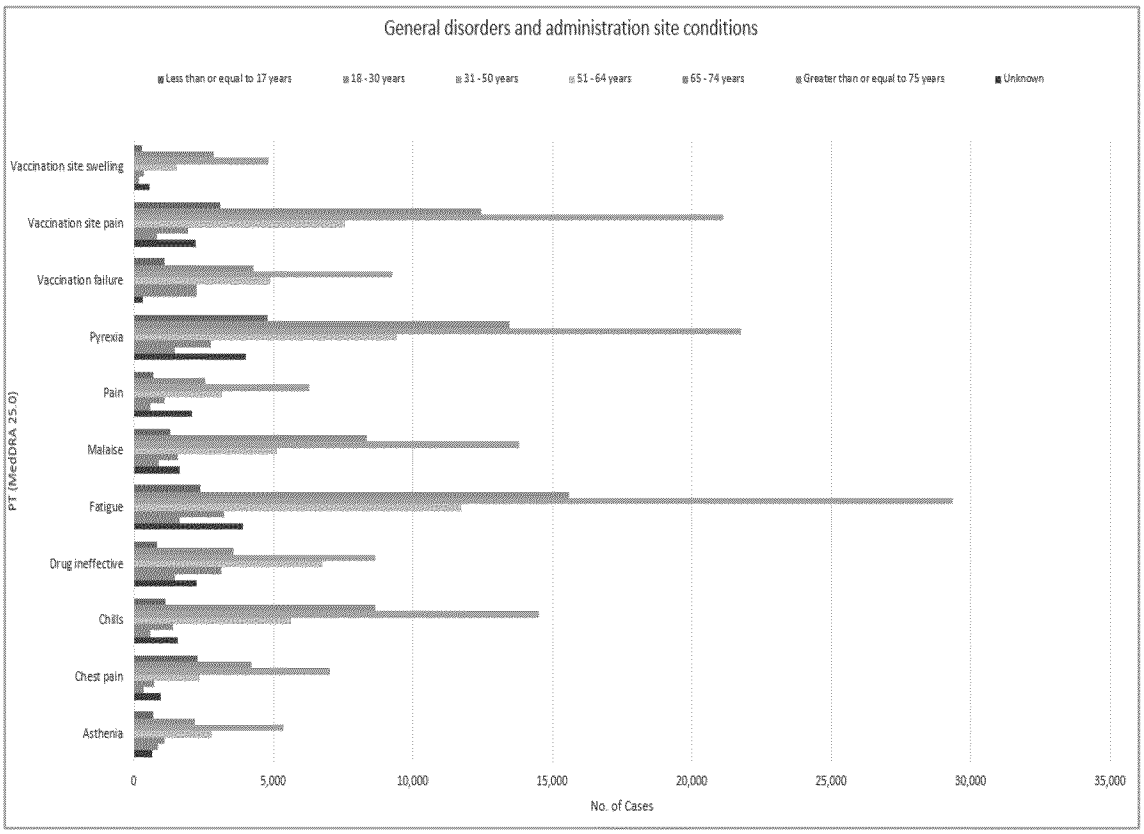
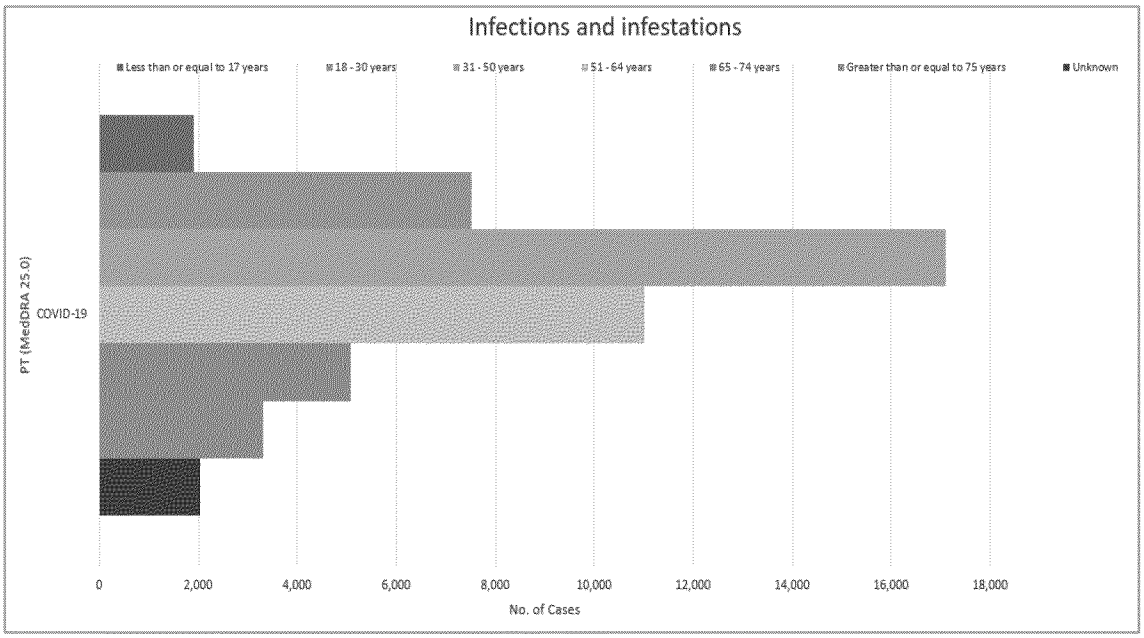
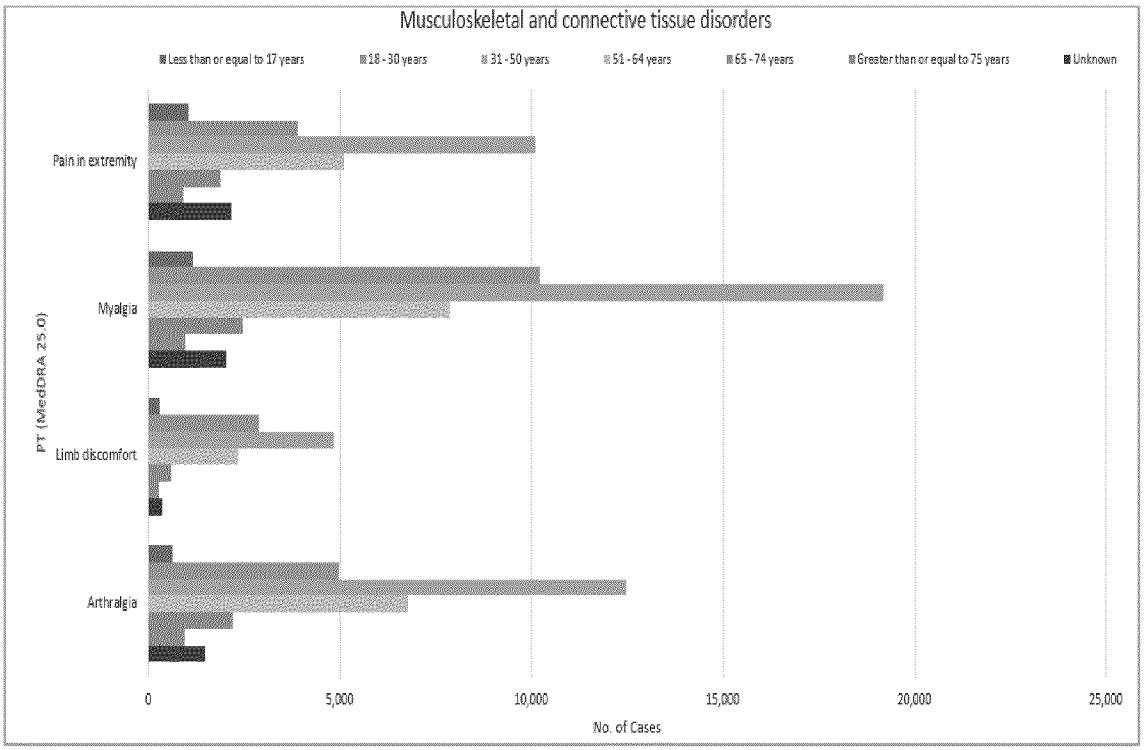


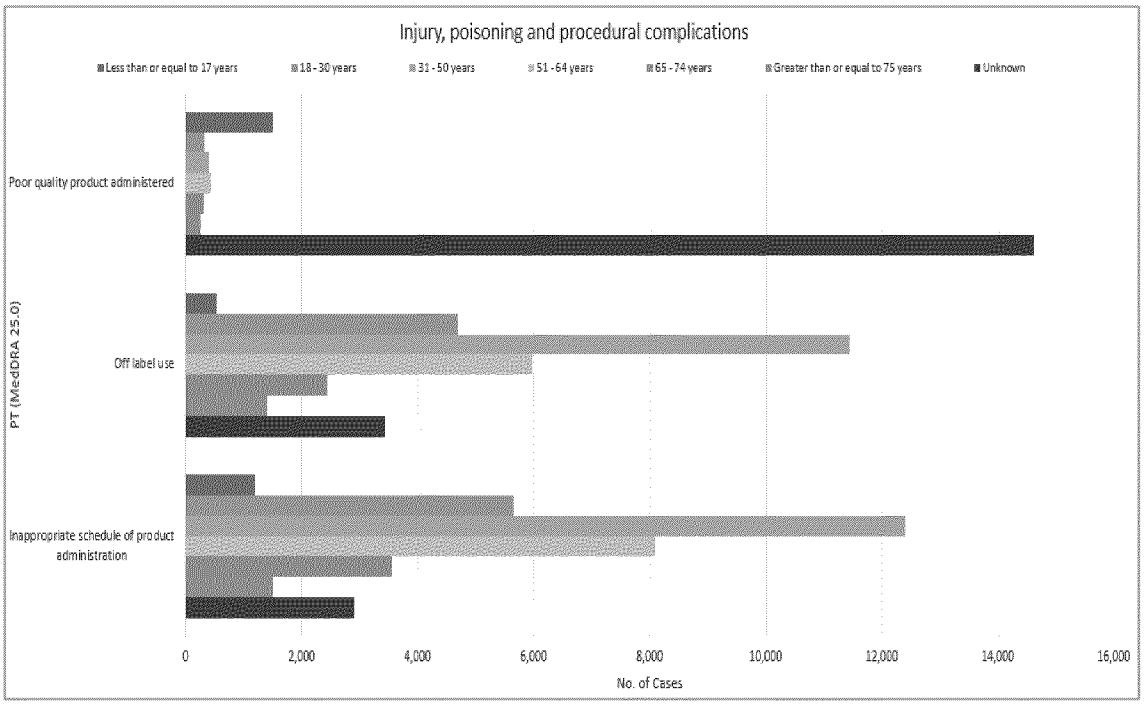
Figure 12. Post-Authorisation Data: Clinical AEs reported in ≥2 % of Cases by Age Group

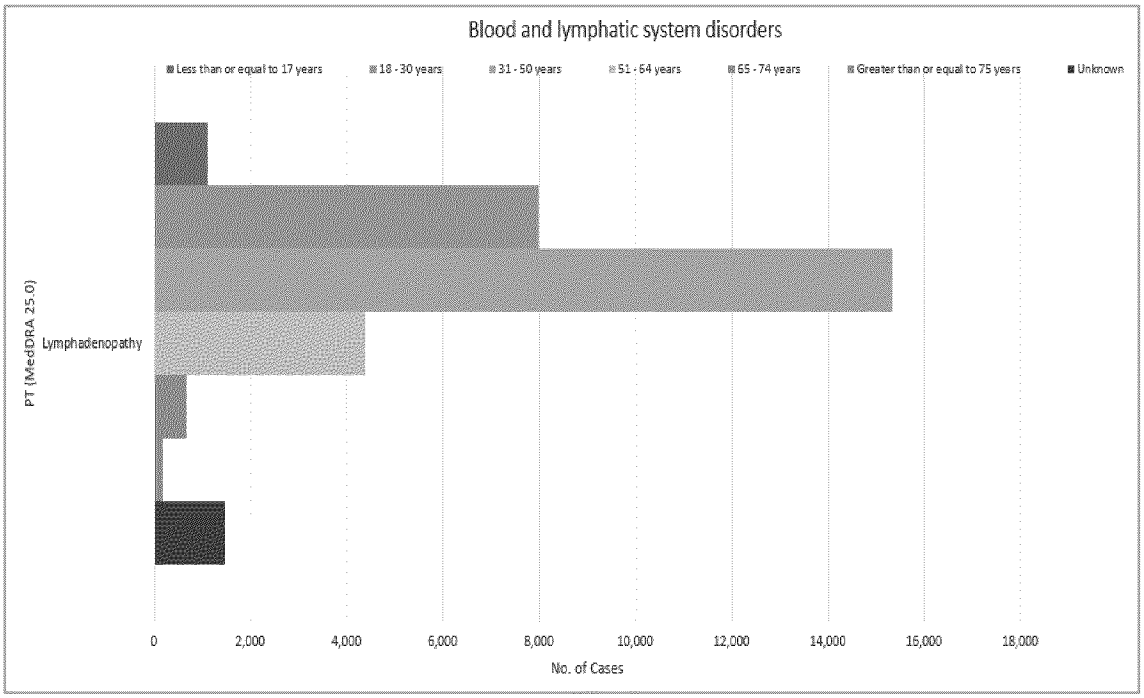


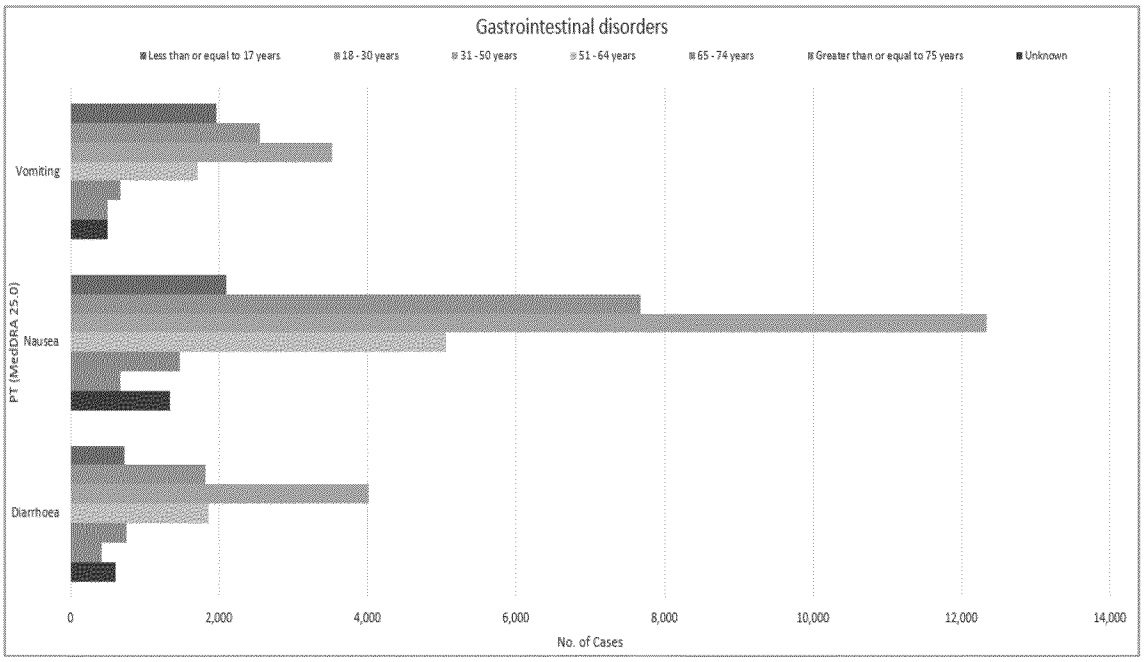


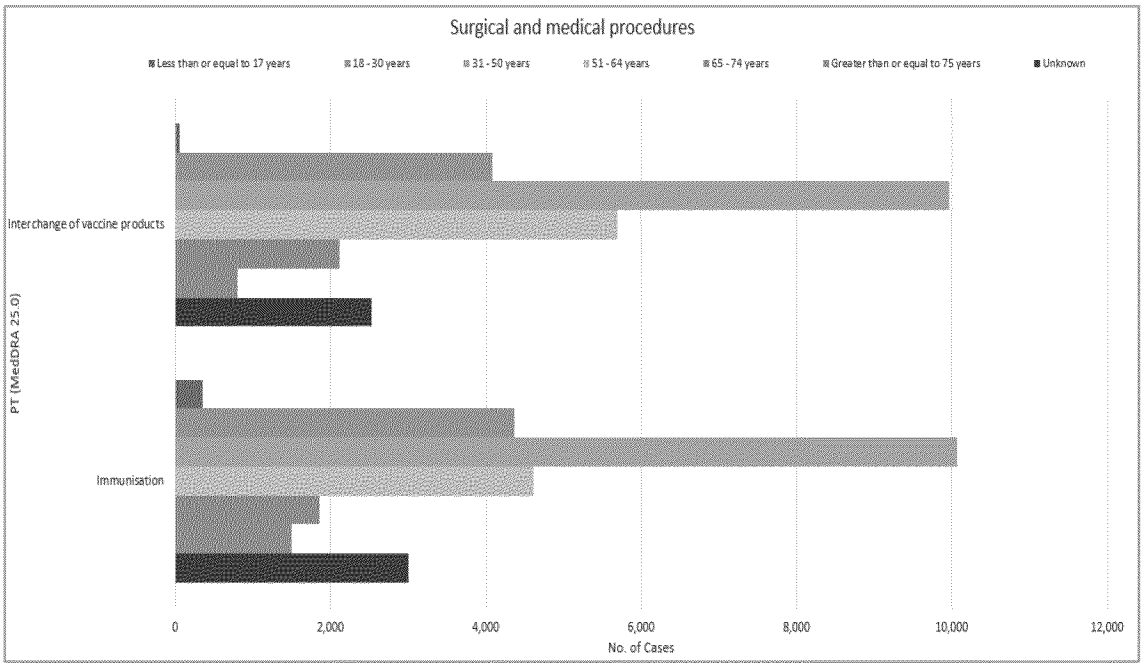


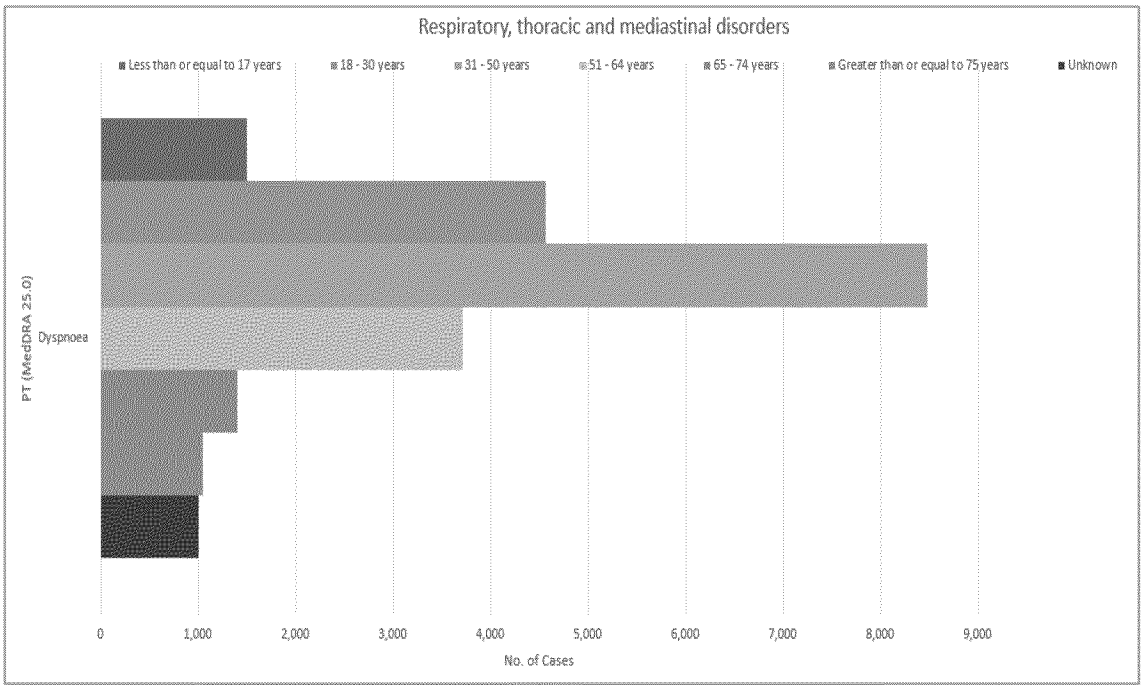


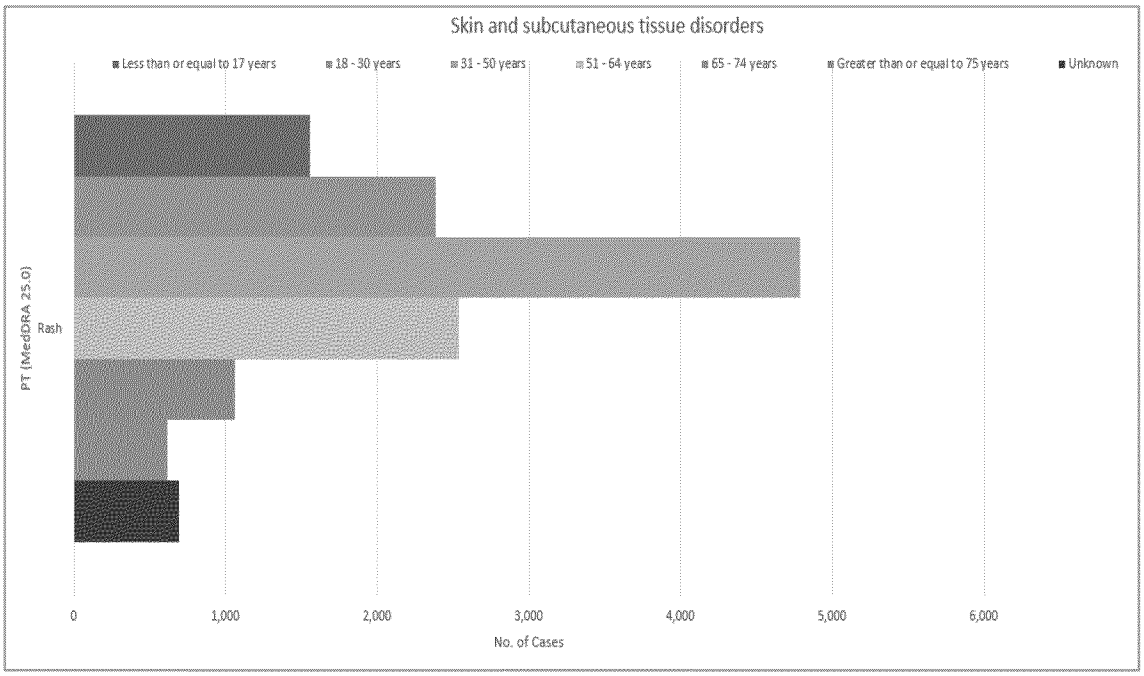


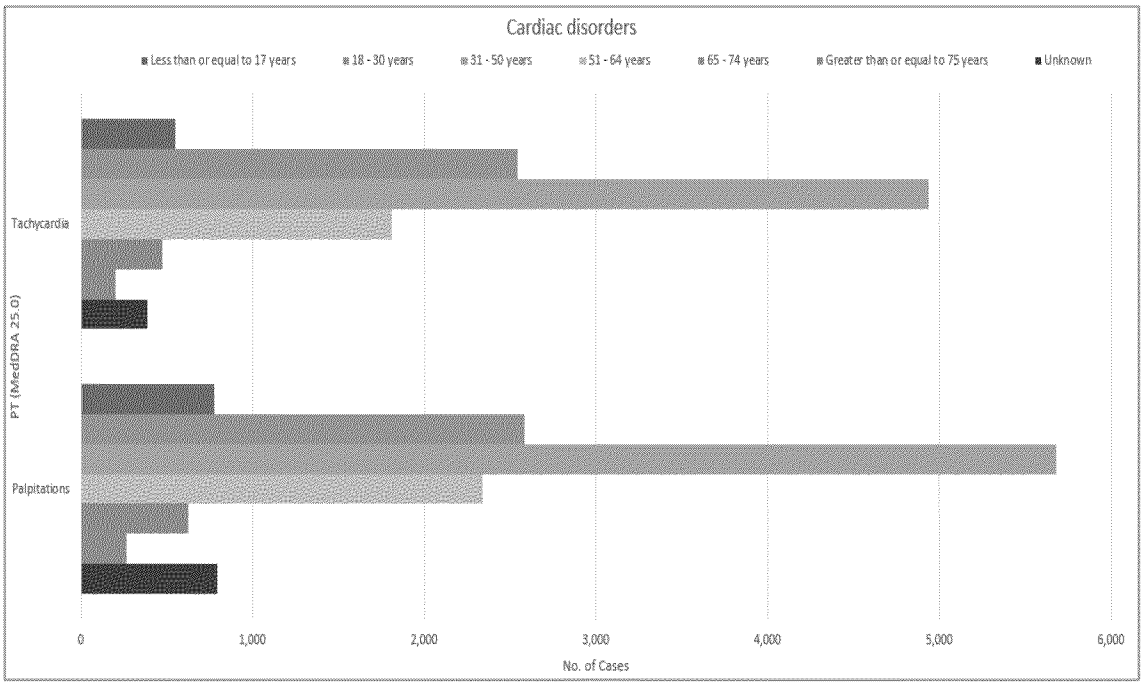


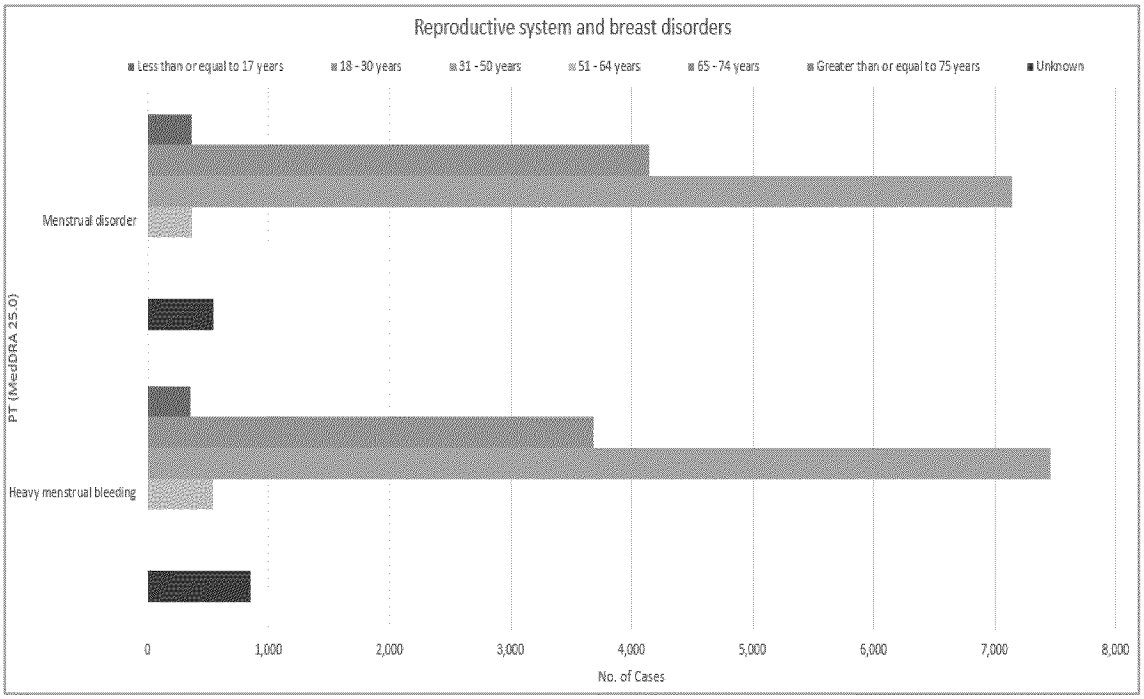












Conclusion

Overall, during the reporting period, the serious cases represented 29.8% of the total PM; fatal outcomes occurred in less than 1% of the cases. About two-thirds of the cases occurred in female subjects and the age group 31-50 years was the group most frequently reporting AEs. The most frequently reported (≥2%) AEs (listed in the current RSI) are in majority non-serious.

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

6.3.1.1.2.1. Analysis by Dose

Potential for local and systemic adverse reactions are analysed by dose of the vaccine in Section 16.3.3.3 *Local Adverse Reactions* and Section 16.3.3.4 *Systemic Adverse Reactions.*

6.3.1.1.2.2. Tris/Sucrose Presentation

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

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

A total of 19,789 case reports with Tris/Sucrose formulation[38] containing 38,950 events (3.9% of the total PM dataset) fulfilled criteria for inclusion in this PSUR reporting period. Data presented in Table 19 through Table 23 refer to the paediatric 5-11 years old orange cap and ≥ 12 years grey cap presentations.[39] Demographic information of Tris/Sucrose cases received during the reporting interval are shown in Table 19. Most cases (9055 cases, 45.8%) were reported in paediatric subjects (aged ≤ 17 years); a demographic and the comparison with AEs reporting rate between Tris/Sucrose cases and paediatric PBS/Sucrose cases is provided in Table 22 and Table 23. There were no significant differences in the demographic data between paediatric subjects receiving Tris/Sucrose formulation and those receiving PBS.

[38] Search criteria: "EUA Tris" and "BLA Tris" in the concentration field.

[39] No data on the paediatric 6 months through 4 years presentation are available since it was first approved on 17 June 2022.

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 5.0 of the EU-RMP adopted on 10 March 2022. The approved BLA US-PVP version 1.4.1 dated 29 April 2022 includes as routine pharmacovigilance activities label information on vial differentiation.

With regard to the reported medical events, the majority were reported in lower proportion in the Tris/Sucrose group compared to the PBS/Sucrose group although there were 7 events (Vaccination site pain, Vomiting, Abdominal pain, Diarrhoea, Rash, Urticaria, Pruritus) with a higher AERP (11.4%, 7.5%, 3.8%, 2.6%, 5.5%, 2.8%, and 2.6%, respectively) in the Tris/Sucrose paediatric group. On review, few occurrences were serious (as important medical events – 97 for PT Vomiting, 49 for Abdominal pain, 42 for Rash, 41 for Urticaria, 24 for Diarrhoea, 20 for Pruritus, and 15 for Vaccination site pain). The clinical outcome of the serious occurrences was resolved/resolving (188), resolved with sequelae (5), not resolved (39), unknown (51), and fatal (5) at the time of reporting. In the 4 cases recording Abdominal pain, Vomiting (2 each), and Diarrhoea (1) as the fatal events, limited information was provided in 4 paediatric subjects. In these 4 cases, it is not clear whether the subjects had any underlying diseases or conditions, and date of death was unknown. In the paediatric PBS/Sucrose cases, these events were assessed as serious as follows: PTs Vomiting (325), Abdominal pain (103), Rash (133), Urticaria (76), Diarrhoea (93), PT Pruritus (76), and PT Vaccination site pain (101). These serious events had the report proportion ≤ 0.5% of the total number of events among all paediatric PBS/Sucrose cases.

Table 19. Demographic Information – Tris/Sucrose Cases (Orange and Grey Cap) Received during the Reporting Interval

		Tris/Sucrose No. of Cases[a,e] (%)[b]/ [Direct exposure][c]	
		Orange Cap N=17,450	**Grey Cap N=2,340**
MC cases	Yes	7902 (45.3)	1597 (68.2)
	No	9548 (54.7)	743 (31.8)
Country of occurrence	Philippines	7220 (41.4)	1 (0.04)
	US	4463 (25.6)	2183 (93.3)
	Australia	1522 (8.7)	-
	Germany	917 (5.3)	50 (2.1)
	Japan	896 (5.1)	1 (0.04)
	Italy	424 (2.4)	45 (1.9)
	Spain	378 (2.2)	3 (0.1)
	Canada	171 (1.0)	2 (0.09)
	Denmark	147 (0.8)	-
	France	141 (0.8)	34 (1.5)
	Total Others	1171 (6.7)	21 (0.9)

Table 19. Demographic Information – Tris/Sucrose Cases (Orange and Grey Cap) Received during the Reporting Interval

		Tris/Sucrose No. of Cases[a,e] (%)[b]/ [Direct exposure][c]	
		Orange Cap N=17,450	**Grey Cap N=2,340**
Gender	Female	6550 (37.5)	361 (15.4)
	Male	6007 (34.4)	240 (10.3)
	Unknown/No Data	4893 (28.0)	1739 (74.3)
Age (years)	N	9472	567
	Min-Max	0.06-100	0.5-99
	Mean / Median	15.5/9	45.5/44
Age Range	≤ 17 years	9028 (51.7) [9015]	42 (1.8) [40]
	0 to 27 days	2 (0.01) [0]	-
	28 days to 23 months	20 (0.1) [11]	2 (0.09) [0]
	2-11 years	8380 (48.0) [8378]	12 (0.5) [12]
	12-17 years	626 (3.6) [626]	28 (1.2) [28]
	18-30 years	123 (0.7)	127 (5.4)
	31-50 years	239 (1.4)	164 (7.0)
	51-64 years	382 (2.2)	118 (5.0)
	65-74 years	341 (2.0)	67 (2.9)
	≥ 75 years	209 (1.2)	53 (2.3)
	Unknown	7127 (40.8)	1769 (75.6)
Case Seriousness	Serious	2070 (11.9)	80 (3.4)
	Non-serious	15,380 (88.1)	2260 (96.6)
Case Outcome	Fatal	30 (0.2)	3 (0.1)
	Not resolved	1618 (9.3)	101 (4.3)
	Resolved/Resolving	4511 (25.9)	78 (3.3)
	Resolved with sequelae	40 (0.2)	5 (0.2)
	Unknown/No data	11,251 (64.5)	2153 (92.0)
Presence of comorbidities [d]	Yes	617 (3.5)	55 (2.4)
	No	16,833 (96.5)	2285 (97.6)

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 during the mother's pregnancy or babies exposed through breastfeeding.
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. In 1 case, the subject received orange and grey cap separately in different periods.

N=Number of cases; MC=Medically confirmed; Min=Minimum; Max=Maximum

Table 20. Demographic Information – Comparison of Paediatric (≤ 17 years) Tris/Sucrose (Grey and Orange Cap) versus Paediatric PBS/Sucrose Cases

		Tris/Sucrose (Grey and Orange Cap) No. of Cases [a] (%)[b] N=9055	PBS/Sucrose No. of Cases (%) N=22,772
MC cases	Yes	6471 (71.5)	13,659 (60.0)
	No	2584 (28.5)	9113 (40.0)
Country of occurrence	Germany	773 (8.5)	3916 (17.2)
	Philippines	1229 (13.6)	3064 (13.5)
	Australia	1508 (16.7)	2155 (9.5)
	Malaysia	7 (0.08)	1190 (5.2)
	Taiwan, Province of China	10 (0.1)	1188 (5.2)
	France	102 (1.1)	1080 (4.7)
	US	2537 (28.0)	1009 (4.4)
	Japan	835 (9.2)	510 (2.2)
	Italy	406 (4.5)	634 (2.8)
	Spain	377 (4.2)	370 (1.6)
	Denmark	146 (1.6)	160 (0.7)
	Canada	134 (1.5)	175 (0.8)
	Ireland	121 (1.3)	171 (0.8)
	Total Others	870 (9.6)	7150 (31.4)
Gender	Female	3804 (42.0)	11,896 (52.2)
	Male	4078 (45.0)	10,012 (44.0)
	Unknown/No Data	1173 (13.0)	864 (3.8)
Age (years)	N	8213	22,089
	Min-Max	0.58-17	0.01-17
	Mean / Median	8.7/9	14.3/15
Age Range	0-27 days	0	3 (0.01)
	28 days to 23 months	11 (0.1)	69 (0.3)
	2-11 years	8390 (92.7)	1410 (6.2)
	12-17 years	654 (7.2)	21,290 (93.5)
Case Seriousness	Serious	1589 (17.5)	6956 (30.5)
	Non-serious	7466 (82.5)	15,816 (69.5)
Case Outcome	Fatal	17 (0.2)	65 (0.3)
	Not resolved	1288 (14.2)	5013 (22.0)
	Resolved/Resolving	4205 (46.4)	11,567 (50.8)
	Resolved with sequelae	24 (0.3)	142 (0.6)
	Unknown/No data	3521 (38.9)	5985 (26.3)
Presence of comorbidities[c]	Yes	289 (3.2)	642 (2.8)
	No	8766 (96.8)	22,130 (97.2)

a. Only paediatric subject received BNT162b2.
b. Due to rounding, sum of percentages may not match 100%.
c. 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.
N=Number of cases; MC=Medically confirmed; Min=Minimum; Max=Maximum

Table 21. Events Reported in ≥2%[a] Cases - Comparison of Paediatric Tris/Sucrose (Grey and Orange Cap) versus PBS/Sucrose Cases

	Tris/Sucrose (Grey and Orange Cap)	PBS/Sucrose
MedDRA SOC MedDRA PT	**N=9055** **n (AERP, %)**	**N=22,772** **n (AERP, %)**
Injury, poisoning and procedural complications[40]		
Poor quality product administered	1222 (13.5)	289 (1.3)
Product administration error	888 (9.8)	162 (0.7)
Product administered to patient of inappropriate age	503 (5.6)	1364 (6.0)
Overdose	478 (5.3)	125 (0.6)
Product preparation error	433 (4.8)	28 (0.1)
Underdose	289 (3.2)	241 (1.1)
Inappropriate schedule of product administration	243 (2.7)	952 (4.2)
Product preparation issue	234 (2.6)	99 (0.4)
Expired product administered [b]	215 (2.4)	72 (0.3)
Vaccination error	208 (2.3)	258 (1.1)
General disorders and administration site conditions		
Pyrexia	1222 (13.5)	3507 (15.4)
Vaccination site pain	1032 (11.4)	2073 (9.1)
Fatigue	371 (4.1)	2010 (8.8)
Chest pain	334 (3.7)	1959 (8.6)
Malaise	287 (3.2)	1000 (4.4)
Drug ineffective	218 (2.4)	601 (2.6)
Vaccination failure	46 (0.5)	1061 (4.7)
Chills	143 (1.6)	978 (4.3)
Chest discomfort	63 (0.7)	822 (3.6)
Asthenia	117 (1.3)	582 (2.6)
Pain	161 (1.8)	528 (2.3)
Nervous system disorders		
Headache	909 (10.0)	3576 (15.7)
Dizziness	355 (3.9)	2390 (10.5)
Syncope	211 (2.3)	685 (3.0)
Gastrointestinal disorders		
Vomiting	683 (7.5)	1275 (5.6)
Nausea	386 (4.3)	1699 (7.5)
Abdominal pain	348 (3.8)	506 (2.2)
Diarrhoea	236 (2.6)	448 (2.0)
Skin and subcutaneous tissue disorders		
Rash	501 (5.5)	1037 (4.6)
Urticaria	254 (2.8)	427 (1.9)
Pruritus	234 (2.6)	484 (2.1)
Musculoskeletal and connective tissue disorders		
Pain in extremity	278 (3.1)	768 (3.4)
Myalgia	172 (1.9)	992 (4.4)

[40] The number of PTs indicative of medication errors may not match with the numbers reported in Section 9.2 *Medication Errors*, since the adopted search criteria are different and the cases retrieved in this table involved only paediatric subjects.

Table 21. Events Reported in ≥2%[a] Cases - Comparison of Paediatric Tris/Sucrose (Grey and Orange Cap) versus PBS/Sucrose Cases

	Tris/Sucrose (Grey and Orange Cap)	PBS/Sucrose
MedDRA SOC MedDRA PT	**N=9055** **n (AERP, %)**	**N=22,772** **n (AERP, %)**
Arthralgia	123 (1.4)	491 (2.2)
Product issues		
Product temperature excursion issue	253 (2.8)	114 (0.5)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	227 (2.5)	1269 (5.6)
Cough	172 (1.9)	445 (2.0)
Blood and lymphatic system disorders		
Lymphadenopathy	203 (2.2)	903 (4.0)
Cardiac disorders		
Palpitations	85 (0.9)	691 (3.0)
Myocarditis	38 (0.4)	632 (2.8)
Tachycardia	82 (0.9)	467 (2.1)
Total number of events	**14,457**	**38,010**

a. Reporting proportion (% of total PM cases) in one or both paediatric populations.
b. Majority of the cases reported uncertain expiry dates.

Conclusion

Overall, more than 45% 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 5.0 of the EU-RMP adopted on 10 March 2022.

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

6.3.1.1.2.3. Booster Doses (Third and Fourth Doses)

A summary of the approvals of booster doses for the different age groups and associated regulatory procedures is provided in Table 22 for the reporting period.

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

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

Table 22. Summary of Approval of Booster Doses in the Reporting Period

	Age Group	Procedure and Description	Approval Date
EU			
First booster	**16+ years**	**EMEA/H/C/005735/II/0104*** • Heterologous vaccination (both in the primary series and for booster vaccinations) PI update based on cumulative review of available immunogenicity, safety and efficacy data. • Further PI update to implement booster (dose) interval reduction from 6 months to 3 months per Agency request based on the totality of available evidence (not MAH's own clinical data). **EMEA/H/C/005735/II/0139** PI update regarding individuals 16+ years based on six-month post (booster) dose 3 data from Studies C4591001 and C4591031 data.	CHMP Opinion: 22 April 2022 EC decision: 04 May 2022 Procedure ongoing pending approval.
	12-15 years	**EMEA/H/C/005735/II/0104*** • Heterologous vaccination (both in the primary series and for booster vaccinations) PI update based on cumulative review of available immunogenicity, safety and efficacy data. • Further PI update to implement booster (dose) interval reduction from 6 months to 3 months per Agency request based on the totality of available evidence (not MAH's own clinical data). **EMEA/H/C/005735/II/0111** PI update to lower the age of the booster dose to patients 12 years of age and older based on RWE data from MoH Israel.	CHMP Opinion: 22 April 2022 EC decision: 04 May 2022 CHMP Opinion: 24 February 2022 EC decision: 28 February 2022
	5-11 years	**EMEA/H/C/005735/II/0129** 5-11 years PI update– one month post dose (booster) dose 3 (1MPD3) based on clinical study C4591007 data.	Procedure ongoing pending approval.
Second booster	**16+ years and 12-15 years**	**EMEA/H/C/005735/II/0140** Bivalent Original/Omicron BA.1 as from 12+ years- Rolling submission.	Procedure ongoing pending approval.
	5-11 years	-	-

Table 22. Summary of Approval of Booster Doses in the Reporting Period

	Age Group	Procedure and Description	Approval Date
		US	
First booster	**16+ years**	US FDA lowered the authorised dosing interval of the homologous booster dose to at least 5 months after completion of the primary series.	03 January 2022
	12-15 years	US FDA authorised the use of the vaccine as a single booster dose at least 5 months after completion of a primary series with BNT162b2.	03 January 2022
	5-11 years	US FDA authorised a third primary series dose of the vaccine administered at least 28 days following the two-dose regimen of BNT162b2 in individuals 5 through 11 years of age who have undergone solid organ transplantation or are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. EUA was granted for a single booster dose at least 5 months after completing a primary series with BNT162b2.	03 January 2022 17 May 2022
Second booster	**50+ years**	EUA was granted for the use of BNT162b2 as second booster for individuals 50+ years at least 4 months after receipt of a first booster dose of any FDA-authorised or approved COVID-19 vaccine.	29 March 2022
	12+ years	The US FDA issues an EUA to approve the use of BNT162b2 as second booster at least 4 months after a first booster dose with any FDA authorised or approved COVID-19 vaccine for 12+ years individuals, who have undergone solid organ transplantation or have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise.	29 March 2022
	5-11 years	-	-

*: The same procedure was issued for two different age groups due to a combined claim in the PI for both age groups (Type II variation 104 for heterologous boosting).

Analysis of Booster Doses

Search criteria: Dose number equal to 3 or Dose number equal to 4 OR Dose Description containing the word "BOOSTER" OR LLT equal to BOOSTER.

The search yielded 119,601 cases (491 CT cases and 119,110 PM cases).

Upon review,

- 455 cases (1 CT and 454 PM) involving babies were excluded due to indirect exposure (transplacental/transmammary) to BNT162b2.
- 906 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 (904 cases) or the case did not contain any information that the individuals received a booster dose (2 cases).

Overall

CT data

Table 23. Selected Case Characteristics of CT Data Involving Participants Who Received Booster Dose(s) of BNT162b2 During The Reporting Period (19 December 2021 through 18 June 2022)

Case characteristics	Overall participants who received at least one booster dose of BNT162b2	Participants who received single booster dose of BNT162b2	Participants who received >1 booster doses of BNT162b2
Number of cases	490 (BNT162b2 [441], blinded therapy [46] and placebo [3])	423 (BNT162b2 [375], blinded therapy [45] and placebo [3])	67 (BNT162b2 [66] and blinded therapy [1])
Cases by protocol ID[41]	C4591001 (347), C4591031 (101), C4591024 (16), C4591007 (14), BNT162-17 (11) and C4591030 (1)	C4591001 (301), C4591031 (86), C4591024 (16), BNT162-17 (10) and C4591007 (10)	C4591001 (46), C4591031 (15), C4591007 (4), BNT162-17 and C4591030 (1 each)
Country of incidence (≥2 cases)	US (358), Argentina (73), Brazil (31), Germany (15), South Africa (4), and Israel (2)	US (310), Argentina (67), Brazil (25), Germany (14), and South Africa (3)	US (48), Argentina, Brazil (6 each), and Israel (2)
Participants' gender	female (228) and male (262)	female (198) and male (225)	female (30) and male (37)
Participants' age in years	n = 490; range: 1.4-87.0; mean = 54.8; median = 61.0	n = 423; range: 1.4-87.0; mean = 55.2; median = 61.0	n = 67; range: 2.0-83.0; mean = 51.8; median = 58.0
Case outcome	fatal (29), resolved/resolving (354), resolved with sequelae (33), not resolved (73), and unknown (1)	fatal (22), resolved/resolving (304), resolved with sequelae (30), not resolved (66), and unknown (1)	fatal (7), resolved/resolving (50), resolved with sequelae (3), and not resolved (7)
Most frequently reported PTs[a] (≥2%)	Condition aggravated (20), Atrial fibrillation (14), Pneumonia (12), Appendicitis, Cerebrovascular accident (11 each), and Prostate cancer (10)	Condition aggravated (19), Atrial fibrillation (12), Cerebrovascular accident (11), Appendicitis, Prostate cancer (10 each), and Pneumonia (9)	Pneumonia (3), Atrial fibrillation, Febrile convulsion, Injury, Osteoarthritis, and Syncope (2 each)

a. Includes all SAEs irrespective of relatedness to BNT162b2/blinded therapy/placebo

[41] Please refer to Section 7.2 *Ongoing Clinical Trials* for details about these clinical trials and to Section 17.2 *Newly Identified Information on Efficacy and Effectiveness* for the newly identified information on efficacy and effectiveness from the interim analysis of studies C4591031 and C4591007.

Post-Authorisation Data

Table 24. Selected Case Characteristics of Post-Authorisation Data Involving Individuals Who Received Booster Dose(s) of BNT162b2 During The Reporting Period (19 December 2021 through 18 June 2022)

Case characteristics	Overall individuals who received at least one booster dose of BNT162b2	Individuals who received single booster dose of BNT162b2[a]	Individuals who received >1 booster doses of COVID-19 vaccine (the latest booster dose was BNT162b2)[b]	Individuals who received unknown booster dose(s) of BNT162b2[c]
Number of cases	117,750	106,889	3427	7434
Total number of events	484,959	451,970	13,627	19,362
MC/NMC cases	MC: 28,695; NMC: 89,055	MC: 25,113; NMC: 81,776	MC: 1104; NMC: 2323	MC: 2478; NMC: 4956
Country of incidence (≥2%)	Germany (25,532), Netherlands (21,182), UK (18,523), France (10,285), US (7953), Austria (6391), and Japan (4930)	Germany (24,922), Netherlands (20,795), UK (17,614), Austria (6382), US (5773), France (5028), and Japan (4895)	US (1403), UK (639), Germany (372), France (192), Netherlands (182), Canada (103), and Sweden (76)	France (5065), US (777), Ireland (528), UK (270), Germany (238), and Netherlands (205)
Subjects' gender	female (80,563), male (33,585), and unknown (3602)	female (73,716), male (30,196), and unknown (2977)	female (1936), male (1215), and unknown (276)	female (4911), male (2174), and unknown (349)
Subjects' age in years	n = 108,038; range: 0.3-120.0; mean = 45.5; median = 43.0	n = 98,367; range: 0.3-120.0; mean = 44.8; median = 42.0	n = 2894; range: 2.0-102.0; mean = 65.4; median = 68.0	n = 6777; range: 0.5-103.0; mean = 47.0; median = 46.0
Case seriousness	serious = 42,918; non-serious = 74,832	serious = 39,781; non-serious = 67,108	serious = 1722; non-serious = 1705	serious = 1415; non-serious = 6019
Case outcome	fatal (1225), resolved/resolving (41,604), resolved with sequelae (1805), not resolved (51,914), and unknown (21,202)	fatal (1093), resolved/resolving (37,881), resolved with sequelae (1722), not resolved (47,915), and unknown (18,278)	fatal (72), resolved/resolving (894), resolved with sequelae (32), not resolved (958), and unknown (1471)	fatal (60), resolved/resolving (2829), resolved with sequelae (51), not resolved (3041), and unknown (1453)
Most frequently reported PTs (≥2%)	Immunisation[d] (25,650), Headache (24,152), Off label use (22,894), Fatigue (21,550), Interchange of vaccine products[e] (20,384), Pyrexia (16,639),	Immunisation[d] (23,292), Headache (23,112), Off label use (20,889), Fatigue (20,740), Interchange of vaccine products[e] (19,823), Pyrexia (15,894),	Off label use (1627), Immunisation[d] (1403), COVID-19 (704), Drug ineffective (568), Incorrect dose administered (512), Fatigue (377), Headache (348),	Immunisation[d] (955), Immunisation reaction (873), Lymphadenopathy (858), Headache (692), Fatigue (433), Pyrexia (401), Influenza like illness (396),

Table 24. Selected Case Characteristics of Post-Authorisation Data Involving Individuals Who Received Booster Dose(s) of BNT162b2 During The Reporting Period (19 December 2021 through 18 June 2022)

Case characteristics	Overall individuals who received at least one booster dose of BNT162b2	Individuals who received single booster dose of BNT162b2[a]	Individuals who received >1 booster doses of COVID-19 vaccine (the latest booster dose was BNT162b2)[b]	Individuals who received unknown booster dose(s) of BNT162b2[c]
	Lymphadenopathy (16,442), Vaccination site pain (15,397), Myalgia (15,323), Malaise (14,845), Chills (13,836), Arthralgia (10,331), Nausea (10,055), COVID-19 (9701), Pain in extremity (6792), Dizziness (6314), Drug ineffective (5850), Vaccination site swelling (5289), Dyspnoea (5079), Vaccination failure (4945), Pain (4748), Chest pain (3988), Limb discomfort (3472), Vaccination site lymphadenopathy (3433), Vaccination site erythema (3386), Vaccination site inflammation (3329), Axillary pain (3141), Rash (3129), Asthenia (3007), Palpitations (2947), Vaccination site warmth (2828), Paraesthesia (2813), Vomiting (2740), Tachycardia (2641), Diarrhoea (2517), and Heavy menstrual bleeding (2368).	Lymphadenopathy (15,510), Vaccination site pain (14,853), Myalgia (14,789), Malaise (14,333), Chills (13,377), Arthralgia (9806), Nausea (9564), COVID-19 (8789), Pain in extremity (6213), Dizziness (5956), Vaccination site swelling (5190), Drug ineffective (5054), Dyspnoea (4755), Vaccination failure (4708), Pain (4326), Chest pain (3681), Limb discomfort (3403), Vaccination site lymphadenopathy (3398), Vaccination site erythema (3281), Vaccination site inflammation (3252), Axillary pain (3022), Rash (2899), Palpitations (2778), Vaccination site warmth (2777), Paraesthesia (2568), Asthenia (2542), Tachycardia (2490), Vomiting (2479), Diarrhoea (2319), Heavy menstrual bleeding (2253), and Influenza (2226).	Pyrexia (344), Interchange of vaccine products[e] (267), Chills (239), Vaccination failure (231), Pain in extremity (203), Pain (202), Malaise (199), Myalgia, Vaccination site pain (188 each), Poor quality product administered (185), Arthralgia (172), Nausea (169), Dizziness (139), Product administration error (116), Dyspnoea (104), Asthenia (99), Vomiting (96), Suspected COVID-19 (85), Expired product administered (81), Diarrhoea (80), Chest pain (76), Lymphadenopathy (74), and Feeling abnormal (69).	Off label use (378), Pain in extremity (376), Asthenia (366), Vaccination site pain (356), Arthralgia (353), Myalgia (346), Nausea (322), Malaise (313), Interchange of vaccine products[e] (294), Chest pain (231), Drug ineffective (228), Poor quality product administered (226), Chills, Dyspnoea, Pain (220 each), Dizziness (219), Paraesthesia (209), COVID-19 (208), Herpes zoster (204), Menstrual disorder (199), Rash (168), Tinnitus (167), and Vomiting (165).

a. Indicates individuals who received one additional (booster) dose of BNT162b2 after completing the primary series of any authorised COVID-19 vaccine

b. Indicates individuals who received 2 or more additional (booster) doses of COVID-19 vaccine (the latest booster dose was BNT162b2) after completing the primary series of any authorised COVID-19 vaccine

Table 24. Selected Case Characteristics of Post-Authorisation Data Involving Individuals Who Received Booster Dose(s) of BNT162b2 During The Reporting Period (19 December 2021 through 18 June 2022)

Case characteristics	Overall individuals who received at least one booster dose of BNT162b2	Individuals who received single booster dose of BNT162b2[a]	Individuals who received >1 booster doses of COVID-19 vaccine (the latest booster dose was BNT162b2)[b]	Individuals who received unknown booster dose(s) of BNT162b2[c]

c. Indicates individuals who received unknown additional (booster) dose(s) of BNT162b2 after completing the primary series of any authorised COVID-19 vaccine.

d. PT Immunisation, initially selected per case processing conventions to retrieve cases reporting third/booster doses was no longer applied after 31 January 2022. Following that, "booster" was added in the dose description field.

e. PT Interchange of vaccine products, initially selected per case processing conventions to retrieve cases reporting heterologous administration of third/booster doses was no longer applied after 31 January 2022. After that, the LLT Interchange of vaccine products was added in the relevant medical history section.

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

Homologous doses schedule (primary series and booster with BNT162b2)

Clinical Trial Data

- Number of cases: 490 (BNT162b2 [441], blinded therapy [46] and placebo [3]) (73.4% of 668 cases, the total CT dataset). Please refer Table 23 for further details.

Post-Authorisation Data

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

- Event seriousness[42]: serious (63,265), non-serious (127,091).
- The most reported (≥2% of homologous doses schedule PM cases) PTs were Headache (10,390), Immunisation[43] (9993), Fatigue (9945), Malaise (8187), Myalgia (7932), COVID-19 (7123), Pyrexia (6602), Vaccination site pain (6486), Chills (6360), Lymphadenopathy (6287), Arthralgia (5138), Vaccination failure (4891), Nausea (4672), Drug ineffective (3064), Vaccination site swelling (2813), Pain in extremity (2459), Vaccination site inflammation (2312), Vaccination site lymphadenopathy (2099), Vaccination site warmth (1900), Pain (1887), Dyspnoea (1815), Dizziness (1794), Vaccination site erythema (1774), Chest pain (1616), Axillary pain (1385), Off label use (1171), Palpitations (1112), and Heavy menstrual bleeding (1034).

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

Post-Authorisation Data

- Number of cases: 23,252 (4.6% of 507,683 cases, the total PM dataset; 19.7% of the PM booster dataset).
- MC cases (3665), NMC cases (19,587).
- Country of incidence (≥2%): UK (9601), Netherlands (5987), Germany (1801), France (1192), Belgium (500), and US (496).
- Subjects' gender: female (16,361), male (6296) and unknown (595).
- Subjects' age in years (n = 20,855), range: 0.3 – 102.0, mean: 46.5, median: 45.0.
- Case outcome: fatal (162), resolved/resolving (7179), resolved with sequelae (322), not resolved (12,429), and unknown (3160).
- In 162 cases (reporting 781 events with a fatal outcome), the reported causes of death (≥5 cases) were coded to the PTs Interchange of vaccine products (21), Off label use (20), Cardiac arrest (14), Sudden death (12), Cerebrovascular accident, Dyspnoea, Immunisation (11 each), Pulmonary embolism (9), Malaise, Myocardial infarction (7 each), Cerebral haemorrhage, COVID-19, Drug ineffective, Myocardial ischaemia, Pneumonia, Thrombosis (6 each), Myocarditis, Oxygen saturation decreased, and Septic shock (5 each). Of note, in 32 cases limited information regarding the cause of death was provided (PT Death).
- Medical history (n = 10,734): the most frequently (≥2%) reported medical conditions included Disease risk factor (1596), Hypertension (888), Interchange of vaccine products (805), Asthma (684), Immunodeficiency (502), Hypersensitivity (289), Diabetes

[42] 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.

[43] PT selected per case processing conventions to collect cases reporting third/booster doses; as of 31 January 2022 this convention was no more applicable.

mellitus (278), Hypothyroidism (271), Steroid therapy (253), Depression (241), Drug hypersensitivity (229) and Clinical trial participant (224).

- COVID-19 Medical history (n = 2649): Suspected COVID-19 (1346), COVID-19 (1340), Post-acute COVID-19 syndrome (22), SARS-CoV-2 test positive (18), COVID-19 pneumonia (6), Coronavirus infection (4), Asymptomatic COVID-19 (2) and Exposure to SARS-CoV-2 (1).
- Among the 23,252 cases reporting administration of heterologous booster dose(s) of BNT162b2 following a specified non-BNT162b2 COVID-19 vaccine, the previous vaccine series consisted of:
  - 9651 subjects immunised with AstraZeneca vaccine;
  - 5334 subjects immunised with Moderna vaccine;
  - 5214 subjects immunised with unknown non-Pfizer-BioNTech COVID-19 vaccine;
  - 2427 subjects immunised with Johnson and Johnson vaccine;
  - 417 subjects immunised with Coronavac (Sinovac) vaccine;
  - 88 subjects immunised with Sinopharm vaccine;
  - 76 subjects immunised with Sputnik vaccine;
  - 29 subjects immunised with Novavax vaccine;
  - 9 subjects immunised with Fiocruz vaccine;
  - 2 subjects each immunised with Medicago-Clinical study and Medigen vaccine;
  - 1 subject each immunised with Cansino vaccine, Covaxin vaccine, and Valneva vaccine.
- Number of events: 140,835.
- Event seriousness[42]: serious (61,291), non-serious (79,594).
- The most reported (≥2% of heterologous dose schedule PM cases) PTs were Off label use (20,437), Interchange of vaccine products[43] (20,376), Immunisation (9982), Headache (5229), Fatigue (4854), Myalgia (3412), Malaise (3362), Pyrexia (3144), Lymphadenopathy (3139), Vaccination site pain (2926), Chills (2918), Arthralgia (2578), Nausea (2382), Pain in extremity (1848), Pain (1362), Drug ineffective (1223), COVID-19 (1192), Dizziness (1161), Vaccination site swelling (1140), Dyspnoea (1091), Chest pain (991), Axillary pain (948), Vaccination site inflammation (942), Palpitations (850), Vaccination site warmth (830), Vaccination site lymphadenopathy (815), Vaccination site erythema (751), Pruritus (630), Rash (617), Swelling (610), Heavy menstrual

bleeding (608), Asthenia, Diarrhoea (565 each), Peripheral swelling (557), Paraesthesia (548), Vomiting (516), and Tachycardia (462).

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

Post-Authorisation Data

- Number of cases: 46,739 (9.2% of 507,683 cases, the total PM dataset; 39.7% of the PM booster dataset).
- MC cases (11,182), NMC cases (35,557).
- Country of incidence (≥2%): Germany (20,876), France (6716), Japan (2922), Austria (2833), US (2553), and UK (1924).
- Subjects' gender: female (31,045), male (13,826) and unknown (1868).
- Subjects' age in years (n = 43,405), range: 1.0 – 104.0, mean: 45.3, median: 43.0.
- Case outcome: fatal (513), resolved/resolving (18,572), resolved with sequelae (1003), not resolved (18,155), and unknown (8496).
- In 513 cases (reporting 1318 events with a fatal outcome), the reported causes of death (≥15 cases) were coded to the PTs Cardiac arrest (38), Cardio-respiratory arrest, Myocardial infarction (35 each), Sudden death (25), Pulmonary embolism (24), Cardiac failure (22), Dyspnoea (19), Cerebral haemorrhage (17), and Acute myocardial infarction (15). Of note, in 150 cases limited information regarding the cause of death was provided (PT Death).
- Medical history (n = 11,782): the most frequently (≥2%) reported medical conditions included Hypertension (1856), Asthma (836), Drug hypersensitivity (642), Seasonal allergy (625), Hypersensitivity (456), Diabetes mellitus (426), Hypothyroidism (384), Obesity (336), Food allergy (314), Type 2 diabetes mellitus (295), Atrial fibrillation and Depression (241 each).
- COVID-19 Medical history (n = 1044): COVID-19 (869), Suspected COVID-19 (153), Exposure to SARS-CoV-2 (15), COVID-19 pneumonia (12), Post-acute COVID-19 syndrome (11), Coronavirus infection, SARS-CoV-2 test positive (4 each), Asymptomatic COVID-19 and Breakthrough COVID-19 (1 each).
- Number of events: 153,862.
- Event seriousness[42]: serious (35,762), non-serious (118,147).
- The most reported (≥2%) PTs were Headache (8533), Lymphadenopathy (7016), Pyrexia (6893), Fatigue (6751), Vaccination site pain (5985), Immunisation[43] (5675), Chills (4558), Myalgia (3979), Dizziness (3359), Malaise (3296), Nausea (3001), Limb discomfort (2798), Arthralgia (2615), Pain in extremity (2485), Dyspnoea (2173), Influenza (1877), Rash (1738), Drug ineffective (1563), Tachycardia (1557), Asthenia (1512), Pain (1499), Paraesthesia (1416), COVID-19 (1386), Chest pain (1381), Vaccination site swelling (1336), Vomiting (1325), Off label use (1286), Herpes

zoster (1203), Menstrual disorder (1101), Diarrhoea (1062), Poor quality product administered (1061), Feeling hot (1017), Immunisation reaction (1016), Influenza like illness (1006), and Palpitations (985).

Analysis booster doses versus primary vaccination series

There were 117,750 PM cases of subjects who received at least one booster dose of BNT162b2.

Among the 117,750 PM cases,

- 106,889 PM cases involved subjects who received single booster dose of BNT162b2
- 3427 PM cases involved subjects who received >1 booster doses of COVID-19 vaccine (the latest booster dose was BNT162b2) and
- 7434 cases involved subjects who received unknown booster dose(s) of BNT162b2.
- The most frequently (≥2%) reported clinical AEs[44] in PM cases of subjects who received the booster dose(s) of BNT162b2 are largely reflective of reactogenicity and events associated with the immunisation process.
- The most frequently (≥2%) reported clinical AEs in PM cases of subjects who received booster dose(s) of BNT162b2 were consistent with those reported in subjects receiving primary vaccination series, as shown in Table 25.
- A higher AERP rate[45] was observed for 9 PTs (Lymphadenopathy [14.0% vs 3.8%], Malaise [12.6% vs 4.6%], Chills [11.8% vs 5.1%], Vaccination site swelling [4.5% vs 1.4%], Vaccination site erythema [2.9% vs 1.0%], Vaccination site lymphadenopathy [2.9% vs 0.2%], Vaccination site inflammation [2.8% vs 0.3%], Axillary pain [2.7% vs 0.5%], and Vaccination site warmth [2.4% vs 0.3%]) was observed in subjects who received the booster dose(s) of BNT162b2 compared to subjects receiving the primary vaccination series. This is consistent with the known BNT162b2 safety profile (as per the RSI), where higher rates of lymphadenopathy and reactogenicity reactions in booster doses versus primary doses were observed in interventional clinical studies.
- No clinically significant differences were noted in the other events.

[44] The PT Immunisation, Interchange of vaccine products, and Off label use are not included in the Table 25.

[45] A PT was considered to have a higher AERP rate if the ratio (AERP of the PT in the booster dataset/AERP of the PT in the primary series dataset) is ≥2.

Table 25. Comparison of clinical AEs reported in ≥2% Booster Dose(s) vs Primary Series Cases

PT Decode (Event)	Booster dose(s) Cases N = 117,750		Primary Series Cases N = 385,599	
	n	AERP[a] (%)	n	AERP[a] (%)
Headache	24,152	20.5	53,743	13.9
Fatigue	21,550	18.3	46,226	12.0
Pyrexia	16,639	14.1	40,964	10.6
Lymphadenopathy	16,442	14.0	14,662	3.8
Vaccination site pain	15,397	13.1	33,834	8.8
Myalgia	15,323	13.0	28,544	7.4
Malaise	14,845	12.6	17,809	4.6
Chills	13,836	11.8	19,668	5.1
Arthralgia	10,331	8.8	19,079	4.9
Nausea	10,055	8.5	20,581	5.3
COVID-19	9701	8.2	37,991	9.9
Pain in extremity	6792	5.8	18,274	4.7
Dizziness	6314	5.4	24,526	6.4
Drug ineffective	5850	5.0	20,669	5.4
Vaccination site swelling	5289	4.5	5372	1.4
Dyspnoea	5079	4.3	16,638	4.3
Vaccination failure	4945	4.2	19,296	5.0
Pain	4748	4.0	11,755	3.0
Chest pain	3988	3.4	13,942	3.6
Limb discomfort	3472	2.9	8093	2.1
Vaccination site lymphadenopathy	3433	2.9	648	0.2
Vaccination site erythema	3386	2.9	3834	1.0
Vaccination site inflammation	3329	2.8	1229	0.3
Axillary pain	3141	2.7	1935	0.5
Rash	3129	2.7	10,473	2.7
Asthenia	3007	2.6	10,681	2.8
Palpitations	2947	2.5	10,113	2.6
Vaccination site warmth	2828	2.4	1195	0.3
Paraesthesia	2813	2.4	12,168	3.2
Vomiting	2740	2.3	8649	2.2
Tachycardia	2641	2.2	8263	2.1
Diarrhoea	2517	2.1	7620	2.0
Heavy menstrual bleeding	2368	2.0	10,516	2.7

a. Calculated as n/N.

Conclusion

Based on the review of the cases reported with the booster dose(s), 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 26 below.

Table 26. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases
FD6840	9639
FE6208	8777
FD4555	7568
FD0168	7566
FD1921	7499
FR8392	6749
FF2382	5860
FF0680	4582
FC0681	4416
FC2473	4358
EY7015	4195
FA4598	4168
FG7911	4035
EY3014	3886
FF3318	3731
FH9951	3377

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium).

The AEs most frequently reported (≥ 4%) with these lot numbers do not differ from those reported in the overall incremental dataset except for the events coded to the PT Product administered to patient of inappropriate age.

During the current reporting period, on a total of 331,982 PM cases reporting a lot/batch number, there were 8068 PM cases including events coded to the PT Product administered to patient of inappropriate age, representing 1.6% of the overall incremental dataset and 2.4% of the total number of cases with lot numbers. These 8068 cases are also included in Section 9.2 *Medication Errors* or Section 16.3.4.6 *Off-Label Use*. The majority of these cases (5988 cases with unknown age) was non-serious and non-medically confirmed and originated from lot FR8392 which contains Tris/Sucrose presentation, 10 micrograms/dose, formulation indicated for age 5 years to < 12 years, per the current BNT162b2 RSI. This lot was administered in the Philippines to populations with an unknown age. Upon review, in 2640 cases, it was reported that the orange cap formulation was administered to adult individuals; while in 3348 cases, it was reported that the orange cap formulation was administered to individuals above 12 years old. No clinical AEs were co-reported.

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

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. In support to this process as needed, a review of AE data related to respective PCs may be requested to support trend analysis and notifications.
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 2441 (0.5%) unlocked[46] case reports (4 from CT and 2437 from PM) containing 8399 events fulfilled criteria for inclusion in this PSUR, compared to 139,698 (21.2%) case reports retrieved in the PSUR #2. Table 27 displays demographic information of the unlocked cases at the end of the reporting interval.

Table 27. Demographic Information - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=2441	CT No. of Cases (%[a]) N=4	PM No. of Cases (%[a]) N=2437
No. of Cases		2441	4	2437
MC	Yes	1203 (49.3)	4 (100)	1199 (49.2)
	No	1238 (50.7)	0	1238 (50.8)
Country of occurrence (≥2% of all cases)	Austria	388 (15.9)	0	388 (15.9)
	Germany	334 (13.7)	0	334 (13.7)
	France	284 (11.6)	0	284 (11.7)
	US	277 (11.3)	4 (100)	273 (11.2)
	Italy	175 (7.2)	0	175 (7.2)
	Sweden	127 (5.2)	0	127 (5.2)
	Romania	95 (3.9)	0	95 (3.9)
	UK	87 (3.6)	0	87 (3.6)
	Philippines	83 (3.4)	0	83 (3.4)
	Japan	78 (3.2)	0	78 (3.2)
	Greece	65 (2.7)	0	65 (2.7)
	Netherlands	62 (2.5)	0	62 (2.5)
	Norway	51 (2.1)	0	51 (2.1)
	Other countries	335 (13.7)	0	335 (13.7)
Gender	Female	1430 (58.6)	1 (25)	1429 (58.6)
	Male	796 (32.6)	3 (75)	793 (32.5)
	Unknown/No Data	215 (8.8)	0	215 (8.9)
Age (years)	N	2160	4	2156
	Min-Max	0.04-99	6-63	0.04-99
	Mean[b]	48.9	45.3	48.9
	Median[b]	48.5	56	48
Age Range	≤ 17	143 (5.9)	1 (25)	142 (5.8)
	18-30	262 (10.7)	0	262 (10.8)
	31-50	749 (30.7)	1 (25)	748 (30.7)
	51-64	516 (21.1)	2 (50)	514 (21.1)
	65-74	254 (10.4)	0	254 (10.4)

[46] 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.

Table 27. Demographic Information - Unlocked Cases at the End of the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=2441	CT No. of Cases (%[a]) N=4	PM No. of Cases (%[a]) N=2437
	≥ 75	247 (10.1)	0	247 (10.1)
	Unknown	269 (11.0)	0	269 (11.0)
	Not applicable	1 (0.0)	0	1 (0.0)
Case Seriousness	Serious	1541 (63.1)	4 (100)	1537 (63.1)
	Non-serious	900 (36.9)	0	900 (36.9)
Case Outcome	Fatal	32 (1.3)	1 (25)	31 (1.3)
	Not resolved	747 (30.6)	1 (25)	746 (30.6)
	Resolved/Resolving	642 (26.3)	2 (50)	640 (26.3)
	Resolved with sequelae	47 (1.9)	0	47 (1.9)
	Unknown	973 (39.9)	0	973 (39.9)
Presence of comorbidities	Yes	366 (15.0)	1 (25)	365 (15.0)
	No	2075 (85.0)	3 (75)	2072 (85.0)

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.

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

The events reported in clinical trial cases that were unlocked at the end of the reporting interval were coded to the PTs Appendicitis, Foreign body in gastrointestinal tract, Overdose, and Rheumatoid arthritis (1 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 reported events by SOC and by PT for events reported in ≥2% of unlocked cases at the end of the reporting interval.

Table 28. Post-Authorisation Data: Events Reported in ≥2% of Unlocked Cases

MedDRA SOC MedDRA PTs	N=2437 n (AERP,[a] %)
Blood and lymphatic system disorders	
Lymphadenopathy[b]	61 (2.5)
Cardiac	
Palpitations[c]	55 (2.3)
Gastrointestinal disorders	
Nausea[b]	95 (3.9)
Diarrhoea[b]	54 (2.2)
Vomiting[b]	50 (2.1)
General disorders and administration site conditions	
Drug ineffective[d]	343 (14.1)
Vaccination failure[d]	265 (10.9)
Fatigue[b]	228 (9.4)
Pyrexia[b]	213 (8.7)

Table 28. Post-Authorisation Data: Events Reported in ≥2% of Unlocked Cases

MedDRA SOC MedDRA PTs	N=2437 n (AERP,[a] %)
Asthenia[b]	110 (4.5)
Vaccination site pain[b]	106 (4.4)
Pain[c]	97 (4.0)
Chills[b]	96 (3.9)
Malaise[b]	95 (3.9)
Chest pain[c]	79 (3.2)
Infections and infestations	
COVID-19[d]	564 (23.1)
Injury, poisoning and procedural complications	
Inappropriate schedule of product administration[e]	143 (5.9)
Off label use[e]	116 (4.8)
Poor quality product administered[e]	84 (3.5)
Expired product administered[e]	53 (2.2)
Product administration error[e]	52 (2.1)
Musculoskeletal and connective tissue disorders	
Pain in extremity[b]	149 (6.1)
Myalgia[b]	141 (5.8)
Arthralgia[b]	127 (5.2)
Nervous system disorders	
Headache[b]	261 (10.7)
Dizziness[c]	110 (4.5)
Paraesthesia[c]	86 (3.5)
Hypoaesthesia[c]	65 (2.7)
Syncope[c]	56 (2.3)
Product issues	
Product temperature excursion issue[e]	51 (2.1)
Reproductive system and breast disorders	
Heavy menstrual bleeding[c]	63 (2.6)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea[c]	109 (4.5)
Surgical and medical procedures	
Interchange of vaccine products[f]	78 (3.2)
Immunisation[g]	49 (2.0)
Total number of events	**4304**

a. 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.
b. Listed or consistent with listed AEs in current RSI.
c. Unlisted in the current RSI.
d. Listed per case processing convention.
e. Per case processing convention, the PT term follows the most conservative listedness assessment of the associated AEs. If the term is reported alone or without associated AEs, the term is assessed as listed.
f. Of note, a majority of the cases reporting Interchange of vaccine products (75/78; 96.2%) co-reported Off label use. These cases described use of vaccines from different manufacturers. Per case processing convention, the PT term follows the most conservative listedness assessment of the associated AEs. If the term is reported alone or without associated AEs, the term is assessed as listed.
g. Of note, a majority of the cases reporting Immunisation (40/49; 81.6%) co-reported Off label use. These cases report a booster being administered and it is captured as an event when it is off-label per the local label. Per case processing convention, the PT terms follows the most conservative listedness assessment of the associated AEs. If the term is reported alone or without associated AEs, the term is assessed as listed.

Conclusion

The data contained in the unlocked cases are 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

Safety Trials

During the reporting period, no interventional safety studies were completed with a final CSR.

Other Trials that reported new significant efficacy information

During the reporting interval, there was a completed clinical trial (C4591017) with a final CSR (available upon request). No clinically important new information has emerged from this clinical trial; overall conclusions for the study are provided below.

Table 29. Summary of Results from Clinical Trial Completed During the Reporting Period

Protocol ID	Protocol Title	Conclusions
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.	The 3 US lots in the primary study met the 1.5-fold equivalence criteria for all 3 between-lot comparisons based on full-length S-binding IgG levels and were considered similar. Safety profiles across all vaccine groups were similar with no safety issues identified in both the primary and booster study. Vaccines in all arms of the study were well-tolerated in both the primary and booster study. The safety profile of BNT162b2 was consistent with previous studies.

7.2. Ongoing Clinical Trials

During the reporting period, there were 14 ongoing[47] 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 new 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 new 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 8 ongoing clinical trials:

- *C4591001[48], A phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.*
- *C4591007, A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children <12 years of age.*
- *C4591031,[49] A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2.*

[47] Includes ongoing studies as well as studies in which participant enrollment and follow-up have been completed, but the analysis and CSR are in-progress.

[48] Two interim CSRs were issued for Study C4591001 during the reporting interval [BNT162b2 (30 µg) Booster (Dose 3) – Phase 1 (4-Month Update) and Phase 3 (6-Month Update) v. 1.0 dated 19 May 2022 and BNT162b2SA VOC Booster Subset v. 1.0 dated 20 May 2022].

[49] Two interim CSRs were issued for Substudy A of Study C4591031 (v. 1.0 on 25 April 2022 and v. 2.0 on 07 June 2022) in the reporting period.

- *BNT162-01,[50] 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,[51] 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,[50] 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, [50,51]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 new safety information has emerged from ongoing clinical trials.

Remaining Trials

There were 4 ongoing clinical trials:

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

[50] Last subject last visit occurred during the reporting interval for the following studies: BNT162-01 (13 Apr 2022); BNT162-04 (07 Feb 2022); BNT162-06 (09 Jan 2022).

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

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

7.3. Long-term Follow-up

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

7.4. Other Therapeutic Use of Medicinal Product

BNT162b2 was also utilised in another Pfizer-sponsored clinical development program (B747). The study B7471026 "*A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older*" was completed during the reporting period.

There was no new clinically important safety information identified for this reporting period. The CSR for this trial is available upon request.

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 11 ongoing[47] sponsor-initiated non-interventional studies and one non-interventional study (C4591035) was completed.

8.1. Completed Non-Interventional Studies

Safety studies

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

Other studies

During the reporting period, the study C4591035 was completed. No new safety information emerged from this non-interventional study; the summary of results from this study is provided in Table 30.

Table 30. Summary of Results from Completed NIS During the Reporting Period

Protocol ID	Protocol Title	Conclusions[a]
C4591035	Coronavirus Disease 2019 (COVID-19) Vaccination and Breakthrough Infections Among Persons with Immunocompromising Conditions in the US.	This study contained the largest population of fully vaccinated IC individuals to date in whom COVID-19 vaccine breakthrough infections have been evaluated. The study findings show that breakthrough infections are generally rare but are more common and severe in people with certain IC conditions. The conclusions support the FDA authorisation and CDC recommendations to offer a 3rd vaccine dose to increase protection among IC individuals and the need for vigilant efforts to maximize vaccine uptake among the IC, especially in the context of waning duration of protection and emerging SARS-CoV-2 variants. Moreover, the findings from this study suggest that breakthrough infections can occur regardless of active treatment status in the IC and that there may be additional vulnerable IC groups that could benefit from increased protection. This study advances the understanding of post-vaccination outcomes across multiple IC condition groups in a real-world setting and may help healthcare providers in the decision-making process when vaccinating and treating patients at high-risk for COVID-19.

a. Di Fusco M, Moran MM, Cane A et al. Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2. J Med Econ. Jan-Dec 2021;24(1):1248-1260. doi: 10.1080/13696998.2021.2002063.
On 04 May 2022 the CSR was finalised with confirmation that this non-interventional study manuscript, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from study C4591035.

8.2. Ongoing Non-Interventional Studies

Safety Studies (see Appendix 4.4 for a list of ongoing non-interventional safety studies and their protocol titles):

PASS[52]: Non-interventional studies C4591008[53], C4591009[54], C4591010[55], C4591012[54], C4591021[54] and C4591022[54] 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 5 ongoing non-interventional studies:

- *C4591006,[56] General Investigation of COMIRNATY intramuscular injection (follow-up study for subjects [healthcare professionals] who are vaccinated at an early post-approval stage).*
- *C4591014,[57] Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.*
- *C4591019, Special investigation of COMIRNATY Intramuscular Injection (Investigation of Patients with Underlying Disease Considered to be at High Risk of Aggravation of COVID-19)*
- *C4591025,[58] A prospective, single-arm, open-label, non-interventional, multicenter to assess the safety of BNT162b2 in domestic post-marketing surveillance.*
- *C4591034, Patient-Reported Health-Related Quality of Life Associated With COVID-19: A Prospective Survey Study on Symptomatic Adults Confirmed With RT-PCR From Outpatient Settings in the US.*

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

---

[52] During the reporting period, interim CSRs were issued for the studies C4591010 (17 February 2022), C4591021 (23 March 2022) and C4591022 (25 January 2022).

[53] 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.

[54] Studies C4591009, C4591012, C4591021 and C4591022 are commitments to the US FDA and are Category 3 commitments in the EU-RMP v.5.0.

[55] Study C4591010 is Category 3 commitment in the EU-RMP v. 5.0.

[56] Studies C4591006 and C4591019 are commitments to the Japanese regulatory.

[57] PAM-MEA-013.

[58] Study C4591025 is a committed study, which was requested by the Ministry of Food and Drug Safety in Korea.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

During the reporting interval, there were 6 relevant cases that originated from non-Pfizer and non-BNT clinical trials. In 3 of these cases, BNT162b2 was a study drug, while in the other 3 cases BNT162b2 was co-administered with the study drug.

Four (4) cases originated from the following non-Pfizer and non-BNT trials:

- NCT04341142 - A novel assessment method for COVID-19 humoral immunity duration using serial measurements in naturally infected and vaccinated subjects (SAEs: COVID-19, Drug ineffective).

- DE-EORTC-1745-186-1 - A phase II study of adjuvant palbociclib as an alternative to chemotherapy in elderly patients with high-risk ER+/HER2- early breast cancer (appalaches) (SAE: Thrombophlebitis).

- RBR-9NN3SCW - Phase 4, randomized, controlled, single-blind study to assess the immunogenicity and safety of a third dose of heterologous booster with recombinant COVID-19 vaccine (Astra Zeneca/Fiocruz), COVID-19 mRNA vaccine (Pfizer/Wyeth) or vaccine recombinant COVID-19 (Janssen) in subjects previously vaccinated against COVID-19 with two doses of Sinovac/Butantan compared to a third homologous booster dose of adsorbed inactivated COVID-19 vaccine (Sinovac/Butantan) in adults (SAEs: Deep vein thrombosis, Pulmonary embolism).

- H3B-6545-G000-102 - An open-label multicenter phase 1b study of H3B-6545 in combination with palbociclib in women with advanced or metastatic estrogen receptor-positive HER2-negative breast cancer (SAE: Myocarditis). This case referred to a 72-year-old female participant with breast cancer and with a history of left ventricular failure; she received the 4th dose of BNT162b2 7 days before the beginning of treatment with palbociclib and 28 days before the beginning of the treatment with H3B-6545. Nine (9) days after the vaccination, she had palpitations and 5 days later she had abnormal electrocardiogram (inverted T waves in V5/V6, which later flattened, and raised troponin); she was hospitalised with focal myocarditis. Palbociclib was interrupted on the same day. Five (5) days after the hospital admission, she recovered from myocarditis.

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

Two (2) cases originated from the following non-Pfizer, non-BNT trials:

- 3101-304-002 - Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group Study to evaluate the efficacy, safety, and tolerability of oral atogepant

for the prophylaxis of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral prophylactic treatments (ELEVATE) [SAEs: Immunisation, Overdose (0.5 ml of Pfizer-BioNTech COVID-19 vaccine), Ventricular tachycardia].

- 21-0012 - A phase 1/2 study of delayed heterologous SARs-CoV-2 vaccine dosing (boost) after receipt of EUA vaccines (SAEs: Condition aggravated, Endometrial thickening).

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

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

9.2. Medication Errors

As part of the AR of the 11th SMSR (Procedure EMEA/H/C/005735/MEA/002.10), the following commitment is included: "*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[59] that occurred in the reporting period are summarised below.

[59] Search criteria: MedDRA (version 25.0): *HLTs (All paths):* Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product prescribing errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR *PTs:* Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Contraindication to vaccination; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage

Clinical Trial Data

During the reporting period, there were 2 serious cases (0.3% of 668 cases, the total CT dataset) indicative of medication errors (PTs: Accidental overdose and Inappropriate schedule of product administration). In the first case, the accidental overdose referred to paracetamol and not to BNT162b2 and in the remaining case reporting inappropriate schedule of product administration, the investigator assessed the event as not related to BNT162b2. There was 1 serious case retrieved during the reporting period of the PSUR #2.

Post-Authorisation Data

From the global safety database, 68,025 cases (13.4% of 507,683 cases, the total PM dataset) potentially indicative of medication errors were retrieved during the reporting period.

Of the 68,025 cases, 1261 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Off-label use or intentional use rather than medication error was reported in 515 cases;
- Reporting information was no longer consistent to meet medication error criteria in 11 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 700 cases;
- Cases consisted of booster dose scheduling outside the prescribing window were reported in 6 cases;
- Medical inquiries only were reported in 4 cases;
- The subject intentionally refused to be vaccinated or was not able to receive the scheduled BNT162b2 in 7 cases;
- In 7 cases, the reported errors were not due to BNT162b2;
- In 6 cases, subjects were exposed to the vaccine during breastfeeding;
- An unspecified number of subjects were described in 5 cases.

The potentially relevant medication error cases during the reporting period were 66,764 (13.1%)[60] reporting 87,307 events, compared to 33,834 relevant cases (5.1%) analysed in the PSUR #2.

process. The HLT Product prescribing errors and issues has been included upon upversioning to MedDRA v. 25.0.

[60] Among the most commonly reported countries (≥2% of cases), significant increase in proportion of cases observed from Austria (21.5 vs 6.9%), Philippines (9.3% vs 0.07%), Sweden (11.5 vs 4.5%) and Australia (2.3% vs 0.4%) when compared to cases reported in PSUR#2. Most of the cases from these 4 countries reported scheduling, formulation or storage errors. In comparison with PSUR#2, there was a significant increase in number of cases identified with new Tris/Sucrose formulation in the current reporting period: Orange cap (755 cases vs 9426 cases)/Grey cap (0 vs 2750 cases), respectively.

The 66,764 relevant medication error cases originated mostly (≥2% of cases) from the following countries: Austria (14,339 cases), US (9592 cases), Germany (8074 cases), Sweden (7666 cases), Philippines (6182 cases), UK (4531 cases), France (2923 cases), Netherlands (2586 cases), Japan (1630 cases), Australia (1506 cases), and Canada (1425 cases).

The most frequently reported (≥2% of cases) medication error PTs were: Inappropriate schedule of product administration (34,486 events), Poor quality product administered (17,837 events), Product administered to patient of inappropriate age (7952 events), Product administration error (6946 events), Product storage error (5882 events), Product temperature excursion issue (4626 events), Expired product administered (2060 events), and Incorrect route of product administration (1889 events).

In some instances, clusters of medication errors were reported. During the reporting interval, 5 different types of medication error cases (>1000 occurrences) were identified coded to the PTs Product storage error, Poor quality product administered, and Product administered to patient of inappropriate age.

All cases demonstrated no-harm and had no co-reported events:

- In 3348 cases, Tris/Sucrose Orange cap presentation of BNT162b2 was given to adolescent patients.
- in 3011 cases, BNT162b2 was thawed and kept in the refrigerator longer than the recommended period.
- in 2640 cases, Tris/Sucrose Orange cap presentation of BNT162b2 was given to adult patients.
- in 1169 cases, BNT162b2 was stored in the cold storage (15 to 25 degrees Celsius) 20 days longer than the recommended 2 weeks period prior to use and the vaccine was administered.
- in 1169 cases, BNT162b2 was stored in the cold storage (15 to 25 degrees Celsius) 13 days longer than the recommended 2 weeks period prior to use and the vaccine was administered.

Medication Errors Analysis

Among the relevant medication error cases (66,764 cases[61]), the following scenarios, were described:

- Medication errors associated with harm [i.e., 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 1326 cases (2% of relevant

[61] Relevant medication error cases 66,764 (1326 harm + 65,350 no-harm + 87 potential + 1 intercepted errors).

medication error cases) compared to 879 cases (2.6% of relevant medication error cases) analysed in the PSUR #2.

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

Medication errors associated with harm (1398 medication error events in 1326 cases)

Of the 1326 cases, 472 were medically confirmed, and 854 were non-medically confirmed. Cases were mostly (>50 occurrences) reported from Germany (390 cases), Poland (206 cases), Iraq (191 cases), France (91 cases), UK (73 cases), Italy (69 cases), US (63 cases).

There were 899 females and 392 male subjects, whereas the gender was not specified for 35 subjects. When provided (n = 1250), the age ranged from 1.0 month to 98.0 years with a mean age of 40.5 years and a median of 40.0 years.

Of the 1398 medication error events, 78 were serious and 1320 were non-serious. The relevant event outcome was reported as fatal (2), resolved/resolving (29), not resolved (20), and unknown (1347).

There were 2 fatal medication error events reported in 2 cases and they were coded to the PT Incorrect dose administered Section 16.3.4.1 *Death*).

- First case: An 84-year-old male subject received BNT162b2 as dose 4 (booster) for COVID-19 immunisation. The subject's relevant medical history included: artificial cardiac pacemaker wearer (ongoing) and prostate problems. Vaccination history included: 3 doses of BNT162b2 and the subject experienced several adverse events after each vaccination including intestinal haemorrhage, headache, vomiting/urge to vomit, malaise, increased bleeding under the skin, and petechiae. It was reported that the subject received an incorrect fourth dose of BNT162b2 (dose unspecified) and experienced a fatal event of intestinal haemorrhage. The other events reported were haemorrhage subcutaneous, petechiae, headache, vomiting, malaise, and contusion. The cause of death was unknown, and it was not reported if an autopsy was performed.

- Second case: An 89-year-old female subject received BNT162b2 second booster dose by mistake (PT Incorrect dose administered) and died due to cardiac failure and acute pulmonary oedema 2 days after the time of vaccination. It was reported that the subject had multiple pre-existing conditions including cardiac diseases, follicular lymphoma, pulmonary tuberculosis, lumbar spinal stenosis, and breast cancer. It was unknown if an autopsy was performed. No further information was available.

Serious medication errors

In 70 cases (involving 78 medication error events; 5.3% of 1326 cases; this includes 2 fatal cases [described above]), serious medication errors potentially contributed to the occurrence of SAEs when compared to 59 serious cases (involving 69 medication error events; 6.7% of 879 cases) analysed in the PSUR #2.

Cases (≥2 occurrences) originated from UK (43 cases), Germany (7 cases), France (4 cases), Poland and Belgium (2 cases each).

The serious events (≥3 occurrences) indicative of medication errors were Medication error (19 events), Product administered at inappropriate site (15 events), Incorrect route of product administration (12 events), Incorrect dose administered (10 events), Product administration error (9 events), Wrong technique in product usage process (5 events), and Expired product administered (3 events).

The most frequently (≥6 occurrences) co-reported clinical events were Headache (19 events), Pain in extremity (16 events), Pain (11 events), Arthralgia, Nausea (10 events each), Fatigue (8 events), Myalgia, Paraesthesia, Pyrexia (7 events each), Chills, Dizziness, Malaise, Periarthritis, Shoulder injury related to vaccine administration, and Vaccination site pain (6 events each).

Upon review of medication error serious events:

Vaccine administration errors (56 events, 50 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, and other administration errors.

- *Errors of vaccination at the wrong anatomical site (18 events)*
  - The vaccine was administered in the shoulder, arm site other than deltoid (8 events each), leg, and bursa (1 event each).
- *Errors in vaccine dosage administered (11 events)*
  - Errors included administration of fourth/second booster dose (3 events), additional dose (1 event), and incorrect unspecified dose administered (7 events).
- *Errors in the route of administration (10 events)*
  - The route of administration for the vaccine was subcutaneous (5 events), intravenous (3 events), intrameningeal, and intradermal (1 event each).
- *Administration technique errors (8 events)*
  - Errors included injury to nerve/blood vessel (3 events), moving the needle around in the arm, injected with force, poor injection technique (1 event each), unspecified technique errors (2 events).
- *Other vaccine administration errors (9 events)*
  - These events reported administration of expired vaccines (3 events), administration of wrong vaccine (1 event), unspecified administration errors (5 events).

Vaccine preparation errors (2 events, 2 cases)

- Errors included dilution before use was not performed or improper dilution (1 event each).

Other errors (20 events, 18 cases)

- Errors included unspecified medication error/unspecified vaccination error (20 events).

Non-serious medication errors

In 1256 cases (involving 1320 medication error events), non-serious medication errors potentially contributed to the occurrence of non-serious AEs, when compared to 820 cases (involving 886 non-serious medication error events) analysed in the PSUR #2. Most of the cases (≥60 occurrences) originated from Germany (383 cases), Poland (204 cases), Iraq (190 cases), France (87 cases), Italy (69 cases), and US (62 cases).

The most frequently (≥105 occurrences) co-reported clinical events were Pyrexia (323 events), Headache (265 events), Vaccination site pain (245 events), Fatigue (178 events), Pain in extremity (150 events), Myalgia (126 events), Asthenia (114 events), and Chills (105 events).

- *Vaccine administration errors[62] (1224 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[63] (19 events)*: Events mainly described errors during dilution and other preparation errors.
- *Vaccine scheduling errors[64] (1 event)*: Event described error in scheduling of second dose administration

[62] PTs Incorrect route of product administration, Incorrect dose administered, Product administered at inappropriate site, Product administered to patient of inappropriate age, Underdose, Expired product administered, Poor quality product administered, Product administration error, Wrong product administered, Accidental overdose, Accidental exposure to product, Extra dose administered, Product administration interrupted.

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

[64] PTs Inappropriate schedule of product administration.

- *Other medication errors[65] (76 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.

9.2.1. Errors pertaining to the new formulation of BNT162b2 – Paediatric Tris/Sucrose Orange Cap presentation (dilute before use) 10 µg/dose for 5 to <12 years of age

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; 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 9426 cases[66,67] reporting 12,051 events indicative of medication errors per the medication error MedDRA search strategy related to Tris/Sucrose Orange cap presentation (paediatric formulation). The majority of these cases (>30 cases) describing medication errors were from Philippines (5994 cases), US (2640 cases), Australia (276 cases), Germany (109 cases), Canada (94 cases), Japan (68 cases), Spain (61 cases), and Korea, Republic of (South Korea) (32 cases).

The events (>200 occurrences) indicative of medication error were coded to the PTs Product administered to patient of inappropriate age (6485 events), Poor quality product administered (1710 events), Product administration error (1143 events), Product preparation error (550 events), Product temperature excursion issue (466 events), Underdose (387 events), Product preparation issue (302 events), Expired product administered (260 events), Vaccination error (214 events), Inappropriate schedule of product administration (204 events).

Medication Errors Harm Analysis

[65] PTs Wrong technique in product usage process, Medication error, Vaccination error, Product temperature excursion issue

[66] Among the reviewed cases, there were additional 1119 cases reported errors in paediatric subjects of 5 to <12 years, who are the authorised individuals to receive Tris/Sucrose Orange cap presentation, but these subjects received PBS/Sucrose Purple cap presentation. As these subjects did not receive Orange cap presentation, these cases are not included in Section 9.2.1. Of note, 24 of 1119 cases involved intentional administration and they were excluded from the analysis of the overall medication error dataset.

[67] Among the reviewed cases, there were additional 199 cases involving children aged 5 - <12 years who were vaccinated with the adult formulation (30 micrograms/dose, PBS presentation) before the approval of the appropriate Tris/Sucrose pediatric presentation in their respective countries; these cases were hence not consistent with medication errors pertaining to the new tris-sucrose pediatric presentation. Of note, 6 of 199 cases involved intentional administration and they were excluded from the analysis of the overall medication error dataset.

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 48 cases (0.5 % of medication error cases relevant to Tris/Sucrose Orange cap presentation).
- Medication errors without harm [i.e., not resulting in adverse reaction(s)][68] were reported in 9367 cases (99.4 % of medication error cases relevant to Tris/Sucrose Orange cap presentation).
- Potential errors were reported in 11 cases (0.1% 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.

Medication errors with harm (55 medication errors in 48 cases)

In 48 cases involving 55 medication error events, 1 event was assessed as serious and the remaining 54 medication errors were assessed as non-serious. These 48 cases originated from Germany (15 cases), US (9 cases), Italy (7 cases), Poland (6 cases), Australia (5 cases), Philippines, Japan (2 cases each), Spain and Lithuania (1 case each).

Serious medication error

In 1 case, a serious medication error was reported that potentially contributed to the occurrence of SAEs.

A consumer reported that a female child subject of unspecified age received Tris/Sucrose Orange cap presentation for COVID-19 immunization. The treating nurse administered the wrong dose of vaccine to the child. She was supposed to dilute it, instead she gave a full vial of the COVID Vaccine (PTs: Product preparation error; Overdose). Following administration, the subject experienced dizziness, nausea, and increased heart rate. These events were considered serious as the subject requiring hospitalisation and it was unknown if the subject recovered from these events. No further information was available.

Non-serious medication errors

In 47 cases (involving 54 medication error events), non-serious medication errors potentially contributed to the occurrence of non-serious AEs.

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

The most frequently reported clinical events (≥4 events) in these cases were coded to the PTs Pyrexia (15 events), Vaccination site pain (11 events), Pain in extremity (10 events), Headache (9 events), Vomiting (5 events), Asthenia and Fatigue (4 events).

- *Errors in the administration of incorrect formulation and/or errors in the administration vaccine dosage due to incorrect formulation (4 events)*
  - Errors in the choice of formulation included adolescent (2)/adult (1) subjects who received paediatric formulation (Tris/Sucrose Orange cap presentation) (3 events).
  - Error included adolescent subject receiving paediatric formulation (Tris/Sucrose Orange cap presentation) that led to error in vaccine dosage (1 event).
- *Errors in the preparation / administration of incorrectly prepared vaccine (6 events)*
  - Errors in preparation: Errors included dilution before use not performed (4 events) or incorrect dilution (1 event)
  - Error in administration of inadequately prepared vaccine: Error involved in administering undiluted vaccine (1 event)
- *Other errors (44 events)*
  - Errors of vaccine dosage included smaller doses (6 events), receiving lower volume of correct dosage, additional dose (1 event each), or unspecified inappropriate dose (3 events)
  - Other errors included unintentional administrations of vaccine to paediatric individuals below 5 years of age (15 events), errors in the route of administration (10 events), administered expired vaccine (3 events), administration technique errors (1 event) or unspecified administration/vaccination errors (4 events).

Medication errors without harm (11,983 medication errors in 9367 cases)

There were 9367 cases involving 11,983 medication error events without harm. The cases (≥32 cases) originated from Philippines (5992 cases), US (2623 cases), Australia (271 cases), Germany (94 cases), Canada (93 cases), Japan (66 cases), Spain (60 cases), and Korea, Republic of (South Korea) (32 cases).

- *Errors in the administration of incorrect formulation and/or errors in administration of vaccine dosage due to incorrect formulation (6682 events)*
  - Errors in the choice of formulation included adolescent (3615)/adult subjects (2839) receiving paediatric formulation (Tris/Sucrose Orange cap presentation) (6454 events), or elderly subjects receiving paediatric formulation (Tris/Sucrose Orange cap presentation) (31 events)

Errors included administration of smaller doses or errors in vaccine dosage as the adult/adolescent subjects receiving paediatric formulation (Tris/Sucrose Orange cap presentation) (195 events), administration of smaller doses as a consequence of giving paediatric formulation (Tris/Sucrose Orange cap presentation) to elderly subjects (2 events).

- *Errors in preparation and/or administration of incorrectly prepared vaccine (1095 events)*

  - Errors in preparation: Errors included dilution before use not performed (412) events), dilution before use with larger/smaller/incorrect volume of diluent (144 events), incorrect/improper dilution (125 events), smaller doses due to use of large volume of diluent (119 events), diluent from the same vial was used for multiple vials (108 events), improper dilution that led to error in vaccine dosage (30 events), smaller doses due to vial mixing error/improper dilution (23 events), dilution before use with a different solvent (21 events), diluted orange cap was given to adult subject (12 events), less/more doses in the vial after preparation (6 events), Orange cap formulation was mixed with Purple cap formulation (5 events), larger doses due to dilution error/improper dilution (3 events), Orange cap presentation was mixed with the amount of diluent recommended for Purple cap presentation, larger doses as the dilution before use was not performed (2 events each), or unspecified preparation/dilution errors (10 events).

  - Errors in administration of incorrectly prepared vaccine: Errors involved administration of undiluted vaccine (33 events), administered vaccine after diluting with incorrect diluent (30 events), administered after improper dilution (8 events), administered orange cap formulation after mixing with purple cap formulation (2 events).

- *Other errors (4206 events)*

  - Errors of vaccine dosage included smaller doses due to product leakage / syringe issue / subject non-compliance / needle issue or due to other issues (72 events), unspecified inappropriate dose (35 events), larger doses (19 events), administration of incorrect dose/booster dose/invalid dose/additional doses (10 events), not enough doses or incorrect dosage in the vial, administration of fourth and fifth doses together/half of the booster dose (2 events each) or given smaller volume of correct dosage (1 event),

  - Other errors reported administration of expired vaccine (1320 events), temperature excursion or administration of vaccine after temperature excursion (946 events), administration of poor quality vaccine/defective material (813 events), inadequate storage or administration of vaccine after inadequate storage (471 events), unspecified vaccination/administration errors (211 events), Inappropriate schedule/administration of second dose of the vaccine earlier or later than the 3-week schedule (204 events),

– These events included unintentional administrations of vaccine to paediatric individual below 5 years of age (33 events), administration technique errors (17 events), wrong product/vaccine administered (15 events), errors of vaccination at the wrong anatomical site (13 events), accidental exposure (9 events), incorrect route of administration (6 events), dispensed vaccine after expiry (2 events), product not completely administered due to interruption, multiple use of single-use product (details unspecified), unspecified prescribing error, product leakage during administration, or the syringe was shaken before administration (1 event each).

Potential medication errors (13 medication errors in 11 cases)

There were 11 cases from US (8 cases), UK, Canada, and Italy (1 case each)

- The potential errors were described as the confusion with the expiration date/formulation to be used (4 events), user requesting clarification if the paediatric vial stored in the standard freezer can be used/about storage instructions in the label and/or package (3 events), beyond use date was not written on the box, user was unsure if the vaccine was given via appropriate route, printing error in the label, reporter was unsure if the subject received vaccine after dilution, adult vial with paediatric label sticker, expiration date in the carton and on the vial was different (1 event each).

9.2.2. Errors pertaining to the new formulation of BNT162b2 – Adult /Adolescent Tris/Sucrose Grey cap presentation (30 mcg/dose –[Do not dilute]- in adults and children 12 years and older):

Search criteria used for selecting the below cases for discussion: Adult/adolescent/elderly subjects received Tris/Sucrose Grey cap (30 mcg/dose) presentation; Tris/Sucrose Grey cap formulation was used or administered to paediatric age group of 5 to <12 years instead of Tris/Sucrose Orange cap presentation.

There were 2750 cases (4.1% of the relevant medication error cases) reporting 5496 events indicative of medication errors related to Tris/Sucrose Grey cap presentation (adult/adolescent formulation). Of the 2750 cases, in 53 cases paediatric subjects of 5 to <12 years of age range received Tris/Sucrose Grey cap presentation instead of Tris/Sucrose Orange cap presentation by mistake. These 2750 cases originated from the US (2684 cases), France (36 cases), Germany (17 cases), Spain, Canada, UK, Australia, Italy (2 cases each), Puerto Rico, Finland and Israel (1 case each).

The medication errors (≥42 occurrences) reported in 2750 cases were coded to the PTs Poor quality product administered (2429 events), Product administration error (1665 events), Product temperature excursion issue (733 events), Expired product administered (193 events), Underdose (96 events), Product preparation issue (94 events), Product storage error (86 events), Inappropriate schedule of product administration (45 events), Product administered to patient of inappropriate age (43 events), and Product preparation error (42 events).

Medication Errors Harm Analysis

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

- Medication errors associated with harm [i.e., resulting in adverse reaction(s)] were reported in 12 cases (0.4 % of medication error cases relevant to Tris/Sucrose Grey cap presentation)
- Medication errors without harm [i.e., not resulting in adverse reaction(s)][69] were reported in 2727 cases (99.2 % of medication error cases relevant to Tris/Sucrose Grey cap presentation)
- Potential error was reported in 11 cases (0.4% of medication error cases relevant to Tris/Sucrose Grey cap presentation)
- There were no cases reporting intercepted medication errors during the reporting interval.

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

Medication errors with harm (17 medication errors in 12 cases)

In 12 cases involving 17 medication error events, all the events were assessed as non-serious. These 12 cases originated from US (10 cases), Australia, and France (1 case each).

Serious medication error

There were no cases that reported serious medication error.

Non-serious medication errors

In 12 cases (involving 17 medication error events), non-serious medication errors potentially contributed to the occurrence of non-serious AEs.

The clinical events (≥2 events) reported in these cases were coded to the PTs Pyrexia (3 events) and Dizziness (2 events).

- *Errors in the administration of incorrect formulation (1 event)*
  - Errors in the choice of formulation included paediatric subjects receiving adult/adolescent formulation (Tris/Sucrose Grey cap presentation [1 event])

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

- *Other errors (16 events)*

  - Errors in vaccine dosage included the 3rd booster dose/additional dose, smaller doses, or unspecified inappropriate doses (2 events each)

  - Other errors included incorrect route of administration (intradermal/IV), administered after expiry/administered expired vaccine, administered poor quality vaccine (2 events each), administration of vaccine 12 hours after first puncture, administration of vaccine after inadequate storage, administration of wrong product, and unspecified vaccination error (1 event each).

Medication errors without harm (5467 medication errors in 2727 cases)

There were 2727 cases involving 5467 medication error events without harm and they are categorised into:

- *Errors in the administration of incorrect formulation and/or errors in the administration vaccine dosage due to incorrect formulation (51 events)*

  - Errors in the choice of formulation included paediatric subjects receiving adult/adolescent formulation (Tris/Sucrose Grey cap presentation) (48 events)

  - Errors included paediatric subject receiving adult/adolescent formulation (Tris/Sucrose Grey cap presentation) that led to error in vaccine dosage (3 events).

- *Errors in the preparation / administration of incorrectly prepared vaccine (206 events)*

  - Errors in preparation: Errors included dilution of vaccine before use (83 events), subjects received smaller doses as the vaccine was diluted before use (59 events), smaller doses due to preparation error (20 events), incorrect/improper dilution (17 events), Grey cap presentation was diluted and given to paediatric subject (9 events), undiluted Grey cap presentation was given to paediatric subject (4 events), Grey cap presentation was diluted with Orange cap presentation (1 event).

  - Errors in administration of incorrectly prepared vaccine: Errors involved administration of diluted vaccine/administered after improper dilution (13 events)

- *Other Errors (5210 events)*

  - Errors of vaccine dosage included administration of doses from 2 different vials (20 events), smaller doses/smaller doses due to improper injection/smaller doses due to syringe leakage/smaller doses as the part of the liquid was not administered (16 events), third/fourth/fifth dose (7 events), additional or booster doses (4 events), larger doses (3 events), doses left in the vial after completion of 6 doses (2 events) or unspecified inappropriate dose (5 events)

- Other errors included temperature excursion or administration of vaccine after temperature excursion (1508 events), administration of poor quality vaccine/defective material (1330 events), administered after expiry/administration of expired vaccine (1237 events), inadequate storage or administration of vaccine after inadequate storage (877 events), vaccine given after 12 hours of initial vial puncture (131 events), inappropriate schedule/second dose was given earlier or later than the 3-week schedule (45 events), technique errors or other administration errors (12 events), incorrect route of administration or errors of vaccination at the wrong anatomical site (8 events), administered vaccine from the old vial, administration of wrong vaccine (1 event each) or other unspecified error (3 events).

Potential medication error (12 medication errors in 11 cases)

- There were 11 cases from US (9 cases), France and Germany (1 case each)

- The potential errors were described as no expiration date on the vial (7 events), confusion in the formulation or expiration date (2 events), reporter was unsure if the subject received vaccine after dilution, user requesting clarification about the expiration date on the label, user suggested to include information note about dilution to avoid confusion as the dilution was performed before use by mistake (1 event each).

Conclusion

Overall, among the 66,764 relevant medication error PM cases, 1326 cases (0.3% of the total interval cases, 2.0% of total relevant medication error cases) were considered harmful, 70 of which (0.1% of total relevant cases) were serious and most of them originated from vaccine administration issues (50 cases of 70 serious cases with harm).
The potential for medication errors with the new presentations are mitigated through the information in the vaccine labelling and available educational materials for the HCPs administering the vaccine.
Some medication errors are expected to occur despite written instructions for handling the vaccine (thawing, dilution, preparation) and educational activities for the HCPs or due to national or regional recommendations regarding dosing schedules that may differ from recommendations in the product labelling. The number and seriousness of the reported medication errors events do not indicate any trend and potential needs for any additional mitigation activity.

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 8 clinical trials that presented important new safety findings for BNT162b2. These are presented in Table 31 below grouped as follows: a) At risk patients; b) Special patient population/Pregnancy; c) Efficacy and Effectiveness and d) Other Safety Information (citations with a brief comment).

See Appendix 5 for the abstracts. Full publications are available upon request.

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

Citation/Comment
a) At Risk patients
1. Majcherek M, Matkowska-Kocjan A, Szymczak D, et al. Two Doses of BNT162b2 mRNA Vaccine in Patients after Hematopoietic Stem Cell Transplantation: Humoral Response and Serological Conversion Predictors. Cancers (Basel). 2022; 14(2):325. This article described a reduced immunoresponse to BNT162b2 in patients treated with immunosuppressants. Section 4.4. Special warnings and precautions for use (Immunocompromised individuals) of the EU SmPC includes a warning regarding vaccination in immunocompromised patients, as follows, "The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals." Use in immunocompromised patients is considered missing information for BNT162b2; please refer to Section 16.4.2 *Description of Missing Information* for the description of this topic and to Section 16.3.5.5 *Use in Immunocompromised Patients* for the summary of the cases received during the reporting period.
b) Special Patients Population (Pregnancy)
2. Citu IM, Citu C, Gorun F, et al. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. J Clin Med. 2022; 11(6):1698. This article contributes to the growing evidence that risk of spontaneous abortion after COVID-19 vaccine immunisation during the first trimester of pregnancy is commensurate with the predicted risk in non-vaccinated pregnant women. Use in pregnancy and while breast feeding patients is considered missing information for BNT162b2; please refer to Section 16.4.2 *Description of Missing Information* for the description of this topic and to Section 16.3.5.3 *Use in Pregnant/Lactating Women* for the summary of the cases received during the reporting period.

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

Citation/Comment
c) Efficacy and Effectiveness
3. Tartof SY, Slezak JM, Puzniak L. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: a retrospective cohort study. The Lancet Regional Health – Americas 2022;9: 100198 Published on line 14 February 2022. 4. Tartof SY, Slezak JM, Puzniak L. Durability of BNT162b2 vaccine against hospital and emergency department admission due to the omicron and delta variants in a large health system in the USA: a test-negative case-control study. Lancet Respir Med 2022; 10:689-99. 5. Kliker L, Zuckerman N, Atari N et al. COVID-19 vaccination and BA.1 breakthrough infection induce neutralising antibodies which are less efficient against BA.4 and BA.5 Omicron variants, Israel, March to June 2022. www.eurosurveillance.org submitted on 12 Jul 2022 / accepted on 28 Jul 2022 / published on 28 Jul 2022.[70] 6. Hansen CH, Friis NU, Bager P et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish nation-wide population-based study. Lancet pre-print https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4165630.[70] Please refer to Section 17.2 *Newly Identified Information on Efficacy and Effectiveness* for the comments on these articles and to Section 16.3.4.5. *Lack of Therapeutic Efficacy* for the review of the cases indicative of LOE reported in the current interval period.
d) Other Safety Information
7. Yanir Y, Doweck I, Shibli R, et al. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss. JAMA Otolaryngol Head Neck Surg. 2022;148(4):299–306. This study suggests that the COVID-19 vaccine might be associated with increased risk of Sudden Sensorineural Hearing Loss; however, the effect size is very small. The study had various limitations and no causality assessment has been conducted. The MAH will continue to monitor using routine pharmacovigilance. Please refer to Appendix 6A.3 for further discussion of this article and for cumulative review of cases indicative of hearing loss.
8. Visser C, Biedermann JS, Nierman M et al. The Immediate Effect of COVID-19 Vaccination on Anticoagulation Control in Patients Using Vitamin K Antagonists. Thromb Haemost 2022; 122:377–385.

[70] Articles 5 and 6 were published/posted after the DLP, but they include information relevant to the reporting period of this PSUR.

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

Citation/Comment
In this study, BNT162b2 was associated with an immediate negative effect on anticoagulation control in patients treated with vitamin K antagonists. The author though cannot exclude the possibility that the effect on anticoagulation control was due to dose adjustments to avoid complications and patients themselves could have decided to decrease the dosage in the days following COVID-19 vaccination as they might be afraid for bleeding complications after intramuscular injection. This could result in a higher percentage of subtherapeutic INRs after vaccination. In addition, the authors use a surrogate variable for bleeding complications (INR >5). The possible effects of vaccines on anticoagulation control remain debated even though several prospective studies have been performed (mostly on the effect of the influenza vaccine on anticoagulation control), but overall results were conflicting. As of now, there is no biological or pharmacological plausibility for a vaccine – drug interaction. The MAH will continue to monitor using routine pharmacovigilance. Please refer to Section 16.3.3.1.19 *Thromboembolic AESIs* for the summary of cases indicative of coagulopathy received in the reporting period.

All Other Published Sources

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

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

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

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

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

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

Unpublished manuscripts

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

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

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

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 (SMSRs), in accordance with the EMA coreRMP19 Guidance (EMA/544966/2020) and, as applicable, with ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, January 2013] considering the information for the evidence from post-EUA/conditional marketing authorisation approval data sources.

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

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

Periodic Report Type	No.	Reporting Period
Summary Bimonthly Safety Report (SBSR)	2	16 December 2021 through 15 February 2022
	3	16 February 2022 through 15 April 2022
Abbreviated SMRS[a]	2	16 December 2021 through 15 January 2022
	3	16 February 2022 through 15 March 2022
	4	16 April 2022 through 15 May 2022
	5	16 May 2022 through 15 June 2022

a. Submitted to non-EEA countries.

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

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Study C4591007 is the ongoing, randomised, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. The Phase 2/3 primary immunogenicity objective in children from 6 months to <5 years of age was immunobridging the immune responses against SARS-CoV-2 wild-type strain from children 2 to <5 years and 6 months to <2 years of age in Study C4591007 compared to young adults 16 to 25 years of age in the Phase 3 efficacy Study C4591001. Immunobridging data after Dose 2 met success criteria for the 6 months to <2 years group and did not meet GMR success criteria (but met seroresponse criteria) for the 2 to <5 years of group, compared to young adults 16 to 25 years of age. Given emerging real-world data in the Omicron wave that two-dose protection against symptomatic infection was only modest, a third dose was evaluated for children <5 years of age. Immunobridging data after Dose 3 met success criteria for the 6 months to <5 years age group, compared to young adults 16 to 25 years of age.

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

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

The observed VE after 3 doses in children 6 months to <5 years of age in Study C4591007 is consistent with real-world effectiveness data for older age groups, which indicate that in adolescents (12 to 17 years of age) and adults (18 years of age and older), three doses of BNT162b2 are needed to provide a high level of protection against symptomatic disease due to Omicron.[71]

14. LATE-BREAKING INFORMATION

As reported in Section 16.1 *Summary of Safety Concerns*, on 08 July 2022 (after the DLP of this PSUR), the MAH submitted the EU RMP version 5.1 to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP

---

[71] Fleming-Dutra KE, Britton A, Shang N, et al. Association of prior BNT162b2 COVID-19 vaccination with symptomatic SARS-CoV-2 infection in children and adolescents during Omicron predominance. JAMA. 2022;[EPub]; doi: 10.1001/jama.2022.7493.

Klein NP, Stockwell MS, Demarco M, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated Emergency Department and Urgent Care encounters and hospitalisations among nonimmunocompromised children and adolescents aged 5-17 Years – VISION Network, 10 States, April 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(9):352-8; doi:10.15585/mmwr.mm7109e3.

Tartof SY, Frankland TB, Slezak JM, et al. Effectiveness associated with BNT162b2 vaccine against emergency department and urgent care encounters for Delta and Omicron SARS-CoV-2 infection among adolescents aged 12 to 17 years. JAMA Network Open. 2022;5(8):e2225162. doi:10.1001/jamanetworkopen.2022.25162.

Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA. 2022;327(7):639-51.

UK Health Security Agency. COVID-19 vaccine surveillance report – week 27, 7 July 2022. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1088974/Vaccine-surveillance-report-week-27.pdf. Accessed 2 Aug 2022.

recommendation received in March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087).

After the DLP, an updated CDS (version 14.0) was made effective on 26 July 2022 to extend the indication of BNT162b2 to individuals 6 months of age and older, to include posology and method of administration for the Tris/Sucrose presentation 3 micrograms/dose, and to add irritability, injection site tenderness, myocarditis and pericarditis as ADRs in section 4.8 *Undesiderable effects*. Please refer to Section 4 *Changes to the Reference Safety Information* for additional details on the changes.

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

Signal Overview

Signals detected for BNT162b2 during the reporting interval are presented below in Table 32 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.

Table 32. Overview of Signals (at DLP 18 June 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Myocarditis and Pericarditis	Closed	Other: Routine safety surveillance	Important identified risk	-
Irritability	New and closed	Clinical Trial C4591007 unblinded review of data in 6 months to <5-year-old (Pfizer)	Identified risk (not "important")	-
Appendicitis	Re-opened and closed	Inquiry from a competent authority (Singapore BoH)	No risk	-
Hemolytic anemia	New and closed	Inquiry from a competent authority (Saudi Arabia SFDA)	No risk	-
Uveitis	New and closed	Inquiry from a competent authority (Health Canada)	No risk	-
Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Capillary Leak Syndrome (CLS)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-051 EPITT 19743

Table 32. Overview of Signals (at DLP 18 June 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Corneal Graft Rejection	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-055 EPITT 19789
Vasculitis	Ongoing and closed	Notification from a competent authority (Netherlands Lareb)	No risk	-
Cerebral venous sinus thrombosis (CVST)	Ongoing and closed	Inquiry from a competent authority (Switzerland Swissmedic)	No risk	-
Lymphocytic colitis	New and closed	Scientific literature[72]	No risk	-
Chronic Urticaria	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Polymyalgia Rheumatica (PMR)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Subacute Thyroiditis (SAT)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Cerebrovascular Accident (CVA)/Stroke	New and closed	Inquiry from a competent authority (Australia TGA)	No risk	-
Amenorrhea	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-052 EPITT 19784
Heavy Menstrual Bleeding	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-053 EPITT 19783
Loss of/Altered Taste and Smell	New and closed	Inquiry from a competent authority (Australia TGA)	No risk	-
Hearing Loss	Re-opened and Ongoing	Inquiry from a competent authority	Not yet determined	-

* Reflects the MAH position and entry into MAH signal log following evaluation. This may not be the same as the position of the competent authority.

Other Safety Topics Not Considered Signals

Continued monitoring or a cumulative review was requested in an assessment report or recommended in a previous SMSR of the following unlisted events/topics that a competent

[72] Chey SW, Westerhoff M, Chey WD. Lymphocytic colitis following mRNA vaccination for SARS-CoV2, American Journal of Gastroenterology. The American Journal of Gastroenterology: October 2021 - Volume 116 - Issue - p S847, doi: 10.14309/01.ajg.0000781256.33033.83

authority did not consider a signal and were also determined to not be a safety signal by the MAH.

Factors that were considered in coming to this conclusion included one or more of the following:

- Whether the AE is new for the product;
- Seriousness, severity, increased frequency or medical significance of the data;
- High or rapidly increasing statistical disproportionality score;
- Potential public health impact;
- Factors suggestive of a relationship to the drug when considering disease knowledge, biological plausibility, mechanism of action of the drug or the drug class, alternative etiologies based on clinical and scientific experience, and temporal clustering of events.

The safety topics reviewed are the following:

Dizziness (Appendix 6A.1)

Acquired haemophilia[73] (Appendix 6A.2)

MIS-C/A (Appendix 6A.4)

Autoimmune hepatitis (Appendix 6A.5)

Glomerulonephritis/nephrotic syndrome (Appendix 6A – Signal Assessment Report EMA/PRAC/416198/2021 – EPITT 19722).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 33 summarises the important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU-RMP version 4.0 adopted on 26 November 2021 (Procedure number: EMEA/H/C/005735/X/0077).

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

[73] This was considered a signal after the DLP. Please refer to the evaluation in Appendix 6A.2.

Table 33. Ongoing Safety Concerns

Important identified risks	Anaphylaxis
	Myocarditis and Pericarditis[74]
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, the MAH submitted the EU-RMP version 5.0:

- Consolidation of the RMPs versions 2.6 (procedure EMEA/H/C/005735/II/0087) and 4.0 (Procedure number: EMEA/H/C/005735/X/0077), adopted on 10 March 2022.

After the DLP of this PSUR, the MAH submitted 3 additional EU-RMPs:

1. version 5.1 on 08 July 2022 (Procedure Number: EMEA/H/C/005735/X/0138):
    - to include the 6 months to <2 years and 2 years to <5 years phase 1 and phase 2/3 data from interventional clinical study C4591007 for the line extension of COMIRNATY® 3 µg Concentrate for dispersion for injection for infants and children between 6 months to 4 years of age;
    - to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received on March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087).
2. Version 6.0 on 19 July 2022 (Procedure Number: EMEA/H/C/005735/II/0140):
    - To support the extension of the indication to ≥12 years of age to receive an additional booster (fourth) dose of bivalent Omicron-(BA.1) modified vaccine.
3. Version 7.0 on 15 August 2022 (Procedure number: EMEA/H/C/005735/II/0143):
    - To support the extension of the indication to introduce a first or second booster dose of a bivalent Omicron variant-modified vaccine, (BNT162b2 15 µg +

[74] "Myocarditis and Pericarditis" has been added as important identified risk in the EU-RMP version 2.3 submitted on 05 August 2021; this version received a positive CHMP opinion on 30 September 2021.

BNT162b2 OMI BA.4/5 15 µg, total 30 µg), given ≥3 months after the primary series or ≥4 months after the third dose in individuals ≥12 years of age.

There are no further changes to propose with regard to the safety concerns in the EU-RMP.

16.2. Signal Evaluation

Please refer to Table 32 for signals that were ongoing and closed during the reporting interval.

Post-approval regulatory requests (worldwide)

According to the corePSUR19 guidance[75], the conclusion of the evaluation resulting from the safety review of hearing loss requested by the PRAC and Health Canada in the context of final ARs of the 13th and 14th SMSRs is summarised below; the complete review is reported in Appendix 6A.3.

Procedure no EMA/PRAC/202255/2022 (13th SMSR-2nd SBSR):
The MAH is requested to discuss the following publications regarding sudden sensorineural hearing loss (SSNHL) in association with COVID-19 vaccination:

- ✓ *Yanir Y, Doweck I, Shibli R, Najjar-Debbiny R, Saliba W. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss [published online ahead of print, 2022 Feb 24]. JAMA Otolaryngol Head Neck Surg. 2022;e214278.*

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

Furthermore, the MAH is requested to conduct age-stratified O/E analyses for the AESI of sudden hearing loss using the age-specific background incidence rates of SSNHL reported in the following publication: Alexander T and Harris J. Incidence of Sudden Sensorineural Hearing Loss. Otol Neurotol. 2013 Dec;34(9):1586-9. doi:10.1097/MAO.0000000000000222.

Procedure no. EMA/PRAC/577594/2022 (14th SMSR-3rd SBSR): *The MAH is requested to perform a cumulative review on the association between sudden sensorineural hearing loss and Comirnaty exposure, including a review of the relevant new literature published after the reporting period of the 14th SSR, and a discussion on the need to update of the Comirnaty product information and/or RMP, if applicable.*

Health Canada 31 May 2022 (13th SMSR-2nd SBSR): *The WHO recently published an update regarding COVID-19 vaccines and hearing loss. Signal detection activities at the*

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

UMC up to 22 Feb 2022 retrieved 164 cases with HLT Hearing losses (142 cases for Comirnaty) and 367 cases with the PT Tinnitus (293 for Comirnaty) with COVID-19 vaccines. Based on well documented cases, alternative causes were not identified for most of the patients and a plausible mechanism of action has been suggested. As such, provide a cumulative review of all cases of tinnitus and hearing loss. This cumulative review should include analyses of all cases, stratified by age, gender, doses administered, time to onset, and any other relevant information. An observed-to-expected analysis should be provided including the appropriate risk window. An appropriate case definition including a causality assessment should also be provided.

Conclusion

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

16.2.1. Evaluation of Closed Signals

Table 34 provides the evaluation of the signals closed during the reporting period.

Table 34. Evaluation of Closed Signals During the Reporting Interval

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

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	the second dose, and regardless of vaccine type. Observed to expected analyses conducted were below 1. Based on the totality of available information, a causal association between BNT162b2 and haemolytic anaemia could not be concluded, and the signal was closed by the MAH.
Uveitis	Uveitis was identified as a signal during the reporting period based on a competent authority (Health Canada) request for a cumulative review. The Pfizer safety database search through 04 April 2022 yielded 538 cases, 121 of which were medically confirmed and did not report confounding factors or an implausible time to onset. Of these, 9 were determined to have a possible causality based on individual assessment. During the placebo-controlled period in the pivotal clinical trial C4591001, one case was reported in the placebo group and no cases were reported in the BNT162b2 group from Dose 1 to 1 month after Dose 2. The medical literature consisted of case reports and case series descriptions with one population-based study estimating the prevalence rates of uveitis coincident with COVID-19 vaccination as 0.9 cases per million doses or less. Observed to expected analyses conducted using both a low and high range of background rates were well below 1 overall, by dose and within age and sex strata. Based on the totality of available information, a causal association between BNT162b2 could not be concluded, and the signal was closed by the MAH.
Exacerbation and/ or flare of underlying autoimmune disease or inflammatory disorders	A cumulative review of autoimmune and inflammatory disorder exacerbations was requested in an updated PSUR Assessment Report received from EMA/PRAC during the reporting period (30 December 2021). The search of the safety database used SMQ Immune-mediated/autoimmune disorders (narrow terms), HLGT Autoimmune disorders, HLGT Immune disorders NEC and HLT Neuromuscular junction dysfunction. There were 2223 cases describing a medical history and adverse event of an autoimmune disease (indicating a potential exacerbation). Overall, cases lacked information to ascertain baseline disease status, treatment and other factors which may affect underlying disease activity, despite most reporting exacerbations or potential relapses within 2 days of vaccination. In the placebo-controlled portion of pivotal clinical trial C4591001, 2955/21926 BNT162b2 participants and 2977/21921 placebo participants had underlying autoimmune conditions. Of these, 7 (0.2%) and 4 (0.1%) of BNT and placebo participants, respectively, reported potential aggravations of their autoimmune disorder from Dose 1 to 1 month post Dose 2. From Dose 1 to unblinding, 8 participants in each group (IR/100 person years = 0.7) reported potential aggravations. The medical literature search yielded many studies of COVID-19 vaccination in patients with underlying autoimmune disorders. The findings consistently showed that reported post-vaccination adverse events were similar to those of healthy vaccinees. Most studies did not have control groups of participants with autoimmune disorders who did not receive COVID-19 vaccination, although those that did, did not report that vaccinees had more exacerbations than non-vaccinees. Based on the totality of the available information, a causal association between BNT162b2 and autoimmune disorder exacerbations could not be concluded, and the signal was closed by the MAH.
Capillary leak syndrome (CLS)	Capillary leak syndrome, or Systemic capillary leak syndrome (SCLS), was identified as a signal by PRAC on 13 January 2022. The safety database search yielded 44 cases, 2 of which were literature case reports, which occurred in individuals from 20 to 101 years of age. Four cases described a medical history of CLS. The majority of cases lacked clinical details or provided evidence of an alternative aetiology other than vaccination. There were no reported events of CLS in the placebo (21921) or BNT162b2 group (21926) in the placebo-controlled portion of C4591001 in participants 16 years and older from dose 1 to 1 month

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	after dose 2. The medical literature has described cases of CLS occurring after COVID-19 infection and there were only individual case reports of CLS occurring after COVID-19 vaccination. Based on the totality of the available information, a causal association between BNT162b2 and CLS/SCLS could not be concluded, and the signal was closed by the MAH.
Corneal graft rejection	Corneal graft rejection was identified as a signal by PRAC on 07 April 2022. The safety database search through 14 April 2022 yielded 42 potential cases describing 40 unique individuals, all adults or elderly. There was no distinguishing trend in the cases with regard to sex, age, dose number, age of graft or time to onset. Of 12 cases with a plausible temporal relationship to vaccination, only 2 did not have reported risk factors for rejection (e.g., increased age of transplant, possible infection, graft surgery complications). Data from large clinical studies C4591001 (snapshot date of 11 April 2022), C4591031 (cut-off date of 08 February 2022) and C4591007 (cut-off dates of 08 October 2021 and 22 March 2022) were searched for PTs, corneal graft rejection and corneal graft failure. Neither of these PTs were reported in the unblinded data from the placebo-controlled portions of the studies. There were 32 clinical trial participants, all ≥16 years of age, who reported a history of corneal transplant or keratoplasty in either Study C4591001 and/or Study C4591031. There were no participants in C4591007 who reported a history of corneal transplant or keratoplasty. The medical literature consisted of case reports which were included in the safety database. There were no mechanistic studies, rather various hypotheses were theorized such as increased vascular permeability, immune responses and immune system deregulation. Based on the totality of the available information, a causal association between BNT162b2 and corneal graft rejection could not be concluded, and the signal was closed by the MAH.
Vasculitis	During the reporting period, vasculitis was reviewed initially following a signal noted by the Lareb (Netherlands) and through 15 April at the request of PRAC in the Assessment Report for SBSR 2. Through 15 April 2022, a search of the safety database yielded 868 reports with individual ages ranging from 2 to 98 years. Reported vasculitides included vasculitis (not otherwise described), giant cell arteritis and Henoch-Schonlein purpura. The cases were generally confounded or lacked necessary details to confirm the diagnoses and/or a causal relationship. Phase 2/3 Study C4591001 placebo-controlled unblinded adverse events in participants 16 years and older from Dose 1 to 1 month after Dose 2 (data cutoff date 13 March 2021) was also reviewed for the PT Vasculitis. In the Phase 2/3 safety population, vasculitis was not reported in any of 21926 participants in the BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) group or in any of 21921 participants in the placebo group. Observed to expected analyses for the 3 most common subtypes of vasculitis (Henoch-Shonlein purpura, Giant cell arteritis, Skin manifestations of vasculitis) have repeatedly been less than one. Based on the totality of the available information, a causal association between BNT162b2 and vasculitis could not be concluded, and the signal was closed by the MAH.
Cerebral venous sinus thrombosis (CVST)	Previous to the current PSUR reporting period, a cumulative review of CVST through 24 November 2021 was conducted by the MAH (SBSR 2, Appendix 3.4) in response to a request from a competent authority (Swissmedic). In the SBSR 2 PRAC Assessment Report, the MAH was requested to provide more detail on some of the cases and a further cumulative review of the topic. A search of the safety database yielded 527 cases that were reported through 24 November 2021 and 297 from 25 November 2021 to 15 April 2022. Of 37 cases in patients younger than 75 years of age with no medical history or information portending an increased risk for the development reported through 24 November 2021, only 3 were assessed as possible (the remaining were unassessable or unlikely per the WHO-UMC case

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	causality criteria). In the interim update through 15 April 2022, the majority of the 297 cases lacked necessary detail for assessment, had implausible time to onset or described known risk factors (other than vaccination) for the development of CVST. When analyzed by age category, the cases were largely unassessable due to lack of sufficient detail for full assessment. Overall, the assessment of AE reports was that the clinical characteristics of the cases, when provided, were aligned with the known profile of CVST. There was 1 event of CVST in a clinical trial participant who received placebo in pivotal clinical trial C4591001. Retrospective epidemiological studies of CVST after vaccination with BNT162b2 did not conclude an increased risk due to the vaccine and a retrospective analysis of 213 post-vaccine CVST cases did not demonstrate a clinically distinct profile of CVST after mRNA vaccination that differed from historical controls. Another large study showed an increased risk of CVST associated with COVID-19 compared to individuals with influenza or following COVID-19 vaccination with an mRNA vaccine. Observed to expected analyses have been conducted for CVST and when low background rates are used, the ratios are >1 in various age and sex strata. This is not seen when using higher background rates. The variation in reported background rates was notable it is possible that the delivery of healthcare, population demographics and underlying health status of the populations used for the background rate estimates differ from those in the vaccinated population. Based on the totality of the available information, a causal association between BNT162b2 and CVST could not be concluded, and the signal was closed by the MAH.
Lymphocytic colitis	During the reporting period, this signal was identified from a published (literature) case report of a 69-year-old woman who presented for evaluation of severe abdominal pain, nausea, and diarrhea after her second vaccination with Pfizer/BNT COVID-19 vaccine. Within 24 hours of vaccination, she reported onset of diarrhea (2-3 loose to watery stools per day). Symptoms intensified over the next several days to 3-5 watery stools per day with incontinence, abdominal cramping, and nausea. GI PCR and COVID testing were negative and ondansetron and loperamide were started with minimal benefit. Two-months later, a GI consultation was obtained due to persistent symptoms. Work up demonstrated no anemia with normal CRP, celiac serologies, and GI PCR. Colonoscopy on day 98 post-onset revealed patchy erythema in the descending colon and rectosigmoid. Histologic evaluation of mucosal biopsies revealed lymphocytic colitis characterized by numerous lymphocytes infiltrating the epithelium and abundant plasma cells in the lamina propria. A previous colonoscopy performed in 2012 was unremarkable. At her most recent follow-up on day 113 post-onset, the patient reported gradual improvement of abdominal symptoms and diarrhea. This case report was recorded in the Pfizer safety database. There was no other relevant literature information on lymphocytic colitis and COVID-19 vaccination. A search of the safety database through 20 Jan 2022 yielded 40 cases for review (incl index case); in all the cases, there was either no Pfizer/BNT COVID-19 vaccine used, an unconfirmed diagnosis, lack of clinical detail, or the presence of alternative explanations or risk factors for lymphocytic colitis. Based on the totality of the available information, a causal association between BNT162b2 and lymphocytic colitis could not be concluded, and the signal was closed by the MAH.
Chronic urticaria	This signal was identified following a request for a cumulative review on the subject from EMA PRAC on 09 May 2022. A search of the Pfizer safety database through 09 May 2022 yielded 244 cases; 31 of which described medical histories of chronic urticaria. Of the cases of new onset chronic urticaria, time to onset ranged from 0 to 90 days post vaccination, cases were reported after dose 1, dose 2

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	and booster doses, 26 cases described the background of underlying autoimmune disorders, 26 reported hypersensitivity conditions and 14 reported histories of COVID-19. In all, 35 cases specifically reported that the urticaria lasted more than 6 weeks (meeting criteria for chronic urticaria). Sixteen of these reported a time to onset that was reasonably temporally associated with vaccination, and among them only 7 (43.7%) of the cases provided a medical history (85.7% of which implied a predisposition to urticaria or an alternate trigger for it). During the placebo-controlled unblinded period of pivotal study C4591001 (data cut-off 15 April 2022), of participants 12 years and older, chronic urticaria was not reported in any of the 23,068 participants in the BNT162b2 group or the 23,063 participants in the placebo group from Dose 1 to data cutoff date. Observed versus expected analyses were < 1 overall, by dose and within strata of age groups. The MAH considers urticaria as an adverse reaction of BNT162b2, however, a causal association between the vaccine and chronic urticaria was not supported based on the available information.
Polymyalgia rheumatica (PMR)	This signal was identified following a request for a cumulative review on the subject by EMA PRAC in the PSUR 1 Assessment Report. A search of the Pfizer safety database through 18 December 2021 yielded 628 cases, the majority of which were excluded from further consideration due to implausible time to onset, medical history or conditions confounding assessment or lack of clinical detail supporting the diagnosis of PMR. Of the reports providing laboratory data (CRP and/or ESR) supportive of the diagnosis of PMR, most were unassessable or unlikely per WHO-UMC causality criteria. The 54 cases reporting an exacerbation of PMR following vaccination were similarly hindered by lack of information. There were no reports of PMR in the pivotal Phase 2/3 Study C4591001 of individuals 16 years of age (21926 vaccine/21921 placebo) and older from Dose 1 to 1 month after Dose 2 that was placebo-controlled (data cutoff date 13 March 2021). Ten subjects reported polymyalgia rheumatica in the medical history and none of these subjects reported a flare up of the underlying disease. The medical literature search yielded several studies that did not support an association between vaccination and autoimmune disorders or flares. Based on the totality of the available information, a causal association between BNT162b2 and PMR could not be concluded, and the signal was closed by the MAH.
Subacute thyroiditis	This signal was identified following a request for a cumulative review on the topic by EMA PRAC on 18 January 2022 following the assessment of PSUR 2. The Pfizer safety database search yielded 498 cases through 18 December 2021. There was a similar number of cases reporting each of the PTs: Thyroiditis subacute, Autoimmune thyroiditis and Thyroiditis. The majority of reports described underlying thyroid disorder or concomitant disorders that represented confounding factors and/or did not provide a sufficient amount of information (medical history, laboratory and other diagnostic data) to allow a proper evaluation. The details of 38 cases that included laboratory work ups confirming hyperthyroid activity, did not provide enough relevant information to confirm the causal association with the vaccine. In the placebo-controlled portion of clinical trial C4591001, in the safety population of participants 16 years and older, there was 1 case of autoimmune thyroiditis reported among 21926 participants in the BNT162b2 group compared with 1 case of autoimmune thyroiditis among 21921 participants in the placebo group from dose 1 to 1 month after dose 2 (data cutoff date 13 March 2021). The medical literature consisted of case reports and case series of patients who developed thyroiditis following vaccination with various COVID-19 vaccines, including BNT162b2. Observed to expected analyses were conducted and ratios were below 1 for all age groups, doses and gender strata. Based on the totality of

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	the available information, a causal association between BNT162b2 and subacute thyroiditis could not be concluded, and the signal was closed by the MAH.
Cerebrovascular accident (CVA)/Stroke	This signal was identified following a request from a competent authority (Australia, TGA) for an analysis on 27 January 2022. The Pfizer safety database search using a search strategy covering ischemic and haemorrhagic strokes, yielded 8934 cases through 18 December 2021. There were 4719 reports of females and 4024 of males, when sex was provided and the mean and median ages were 66.9 and 70 years of age, respectively. Cases were reviewed by age group. As would be expected based on the known epidemiology of stroke, the number of reported cases was highest in the oldest individuals and proportionally decreased with age; the number of ischemic strokes was greater than haemorrhagic strokes. Most of the reports described known risk factors for stroke and many of the cases in younger individuals were inconsistent with actual strokes upon individual case review. Of the 10 relevant studies in the medical literature, two studies (Shimazawa R et al [case reports] and Hippisley-Cox J et al) reported a correlative association between BNT162b2 vaccine and ischemic or haemorrhagic stroke. The study by Shimazawa R et al was based on 10 post-vaccination fatalities in Japan. Of these 10 cases, 4 females died of ICH. Insufficient details precluded further assessment. The study by Hippisley-Cox et al reported an increased risk of ischaemic stroke after a first dose of BNT162b2 but contextualized that this risk is far greater with COVID-19, emphasizing the importance of vaccination. Seven studies (Jabagi MJ et al, Simpson C.R et al, Cari L et al, Barda N et al, Koh JS et al, Klein NP et al, and Sessa M et al) did not support an association between BNT162b2 vaccine and haemorrhagic or ischemic stroke. In the remaining publication by Patone M et al, an increased risk of haemorrhagic stroke after BNT162b2 vaccination was reported in a study in England but was not replicated in a Scottish study that was somewhat smaller. Overall, the literature data does not support a clear causal association between BNT162b2 and stroke. The medical literature also did not provide a plausible mechanism for how BNT162b2 could increase the risk of haemorrhagic or ischemic strokes. All observed to expected ratios across all age, sex and dose stratifications were below 1 for haemorrhagic and ischemic strokes. Based on the totality of the available information, a causal association between BNT162b2 and hemorrhagic and ischemic stroke could not be concluded, and the signal was closed by the MAH.
Amenorrhea	Amenorrhea was identified as a signal by PRAC on 14 February 2022. A search of the Pfizer safety database through 15 February 2022 yielded 9634 reports which were mostly non-serious and non-medically confirmed. Ages ranged from 11 to 66 years (mean 33.4). Of the cases without confounders and occurring in women younger than 45 years of age, causality assessments using the WHO-UMC criteria were all unlikely or unassessable. In the placebo-controlled portion of the C4591001 study, prior to treatment assignment unblinding, there were 8 events of amenorrhoea, with an equal split of 4 events after receipt of placebo vaccination and 4 events after receipt of active vaccination. Participants were followed up for a mean period of 135.8 days following the second dose of blinded study vaccine until unblinding (median 145 days; range 85-171 days). The medical literature consisted of studies obtaining mostly self-reported data. One study of almost 4000 women in the US found COVID-19 vaccination (mostly mRNA vaccines) was associated with a < 1 day change in cycle length for dose 1 and dose 2 compared to pre-vaccine cycles. The Lareb (Netherlands) reported amenorrhoea as the most reported category of menstrual abnormalities although changes were small and quickly reversed. A retrospective study in the UK of >1200 women 18 and older did not find an association between COVID-19 vaccination and menstrual changes.

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	Based on the totality of the available information, a causal association between BNT162b2 and amenorrhea could not be concluded, and the signal was closed by the MAH. On 13 June 2022, the PRAC requested that an updated analysis of the topic be submitted in the PSUR 4.
Heavy menstrual bleeding	Heavy menstrual bleeding (HMB) was identified as a signal by PRAC on 14 February 2022. A search of the Pfizer safety database through 15 February 2022 yielded 23,659 cases of heavy menstrual bleeding. The majority are non-serious and non-medically confirmed. Of the much smaller subset of serious, medically confirmed reports that provided information about menstrual patterns, 4 were assessed as possibly related to vaccine using the WHO-UMC causality criteria as requested; one of the 4 was 1 of 2 cases that described a rechallenge. In addition, the O/E ratios do not indicate that reported events are higher than expected based on background incidence rates. In the placebo-controlled portion of the C4591001 study, prior to treatment assignment unblinding, there were 6 events of heavy menstrual bleeding; 4 of these events were after receipt of active vaccination and 2 events after receipt of placebo. The event in the C4591031 study occurred during the placebo-controlled portion of the study and was in a participant who received placebo. In the C4591001 study, participants were followed up for a mean period of 137.5 days following the second dose during the placebo-controlled follow-up period until unblinding (median 132 days; range 89 – 176 days). The participant in the C4591031 study was followed up for 96 days from blinded study vaccine (placebo) until unblinding. The medical literature on the topic reveals that menstrual abnormalities in general are very common and there have been correlations between SARS-CoV-2 pandemic stress, anxiety, and depression with menstrual cycle abnormalities[76]. A clear pathophysiological mechanism for heavy menstrual bleeding itself is not understood. A well-designed US study of self-reported menstrual cycle data by Alison Edelman et al. did not support a significant effect of vaccination on the number of days of menstrual bleeding. Studies are limited by their retrospective nature and self-reporting. While most menstruating women do not report menstrual changes associated with COVID-19 vaccination, it seems that variables such as age, BMI, changes in cycle over the previous year and the presents of fibroids and smoking may be playing a role. Based on the totality of the available information, a causal association between BNT162b2 and HMB could not be concluded, and the signal was closed by the MAH. On 13 June 2022, the PRAC responded with a list of questions that the MAH is in the process of preparing for submission by 24 August 2022.
Loss of/altered taste and smell	This was identified as a signal during the reporting period following a request for a competent authority (Australia, TGA) for an analysis of the topic. A search of the safety database through 01 March 2022, yielded 12,140 potentially relevant cases (1% of all AE reports for BNT162b2). There were 17 fatal cases all unrelated to vaccination but related to intercurrent diseases. To enable a focused review of the most informative cases, the MAH applied an exclusion algorithm focusing on serious and medically confirmed cases, excluding most confounding conditions and concomitant medications which could have contributed to the events. The identified 154 were further reviewed. 76 cases had insufficient information to make a thorough medical evaluation. 67 cases had alternative explanations or confounding factors which could have contributed to the events and there were 11 remaining cases, only five out of the 11 cases where judged "possible related"

[76] Takmaz, T et al. The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers. J Obstet Gynaecol Res 2021 47(9):3241-3249.

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
	according to WHO causality assessment. There were no cases with a probable or definite relationship. Review of post-marketing data did not support a causal relationship between vaccination with BNT162b2 and the development of taste and smell disorders. Based on the mid-range background rates from ACCESS, O/E ratios were greater than 1 overall for all ages globally using the 7-day risk window. Using both mid- and high-range ACCESS background rates, the O/E ratios were >1 for certain age groups using both the 7- and 21-day risk windows, suggesting that the number of reported cases may be higher than expected compared to unvaccinated persons The O/E ratios for these events may be overestimated for a few reasons. First, these pre-COVID (2017-2019) background rates from ACCESS reflect the incidence of anosmia and/or ageusia that was treated in either an inpatient or outpatient setting. Given that these symptoms may be mild in some cases, these rates might underestimate the overall incidence (and thus expected cases) of these conditions in a general, unvaccinated populations if not all cases are reported to healthcare providers. Second, they may also underestimate the incidence rate during the COVID-era since anosmia and/or ageusia are symptoms of SARS-COV-2 infection. For example, the reported incidence rates for anosmia/ageusia were 1.4-2.3 times higher in 2020 than during 2017-2019 in both of the ACCESS sources used for background estimates. In 2020, the ES_SIDIAP_PC database rate was 35.23/100,000 persons per year, and in the ES-FISABIO database the rate was 67.5/100,000 persons per year. Third, observed cases may include cases of anosmia or ageusia due to recent or current SARS-COV-2 infection that was not documented or diagnosed during the risk window period. Fourth, due to the unprecedented attention to COVID-19 vaccination and outreach to encourage AE reporting, the long-held assumption that reported cases are an underestimation of actual cases may be incorrect. Finally, the ACCESS rates for anosmia and ageusia were defined with ICD codes that captured anosmia, parosmia, and parageusia, while the observed case definition included PTs for additional related conditions. In the pivotal clinical trial C4591001, during the placebo-controlled follow up period from Dose 1 to 1 month after Dose 2 of BNT162b2, 17 events of interest were reported in the vaccine group (N=21926) and 10 in the placebo group (N=21921) in participants ≥ 16 years of age. None of the 5 relevant PTs were reported by 12-15 year old from Dose 1 to 1 month post-Dose 2 in C4591001. None of the 5 PTs were reported by 5 to <12 year old from Dose 1 to 1 month Dose 2 in C4591007. There was a limited amount of medical literature on this topic and it was not supportive of a known relationship between vaccination and loss of taste or smell. Based on the totality of the available information, a causal association between BNT162b2 and anosmia and ageusia could not be concluded, and the signal was closed by the MAH.
Important Risks	
Myocarditis and Pericarditis	During the reporting period, myocarditis and pericarditis, which have been considered important identified risks in the US-PVP and EU-PVP, were moved from important potential risks to important identified risks in the company core list of safety concerns. After the DLP of this PSUR, they were also added as adverse reactions to the company CDS v. 14.0 dated 26 July 2022 (Section 4.8, Appendix A and Appendix B). The changes to the core list of safety concerns and CDS were made based on the summation of data that has accumulated in the surveillance of this issue, including the published incidence and reporting rates from multiple sources with consistent findings.

Table 34. Evaluation of Closed Signals During the Reporting Interval

Signal	Evaluation
Risks Not Categorized as Important	
Irritability	During the reporting period, placebo-controlled safety data from Clinical Trial C4591007 was unblinded for submission to regulatory authorities to support authorisation of vaccination in individuals 6 months to < 5 years of age. Irritability was the most frequently reported systemic event reported within 7 days after each of the 3 doses of BNT162b2 (3 µg) for the 6 months to < 2 years age group. Irritability was reported by 51.2%, 47.4% and 43.6% of participants in the BNT162b2 group and 47.2%, 40.7% and 37.6% in the placebo group, after dose 1, 2 and 3, respectively. Based on these data, irritability was determined to be an adverse reaction for the age group 6 months to < 2 years.

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 35. Signal Evaluation Plan for Ongoing Signals

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

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 part of the AR of the 2nd PSUR (Procedure number EMEA/H/C/PSUSA/00010898/202112), the following request was received:

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

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. [77]

Clinical Trial Data

- Number of cases: 3 (0.45% of 668 cases of the total CT dataset), compared to 2 cases (0.28%) retrieved in the PSUR #2.

The investigator and the Sponsor reported that there was not a reasonable possibility that the events anaphylactic reactions in all cases were related to the blinded study vaccine/BNT162b2, or clinical trial procedure. In 2 cases the anaphylaxis reactions were associated with food allergies and in the remaining case anaphylaxis reaction was attributed to another product (etoricoxib).

Post-Authorisation Data

- Number of cases: 1037 (0.20% of 507,683 cases, the total PM dataset), compared to 3507 cases (0.53%) retrieved in the PSUR #2.
- MC cases (690), NMC cases (347).
- Country of incidence (top 10): Japan (184), Germany (158), Australia (113), UK (105), US (59), Poland (48), France (47), New Zealand (41), Philippines (26), and Sweden (24); the remaining 232 cases were distributed among 34 countries.
- Subjects' gender: female (768), male (219) and unknown (50).
- Subjects' age in years: n = 949, range: 5 - 99, mean: 40.2, median: 40.0.
- Medical history (n = 422): the most frequently (≥ 10 occurrences) reported medical conditions Asthma (90), Food allergy (83), Drug hypersensitivity (66), Hypersensitivity (55), Hypertension (42), Seasonal allergy (38), Anaphylactic reaction (30), COVID-19 (21), Mite allergy (20), Allergy to arthropod sting (19), Allergy to animal (14), Dermatitis contact (14), Contrast media allergy (12), Mast cell activation syndrome (12), Multiple allergies (12), Diabetes mellitus (11), Urticaria (11), Allergy to chemicals (10), Anaphylactic shock (10), Migraine (10), Obesity (10), and Rubber sensitivity (10).
- COVID-19 Medical history (n = 22): COVID-19 (21), Suspected COVID-19 (3), and Post-acute COVID-19 syndrome (1).
- Co-suspects (n = 21 cases): Relevant co-suspect vaccines/medications reported more than once were: adalimumab, herbal pollen NOS, JNJ 78436735 (2 each).
- Number of relevant events: 1073.
- Relevant event seriousness: serious (1073).

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

- Reported relevant PTs: Anaphylactic reaction (802), Anaphylactic shock (238), Anaphylactoid reaction (33).
- Time to event onset (n = 781), range: <24 hours to 365 days, median: 0 days.
  - <24 hours: 659 events (6 of which had a fatal outcome);
  - 1 day: 46 events;
  - 2-7 days: 36 events;
  - 8-14 days: 14 events;
  - 15-30 days: 8 events;
  - 31-180 days: 17 events;
  - > 181 days: 1 event.
- Duration of relevant events (n = 249 out of 1037 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 246 days, median 0 days.
  - <24 hours: 152 events;
  - 1 day: 47 events;
  - 2 - 7 days: 38 events;
  - 8-14 days: 3 events;
  - 15-31 days: 3 events;
  - 32-181 days: 4 events;
  - > 181 days 2 events.
- Relevant event outcome[78]: fatal (8[79]), resolved/resolving (647), resolved with sequelae (23), not resolved (134), unknown (263).

Of the 7 cases reporting relevant events with fatal outcome, 4 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. The remaining 3 cases are described below.

In a non-medically confirmed case, a 96-year-old male subject became "ill" 35 minutes following BNT162b2 vaccination (unknown dose number). The subject was found collapsed in parked car and resuscitation was attempted. According to the coroner, the subject died of anaphylaxis reaction. Ischaemic heart disease and old age were secondary causes.

An 80 -year- old female subject fainted while shopping about 39 minutes after dose 1 and, despite resuscitation, died at the hospital. Her primary physician reported that she was treated at the cardiology clinic but had not had an ordered ECG and had stopped taking her

[78] 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.

[79] Of note, after the DLP, 2 fatal cases were found to be duplicates and one of them was made invalid. Excluding the invalid case, there were 7 cases reporting events with a fatal outcome.

antihypertensive medication. Autopsy results noted that the primary cause of death was atherosclerosis and secondary cause was aortic aneurysm dissection to the pleural cavities.

A 67- year- old male subject with a history of diabetes and idiopathic thrombocytopenic purpura on multiple medications, received dose 3 and less than 30 minutes later presented to the hospital with chest and GI discomfort. His systolic blood pressure was 72 and a diagnosis of anaphylaxis was made. He was given adrenaline with no response and shortly thereafter an ECG showed signs of a myocardial infarction. He was transferred to another hospital for treatment but had a cardiac arrest during angiography. He remained hospitalised until he died due to mesenteric ischemia 12 days post vaccination.

Of the 433 cases reporting medical history/co-suspects, 324 cases reported relevant medical history/risk factors (e.g., asthma, drug hypersensitivity, food allergies, autoimmune disorders, hypersensitivity, prior anaphylactic reactions) and/or co-suspect (e.g., adalimumab, infliximab, influenza vaccine inact SAG 4V, herbal pollen NOS, JNJ 78436735, immunoglobulin human normal), which may have contributed to the anaphylaxis related events.

Analysis by age group

PM: Paediatric (120), Adults (751), Elderly (80) and Unknown (86).

- No significant difference was observed in the reporting proportion of anaphylaxis relevant PTs between paediatric, adult and elderly populations (0.38% in paediatric vs 0.21% in adults vs 0.14% in elderly).

Analysis by presence of comorbidities[80]

Number of subjects with comorbidities: 181 (17.5% of the cases reporting anaphylaxis).

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

Literature Data

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

O/E Analysis

O/E analysis was performed for Anaphylaxis (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

[80] CT and PM pooled data.

Risk Assessment of New Information

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

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

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

This risk will continue to be monitored through routine pharmacovigilance.

16.3.1.2. Important Identified Risks – Myocarditis and Pericarditis

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

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.

Literature Data

During the reporting period an unpublished presentation including significant information on myocarditis was reviewed. Please refer to Section 11 *Literature* for details.

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".[81]

This risk will continue to be monitored through routine pharmacovigilance.

16.3.1.2.1. Important Identified Risks – Myocarditis

Search criteria[82] - PTs: Autoimmune myocarditis; Carditis; Chronic myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myopericarditis; Myocarditis.

Overall - All Ages

Clinical Trial Data

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

---

[81] Myocarditis and pericarditis are listed in Section 4.8 of the EU-SmPC and have been added as ADRs in Section 4.8, Appendices A and B of the CDS v. 14.0 made effective on 26 July 2022, after the DLP of this PSUR (please refer to Section 4 *Changes to Reference Safety Information* and Section 14 *Late-breaking Information*).

[82] The SMQ (narrow) Noninfectious myocarditis/pericarditis that became available upon the upversioning to MedDRA v. 25.0 is used as search criteria. Three new PTs (Carditis, Chronic myocarditis and Myopericarditis) are included in the search criteria for myocarditis, compared to the criteria specified for myocarditis in the EU-RMP v 4.0, used in the previous PSUR.

Post-Authorisation Data

- Number of cases: 5422 (1.1% of 507,683 cases of the total PM dataset), compared to 6347 cases (1.0%) retrieved in the PSUR #2.[83]
- Country/region of incidence (≥10): Germany (1342), UK (1230), Australia (509), France (344), Taiwan, Province Of China (280), Canada (216), Austria (193), Japan (163), Italy (151), Sweden (119), US (118), New Zealand (107), Greece (77), Israel (64), Finland (51), Spain (45), Netherlands (44), Hong Kong (41), Poland (35), Belgium, Denmark (29 each), Switzerland (25), Norway, Portugal (24 each), Malaysia (22), Ireland (21), Czech Republic (16), Brazil (15), Romania (10). The remaining 78 cases were distributed among 25 countries.
- MC (2710), NMC (2712).
- Subjects' gender: female (1997), male (3307) and unknown (118).
- Subjects' age in years: n = 4981, range: 6 -98, mean: 35.3, median: 32.
- Medical history (n = 1699): the most frequently (≥50 occurrences) reported medical conditions included Hypertension (214), Asthma (140), Seasonal allergy (130), Tobacco user (96), Drug hypersensitivity (67), Immunodeficiency (64), Obesity (62), Hypothyroidism, Non-tobacco user (59 each), and Food allergy (58).
- COVID-19 Medical history (n = 371): COVID-19 (191), Suspected COVID-19 (179), Post-acute COVID-19 syndrome (9), SARS-CoV-2 test positive (6), Asymptomatic COVID-19 (2), Coronavirus infection, COVID-19 pneumonia, COVID-19 treatment (1 each).
- Co-suspect vaccines/medications (>1 occurrence): COVID-19 vaccine mRNA (MRNA 1273) (10), influenza vaccine (5), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (4), adalimumab, COVID-19 vaccine, and pembrolizumab (2 each).
- Number of relevant events: 5458.
- Relevant event seriousness: serious (5458).
- Reported relevant PTs: Myocarditis (4639), Myopericarditis (697), Carditis (113), Eosinophilic myocarditis (4), Giant cell myocarditis, Hypersensitivity myocarditis (2 each), and Immune-mediated myocarditis (1).
- Relevant event outcome[78]: fatal (87), resolved/resolving (1925), resolved with sequelae (160), not resolved (1608), unknown (1682).
- Of the 5422 cases, in 1108 cases (20.4% of the cases reporting myocarditis related events) the events were confounded by subject' s relevant medical history (1016 cases; e.g., COVID-19, seasonal allergy, tobacco user, drug hypersensitivity, food allergy, myocarditis, mite allergy, autoimmune thyroiditis, cardiac failure, allergy to animal,

[83] During the reporting period of PSUR #2 there were 6347 events of myocarditis: Eosinophilic myocarditis (4), Autoimmune myocarditis, Hypersensitivity myocarditis (3 each), Immune-mediated myocarditis (1).

overweight, alcohol use, cardiac disorder, pericarditis, allergy to metals, breast cancer, chemotherapy, allergy to plants, dust allergy, rheumatoid arthritis, influenza, myopericarditis, systemic lupus erythematosus, mycotic allergy, radiotherapy, allergy to arthropod sting, allergy to chemicals, Epstein Barr virus infection, autoimmune disorder, Lyme disease, rheumatic disorder) and/or relevant co-suspect/concomitant medications (92 cases; e.g., influenza vaccine, isotretinoin, mesalazine, olanzapine, quetiapine, rituximab, cyclophosphamide, epirubicin, hepatitis B vaccine RHBSAG (yeast), minocycline, norepinephrine, sulfasalazine, zuclopenthixol, COVID-19 vaccine mRNA (mRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), COVID-19 vaccine, pembrolizumab, clozapine, hepatitis A vaccine, influenza vaccine INACT SAG 3V, ipilimumab, JNJ 78436735, nivolumab). Of the 5422 cases, 236 cases involved elderly (age >70 years) subjects and 61% cases involved male subjects.

Age-stratified data[84]

Subjects aged less than 5 years

Clinical Trial Data

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

Post-Authorisation Data

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

Subjects aged 5 - 11 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 48 cases (0.01 % of 507,683 cases of the total PM dataset; 0.6 % of the 8375 subjects aged 5-11 years); 10 cases (0.002%) were retrieved in the PSUR #2.
- Country/region of incidence: Australia (15), Canada, Japan (6 each), Italy, Portugal, Spain (3 each), Greece, Taiwan, Province of China (2 each), Austria, Denmark, Finland, France, New Zealand, Philippines, UK, US (1 each).
- Subjects' age in years: n = 48, range: 6 – 11, mean: 9.2, median: 9.5.
- Medical history (n = 8): Asthma, Atrioventricular block, Attention deficit hyperactivity disorder, Autoimmune thyroiditis, Cardiac failure, Cerebral palsy, Condition aggravated, Dependence on respirator, Ejection fraction decreased, Hypoxic-ischaemic encephalopathy, Intellectual disability, Motor dysfunction, Myocarditis, Neonatal

[84] Cases where the age was reported as Child (3 cases), Adolescent (23 cases), Adult (103 cases) and Elderly (11 cases) are included in the subgroup of Age Unknown age and in the overall.

asphyxia, Non-tobacco user, Obesity, Respiratory tract infection, Rhinitis allergic, Type 1 diabetes mellitus (1 each).

- COVID-19 Medical history (n = 4): COVID-19 (4).
- Co-suspect vaccine/medications: None.
- Most frequently co-reported PTs (>5 occurrences): Chest pain (28), Dyspnoea, Pyrexia (10 each), Troponin increased (7), Chest discomfort, Electrocardiogram abnormal, Tachycardia (6 each).

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

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

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

An 11-year-old female subject from [redacted]:

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

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

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

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

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

Subjects aged 12 - 15 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 366 (0.07 % of 507,683 cases of the total PM dataset; 2.7 % of the 13,366 subjects aged 12-15 years), compared to 488 cases (0.07% of all cases in the total PM dataset) retrieved in the PSUR #2.
- Country/region of incidence (≥10): Taiwan, Province of China (87), Germany (64), UK (30), Australia, Japan (23 each), Canada (18), France (15), Italy (14), Israel, Malaysia (11 each), Hong Kong (10). The remaining 60 cases were distributed among 20 countries.
- Subjects' age in years: n = 366, range: 12-15.3, mean: 13.9, median: 14.

- Medical history (n = 72): the most frequently (≥2 occurrence) reported medical conditions included Asthma (7), Attention deficit hyperactivity disorder, Food allergy, Obesity, Seasonal allergy (4 each), Glucose-6-phosphate dehydrogenase deficiency, Hypersensitivity, Migraine, Non-tobacco user, Pericarditis, Rhinitis allergic (3 each), Anxiety, Autism spectrum disorder, Childhood asthma, Cough, Dermatitis atopic, Mite allergy, Pneumonia, Prophylaxis, Tonsillectomy (2 each).

- COVID-19 Medical history (n = 11): COVID-19 (9), Suspected COVID-19 (2), Post-acute COVID-19 syndrome (1).

- Co-suspect vaccine/medications: None.

- Most frequently co-reported PTs (>5 occurrences): Chest pain (174), Pyrexia (80), Chest discomfort (64), Dyspnoea (60), Headache (39), Palpitations (36), Pericarditis (34), Fatigue (31), Tachycardia (25), Inappropriate schedule of product administration, Troponin increased (23 each), Vomiting (20), Electrocardiogram ST segment elevation (18), Dizziness, Nausea (17 each), Malaise (16), C-reactive protein increased (15), Myalgia, Troponin I increased (14 each), Cough (13), Asthenia, Off label use, Pain in extremity (11 each), Blood creatine phosphokinase MB increased, Vaccination site pain (10 each), Chills (9), Blood creatine phosphokinase increased, Diarrhoea, Pain (8 each), Decreased appetite, Immunisation, Pericardial effusion, Syncope (7 each), Arthralgia, Electrocardiogram abnormal, Heart rate increased, Multisystem inflammatory syndrome in children, Nasopharyngitis (6 each).

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

A 13-year-old male subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardiac failure, Myocarditis.
- Time to onset (myocarditis): 69 days after dose 2.
- Causes of death: Cardiac failure; Myocarditis.
- Autopsy: Not reported if autopsy was performed.

A 13-year-old male subject from [redacted]:

- Medical history: Abdominal pain, Chest pain.
- Co-suspect medications: None.
- PTs with fatal outcome: Anuria, Asthenia, Cardiac arrest, Compartment syndrome, Enterovirus infection, Malaise, Multi-organ disorder, Multiple organ dysfunction syndrome, Myocarditis, Pulseless electrical activity, Renal failure, Rhinovirus infection, Ventricular tachycardia.
- Time to onset (myocarditis): 5 days after dose 2.

- Causes of death: Asthenia; Cardiac arrest; Compartment syndrome; Enterovirus infection; Malaise; Multi-organ disorder; Myocarditis; Pulseless electrical activity; Renal failure; Rhinovirus infection; Ventricular tachycardia.
- Autopsy: Not reported if autopsy was performed.

A 13-year-old female subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): 6 days after dose 1.
- Causes of death: Myocarditis.
- Autopsy: Adverse event following immunisation.

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

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

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

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

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Duration of event[b] n=39, median=7 days	Up to 3 days	3	8	0
	4-6 days	0	6	0
	7-25 days	4	11	0
	26-134 days	2	5	0

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

Subjects aged 16 - 17 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 345 (0.07 % of 507,683 cases of the total PM dataset; 4.2 % of the 8313 subjects aged 16-17 years), compared to 470 cases (0.07%) retrieved in the PSUR #2.
- Country of incidence (≥10): Germany (88), Taiwan, Province of China (55), UK (29), Australia (18), Austria (17), France, Poland (14 each), Italy, Japan (12 each), Greece (11). The remaining 75 cases were distributed among 26 countries.
- Subjects' age in years: n = 345, range: 16 -17, mean: 16.6, median: 17.0.
- Medical history (n = 71): the most frequently (>2 occurrence) reported medical conditions included Seasonal allergy (9), Asthma, Obesity (4 each), Food allergy, Mite allergy, Nasopharyngitis, Overweight (3 each).
- COVID-19 Medical history (n = 10): COVID-19 (8), Suspected COVID-19 (2).
- Co-suspect vaccine/medications: Clonazepam, infliximab, and levomethadone (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (147), Pyrexia (72), Dyspnoea (53), Chest discomfort (43), Palpitations (34), Tachycardia (33), Fatigue (29), Headache (27), Inappropriate schedule of product administration (26), Pericarditis (24), Troponin increased (23), Dizziness, Vomiting (18 each), Malaise, Nausea (17 each), Asthenia (12), Chills, Immunisation, Off label use (10 each), Arrhythmia, Blood creatine phosphokinase increased, C-reactive protein increased, Electrocardiogram ST segment elevation, Pain in extremity, Pericardial effusion, Syncope, Troponin I increased (9 each), Cough (8), Myocardial necrosis marker increased, Pain, Troponin T increased (7 each), Angina pectoris, Back pain, Blood creatine phosphokinase MB increased, Diarrhoea, Electrocardiogram abnormal, Lethargy (6 each).

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

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

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

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

Subjects aged 18 - 24 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 968 (0.2 % of 507,683 cases of the total PM dataset, 0.18 % of the 38293 subjects aged 18-24 years), compared to 1187 cases (2.3%) retrieved in the PSUR #2.

- Country of incidence (≥10): Germany (289), UK (114), France (105), Australia (99), Taiwan, Province of China (46), Italy (43), Austria (38), Sweden (32), Japan (25), US (18), Greece, New Zealand (16 each), Israel (14), Canada, Spain (13 each), Finland (11), Denmark (10). The remaining 66 cases were distributed among 18 countries.
- Subjects' age in years: n = 968, range: 18-24, mean: 21, median: 21.
- Medical history (n = 237): the most frequently (>2 occurrence) reported medical conditions included PT Tobacco user (28), Asthma (23), Seasonal allergy (16), Myocarditis (12), Hypertension, Non-tobacco user (11 each), Immunodeficiency, Obesity (9 each), Attention deficit hyperactivity disorder (8), Hypersensitivity, Nicotine dependence (7 each), Alcohol use, Contraception, Mite allergy (6 each), Acne, Crohn's disease, Drug hypersensitivity, Migraine, Overweight, Substance use (5 each), Anaemia, Autism spectrum disorder, Epstein-Barr virus infection (4 each), Appendicectomy, Chest pain, Food allergy, Hypothyroidism, Oral contraception, Pericarditis, Pharyngitis, Psoriasis, Syncope, Wisdom teeth removal (3 each).
- COVID-19 Medical history (n = 52): COVID-19 (26), Suspected COVID-19 (22), SARS-CoV-2 test positive (3), and Asymptomatic COVID-19 (1).
- Co-suspect vaccine/medications: Drug COVID-19 vaccine, COVID-19 vaccine MRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), insulin, levothyroxine, and zuclopenthixol (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (354), Dyspnoea (168), Pyrexia (134), Pericarditis (116), Fatigue (115), Palpitations (112), Chest discomfort (104), Troponin increased (75), Tachycardia (74), Headache (61), Inappropriate schedule of product administration (59), Off label use (48), Dizziness, Immunisation (46 each), Interchange of vaccine products (38), Asthenia (33), Chills (32), Malaise, Myalgia (29 each), Angina pectoris (28), Pain, Syncope (25 each), Nausea (23), Arrhythmia, Dyspnoea exertional (21 each), Pericardial effusion (20), Influenza like illness (19), Cough, Vomiting (18 each), Pain in extremity (17), C-reactive protein increased, Heart rate increased (15 each), Electrocardiogram ST segment elevation, Hyperhidrosis, Lethargy (14 each), Electrocardiogram abnormal (13), Diarrhoea (12), Oropharyngeal pain (11), Arthralgia, Blood creatine phosphokinase increased, COVID-19, Myocardial infarction, Myocardial necrosis marker increased, Troponin I increased, Troponin T increased (10 each), Acute myocardial infarction, Paraesthesia (9 each), Abdominal pain, Abdominal pain upper, Back pain, Cardiac failure, Drug ineffective, Feeling abnormal, Inflammation, Sinus tachycardia (8 each), Hypertension, Hypoaesthesia, Limb discomfort, Lymphadenopathy, Night sweats, Pulmonary embolism, Vaccination site pain, Ventricular hypokinesia (7 each), Costochondritis, Feeling hot, Incorrect route of product administration, Insomnia, Left ventricular dysfunction, Loss of consciousness, Somnolence (6 each).

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

A 23-year-old male subject from [redacted]:

- Medical history: Non-tobacco user.
- Co-suspect medications: None.

- PTs with fatal outcome: Circulatory collapse, Endocarditis, Myocarditis, Sudden cardiac death.
- Time to onset (myocarditis): unknown days after dose 2.
- Causes of death: Circulatory collapse; Endocarditis; Myocarditis; Sudden cardiac death.
- Autopsy: Autopsy was performed, results were not provided at the time of reporting.

A 20-year-old male subject from [redacted]:

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

A 19-year-old male subject from [redacted]:

- Medical history: Asthma, COVID-19, Interchange of vaccine products, Rhinitis allergic.
- Co-suspect medications: None.
- PTs with fatal outcome: Arrhythmia, Hernia, Hypoxia, Loss of consciousness, Myocardial necrosis, Myocardial necrosis marker increased, Myocarditis, Sudden death, Ventricular hypokinesia.
- Time to onset (myocarditis): 3 days after dose 3.
- Causes of death: Arrhythmia; Hernia; Hypoxia; Loss of consciousness; Myocardial necrosis; Myocardial necrosis marker increased; Myocarditis; Sudden death; Ventricular hypokinesia.
- Autopsy: The autopsy revealed extensive necrosis of the left ventricular myocardium (myocardial necrosis); myocarditis/fulminant myocarditis.

A 23-year-old male subject from [redacted]:

- Medical history: Hypertension, Obesity.
- Co-suspect medications: None.
- PTs with fatal outcome: Death, Myocarditis.
- Time to onset (myocarditis): 16 days after dose 3.
- Cause of death: Myocarditis.
- Autopsy: Information not available.

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

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

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

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

Subjects aged 25 - 29 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 519 (0.1% of 507,683 cases of the total PM dataset, 1.2 % of the 43518 subjects aged 25-29 years), compared to 589 cases (0.09%) retrieved in the PSUR #2.
- Country of incidence (≥10): Germany (150), UK (113), Australia (54), France (39), Austria (27), Sweden, Taiwan, Province of China (17 each), Japan (14), Italy (13), New Zealand (11). The remaining 64 cases were distributed among 25 countries.
- Subjects' age in years: n = 519, range: 25-29, mean: 27.1, median: 27.
- Medical history (n = 141): the most frequently (>2 occurrence) reported medical conditions included Seasonal allergy (20), Asthma (14), Tobacco user (13), Food allergy (10), Hypertension, Mite allergy (8 each), Allergy to animal, Chest pain (7 each), Non-tobacco user (6), Hypersensitivity, Hypothyroidism (5 each), Anxiety, Depression, Drug hypersensitivity, Migraine, Myocarditis, Steroid therapy (4 each), Autoimmune thyroiditis, Contraception, Gastrooesophageal reflux disease, Polycystic ovaries (3 each).
- COVID-19 Medical history (n = 43): COVID-19 (22), Suspected COVID-19 (21), Post-acute COVID-19 syndrome (2), and SARS-CoV-2 test positive (1).
- Co-suspect vaccine/medications (n = 8): COVID-19 vaccine mRNA (MRNA 1273) (3), adalimumab, fluticasone, influenza vaccine, levothyroxine, and methylphenidate (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (217), Dyspnoea (153), Palpitations (122), Fatigue (110), Tachycardia (98), Pericarditis (88), Chest discomfort, Pyrexia (71 each), Headache (47), Immunisation (42), Dizziness (39), Arrhythmia (31), Myalgia (25), Off label use, Pain in extremity (24 each), Interchange of vaccine products, Troponin increased (23 each), Heart rate increased, Inappropriate schedule of product administration, Malaise, Pain (22 each), Angina pectoris (21), Lymphadenopathy (18), Asthenia, Nausea (16 each), Chills, Pericardial effusion (15 each), Influenza like illness, Paraesthesia, Syncope, Vaccination site pain (14 each), Arthralgia (13), Lethargy (10), COVID-19, Dyspnoea exertional, Influenza, Migraine, Vomiting (9 each), Back pain, Cardiac flutter, Heart rate irregular, Tremor (8 each), Abdominal pain upper, Blood pressure increased, Cardiac disorder, Diarrhoea, Extrasystoles, Hyperhidrosis, Peripheral swelling (7 each), Abdominal pain, Cough, Electrocardiogram ST segment elevation, Feeling abnormal, Hypertension, Inflammation, Myocardial infarction, Rash, Sleep disorder (6 each).

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

A 29-year-old male subject from [redacted]:

- Medical history: Hepatic steatosis.

- Co-suspect medications: COVID-19 vaccine mRNA (MRNA 1273).
- PTs with fatal outcome: Arrhythmia, Myocarditis.
- Time to onset (myocarditis): unknown days after dose 2.
- Causes of death: Arrhythmia; Myocarditis.
- Autopsy: Autopsy revealed arrhythmia

A 27-year-old male subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use, Chest pain.
- Time to onset (myocarditis): 10 days after dose 3.
- Causes of death: Myocarditis.
- Autopsy: Not reported if autopsy was performed

A 26-year-old male subject from [redacted]:

- Medical history: Aneurysm, Surgery, Vein of Galen aneurysmal malformation.
- Co-suspect medications: Influenza vaccine.
- PTs with fatal outcome: Myocarditis, Arrhythmia, Inflammation, Left ventricular dysfunction.
- Time to onset (myocarditis): 4 days after dose 3.
- Causes of death: Arrhythmia; Inflammation; Left ventricular dysfunction; Myocarditis.
- Autopsy: Autopsy results showed myocarditis.

A 26-year-old female subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use.
- Time to onset (myocarditis): unknown days after dose 2.
- Causes of death: Myocarditis.
- Autopsy: Autopsy results showed myocarditis.

A 27-year-old female subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis, Interchange of vaccine products, Off label use.
- Time to onset (myocarditis): unknown days after dose 2.
- Causes of death: Myocarditis.
- Autopsy: Autopsy results showed myocarditis.

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

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

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

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

Subjects aged 30 - 39 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 983 (0.2 % of 507,683 cases of the total PM dataset, 1.0 % of the 97870 subjects aged 30-39), compared to 995 cases (0.15%) retrieved in the PSUR #2.

- Country of incidence (≥10): UK (310), Germany (247), Australia (114), France (51), Austria (35), Taiwan, Province of China (33), New Zealand, Sweden (18 each), Italy, US (17 each), Finland (13), Canada, Greece (12 each), Japan (11), and Belgium (10). The remaining 65 cases were distributed among 23 countries.
- Subjects' age in years: n = 983, range: 30-39, mean: 34.3, median: 34.
- Medical history (n = 290): the most frequently (>2 occurrence) reported medical conditions included Asthma (27), Seasonal allergy (26), Hypothyroidism (18), Tobacco user (17), Immunodeficiency (14), Drug hypersensitivity (13), Hypertension, Migraine, Myocarditis, Non-tobacco user (12 each), Food allergy (11), Breast feeding, Clinical trial participant (10 each), Diabetes mellitus, Dyspnoea, Obesity, Pregnancy (9 each), Autoimmune thyroiditis, Steroid therapy (6 each), Alcohol use, Colitis ulcerative, Dust allergy, Fibromyalgia, Histamine intolerance, Hyperhidrosis, Malaise, Pain, Pericarditis (5 each), Chest pain, Coeliac disease, Depression, Headache, Lymphadenopathy, Mast cell activation syndrome, Mite allergy, Pneumonia, Polycystic ovaries, Post viral fatigue syndrome (4 each), Allergy to animal, Allergy to metals, Cardiac disorder, Crohn's disease, Drug intolerance, Fatigue, Gastrooesophageal reflux disease, Hypersensitivity, Hypophosphataemia, Lactose intolerance, Multiple sclerosis, Muscular weakness, Mycotic allergy, Myocardial infarction, Nicotine dependence, Osteoporosis, Pancreatic failure, Postural orthostatic tachycardia syndrome, Pulmonary embolism, Small fibre neuropathy (3 each).
- COVID-19 Medical history (n = 82): COVID-19 (41), Suspected COVID-19 (39), Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (1 each).
- Co-suspect vaccine/medications: Drug COVID-19 vaccine mRNA (MRNA 1273) (3), Amoxicillin, clozapine, colchicine, COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19), ipilimumab, losartan, nivolumab, propranolol (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (383), Dyspnoea (294), Palpitations (284), Fatigue (276), Pericarditis (240), Tachycardia (215), Pyrexia (128), Chest discomfort (110), Headache (104), Immunisation (100), Dizziness (92), Off label use (78), Inappropriate schedule of product administration (60), Interchange of vaccine products (58), Arrhythmia (54), Pain in extremity (51), Heart rate increased (48), Malaise, Myalgia (46 each), Pain (44), Asthenia (40), Syncope (39), Paraesthesia (38), COVID-19 (36), Drug ineffective (35), Angina pectoris, Troponin increased (34 each), Arthralgia, Hypoaesthesia (33 each), Chills, Nausea (32 each), Hyperhidrosis, Lymphadenopathy, Vomiting (25 each), Dyspnoea exertional (24), Cardiac flutter (23), Vaccination site pain (22), Cough, Feeling abnormal, Pericardial effusion (21 each), Exercise tolerance decreased (20), Discomfort, Influenza like illness (19 each), Anxiety, Back pain, Hypertension (18 each), Diarrhoea (16), Heavy menstrual bleeding, Insomnia, Neck pain (15 each), Burning sensation (14), Hypotension, Loss of personal independence in daily activities, Oropharyngeal pain (13 each), Heart rate irregular, Menstruation irregular, Presyncope, Product use issue (12 each), Cardiac discomfort, Condition aggravated, Extrasystoles, Inflammation, Lethargy, Muscle twitching, Myocardial infarction, Pulmonary oedema, Rash (11 each), Cardiac disorder, Cardiomegaly, Disturbance in attention, Tinnitus (10 each), Atrial fibrillation, Cardiac failure, Electrocardiogram abnormal, Maternal exposure during pregnancy, Migraine, Muscular weakness, Panic

attack, Pruritus, Somnolence, Supraventricular tachycardia, Thrombosis, Tremor (9 each), Abdominal pain upper, Fibrin D dimer increased, Influenza, Limb discomfort, Musculoskeletal stiffness, Night sweats, Pleural effusion, Vision blurred (8 each), Abdominal pain, Amenorrhoea, Body temperature increased, Ejection fraction decreased, Heart rate decreased, Loss of consciousness, Muscle spasms, Sleep disorder, Suspected COVID-19, Ventricular extrasystoles (7 each), Asthma, Blood pressure increased, Cardiac arrest, Cardiovascular disorder, Congestive cardiomyopathy, Eczema, Feeling cold, Gait disturbance, Haemorrhage, Heart rate, Illness, Menstrual disorder, Nasopharyngitis, Pulmonary embolism (6 each).

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

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

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

A 33-year-old female subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Abdominal pain, Arrhythmia, Cardiac arrest, Chest pain, Circulatory collapse, Myocarditis, Resuscitation.
- Time to onset (myocarditis): 20 days after dose 1.
- Causes of death: Abdominal pain; Arrhythmia; Cardiac arrest; Chest pain; Circulatory collapse; Myocarditis.
- Autopsy: Autopsy information was not reported.

A 34-year-old male subject from [redacted]:

- Medical history: Dyspnoea, Malaise.
- Co-suspect medications: None.
- PTs with fatal outcome: Arrhythmia, Cardiac arrest, Cardiogenic shock, Circulatory collapse, Dyspnoea, Hypertension, Hypoxia, Left ventricular dysfunction, Myocarditis, Pulmonary oedema, Syncope.
- Time to onset (myocarditis): Unknown days after unknown dose.
- Causes of death: Arrhythmia; Cardiac arrest; Cardiogenic shock; Circulatory collapse; Dyspnoea; Hypertension; Hypoxia; Left ventricular dysfunction; Pulmonary oedema; Syncope.
- Autopsy: Autopsy revealed cause of death as myocarditis.

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

- Medical history: Depressed mood, Familial risk factor, Perinatal depression, Pregnancy, Tobacco user.
- Co-suspect medications: None.
- PTs with fatal outcome: Hypoaesthesia, Menstruation irregular, Myocardial injury, Myocarditis, Myopericarditis, Neck pain, Pain in extremity, Pain in jaw, Paraesthesia, Pleural effusion, Thrombosis, Vaccination site pain.
- Time to onset (myocarditis and myopericarditis): Unknown duration after first dose.
- Causes of death: COVID-19 immunisation; Myocarditis.
- Autopsy: Autopsy revealed extensive and severe bilateral lung congestion but no evidence of ischemic, hypertensive or valvular heart disease. No evidence of subarachnoid haemorrhage was present. COVID-19 swabs were negative. Histology showed a single focus of myocarditis, with extensive lung congestion suggestive of sudden cardiac death and smoking related changes.

A 38-year-old female subject from [redacted]:

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

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

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

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

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

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: 1 case of BNT162b2 (0.15 % of 668 cases of the total CT dataset); 1 case (0.14%) was retrieved in the PSUR #2.
- Country of incidence: [redacted].
- Subject's gender: Male (1).

- Subject's age in years: 43 years.
- Medical history: PT Abstains from alcohol, Abstains from recreational drugs, Anxiety, Attention deficit hyperactivity disorder, Clinical trial participant, Dyspepsia, Gastrooesophageal reflux disease, Neuralgia, Non-tobacco user, Postural orthostatic tachycardia syndrome, Prophylaxis, Seasonal allergy, Stress, Tachycardia, Thyroiditis, Vasectomy (1 each).
- COVID-19 Medical history: COVID-19 (1).
- Co-suspects: None.
- Number of relevant serious events: 1.
- Reported relevant PTs: Myocarditis (not related to BNT162b2).
- Relevant event outcome: Resolved (1).
- Time to onset of relevant events: 98 days.
- Duration of myocarditis was reported as 2 days.

Post-Authorisation Data

- Number of cases: 1752 (0.3 % of 507,683 cases of the total PM dataset, 0.7 % of the 236404 subjects ≥ 40 years), compared to 1876 cases (0.3%) retrieved in the PSUR #2.
- Country of incidence (≥10): Germany (472), UK (464), Australia (168), France (116), Austria (66), Japan (58), New Zealand (53), Italy (41), Taiwan, Province of China (39), Canada (38), Sweden (37), Greece, US (25 each), Norway (16), Netherlands (15), Finland (14), Israel (12), Spain (11), Belgium, Denmark (10 each). The remaining 62 cases were distributed among 21 countries.
- Subjects' age in years: n = 1752, range: 40-98, mean: 55, median: 53.
- Medical history (n = 754): the most frequently (>5 occurrences) reported medical conditions included Hypertension (164), Seasonal allergy (53), Asthma (50), Drug hypersensitivity (35), Immunodeficiency (34), Obesity (32), Hypothyroidism, Tobacco user (30 each), Atrial fibrillation (29), Diabetes mellitus (28), Cardiac failure (26), Dyslipidaemia (25), Food allergy, Non-tobacco user, Type 2 diabetes mellitus (23 each), Hypersensitivity (21), Gastrooesophageal reflux disease (18), Anxiety, Depression (17 each), Clinical trial participant (16), Autoimmune thyroiditis, Breast cancer, Chronic obstructive pulmonary disease, Hyperlipidaemia (15 each), Migraine, Myocarditis (14 each), Coronary artery disease (13), Cardiac disorder, Chemotherapy, Ex-tobacco user, Hypercholesterolaemia, Overweight (12 each), Myocardial infarction, Sleep apnoea syndrome, Thyroidectomy, Tobacco abuse (11 each), Allergy to animal, Allergy to metals, Fibromyalgia, Rubber sensitivity (10 each), Appendicectomy, Arteriosclerosis, Fatigue, Interchange of vaccine products, Rheumatoid arthritis (9 each), Alcohol use, Menopause, Mite allergy, Osteoporosis, Radiotherapy, Systemic lupus erythematosus (8 each), Blood cholesterol increased, Cardiac ablation, Dyspnoea, Gout, Hysterectomy, Mitral valve incompetence, Nasopharyngitis, Pulmonary embolism, Steroid therapy, Surgery (7 each), Abstains from alcohol, Allergy to arthropod sting, Allergy to plants,

Arrhythmia, Arthritis, Blood cholesterol abnormal, Cerebrovascular accident, Cholecystectomy, Chronic kidney disease, Colitis ulcerative, Hormone replacement therapy, Inflammatory bowel disease, Influenza, Insomnia, Neoplasm, Nicotine dependence, Osteoarthritis, Supraventricular tachycardia, Tachycardia (6 each).

- COVID-19 Medical history (n = 132[85]): Suspected COVID-19 (70), COVID-19 (65), Post-acute COVID-19 syndrome (5), Asymptomatic COVID-19, Coronavirus infection, COVID-19 pneumonia, COVID-19 treatment, SARS-CoV-2 test positive (1 each).
- Co-suspect vaccine/medications: Influenza vaccine (3), pembrolizumab (2), adalimumab, cisplatin, COVID-19 vaccine, COVID-19 vaccine mRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), gabapentin, glyceryl trinitrate, hepatitis A vaccine, ibuprofen, influenza vaccine INACT SAG 3V, paracetamol, risankizumab, rivaroxaban, vinorelbine, vitamins NOS (1 each).
- Most frequently co-reported PTs (>5 occurrences): Chest pain (572), Dyspnoea (509), Fatigue (493), Palpitations (463), Pericarditis (407), Tachycardia (339), Off label use (285), Interchange of vaccine products (266), Immunisation (264), Pyrexia (235), Headache (189), Chest discomfort (180), Dizziness (174), Arrhythmia (139), Asthenia (101), Malaise, Syncope (89 each), Inappropriate schedule of product administration, Pain in extremity (88 each), Nausea (86), Pain (83), Angina pectoris (73), Cardiac failure (71), Chills (67), Myalgia (66), Arthralgia (64), Pericardial effusion (61), Heart rate increased (58), Dyspnoea exertional, Troponin increased (57 each), Atrial fibrillation (53), Hyperhidrosis (52), Myocardial infarction (50), Cough (49), Back pain (45), Hypertension (43), Paraesthesia (42), Vomiting (40), Diarrhoea, Lethargy (39 each), COVID-19, Lymphadenopathy (35 each), Cardiac flutter, Vaccination site pain (33 each), Extrasystoles, Influenza like illness (32 each), Cardiac disorder, Hypoaesthesia (30 each), Decreased appetite (28), Drug ineffective, Insomnia (27 each), Thrombosis (26), Abdominal pain upper, Blood pressure increased (25 each), Cardiomyopathy, Condition aggravated, C-reactive protein increased, Exercise tolerance decreased (24 each), Anxiety, Feeling abnormal, Neck pain (23 each), Electrocardiogram abnormal, Somnolence, Vertigo (21 each), Abdominal pain, Acute myocardial infarction, Cardiac discomfort, Inflammation, Pulmonary embolism, Tremor (20 each), Cardiac arrest, Gait disturbance, Muscular weakness, Ventricular extrasystoles (19 each), Hypotension (18), Cerebrovascular accident, Limb discomfort, Rash (17 each), Cardiomegaly, N-terminal prohormone brain natriuretic peptide increased, Peripheral swelling, Swelling, Ventricular tachycardia, Vision blurred (16 each), Breast pain, Bundle branch block left, Dyspepsia, Heart rate irregular, Impaired work ability, Musculoskeletal chest pain, Pneumonia, Presyncope (15 each), Axillary pain, Congestive cardiomyopathy, Coronary artery disease, Discomfort, Feeling hot, Influenza, Oedema peripheral, Pulmonary oedema, Tinnitus, Troponin T increased (14 each), Disturbance in attention, Ejection fraction decreased, Loss of personal independence in daily activities, Oedema, Pain in jaw, Sinus tachycardia (13 each), Acute coronary syndrome, Blood creatine phosphokinase increased, Feeling cold, Illness, Left ventricular dysfunction, Oropharyngeal pain, Performance status decreased, Suspected COVID-19, Weight

[85] More than 1 COVID-19 medical history is reported in some cases.

decreased (12 each), Atrial flutter, Atrioventricular block, Migraine, Musculoskeletal pain, Pleural effusion (11 each), Cardiogenic shock, Fibrin D dimer increased, Heart rate abnormal, Joint swelling, Memory impairment, Supraventricular tachycardia, Ventricular hypokinesia (10 each), Bradycardia, Confusional state, Electrocardiogram ST segment elevation, Feeling of body temperature change, Head discomfort, Lymph node pain, Mitral valve incompetence, Muscle spasms, Muscle twitching, Myositis, Orthopnoea, Sleep disorder, Stress, Throat tightness (9 each), Acute kidney injury, Blood pressure decreased, Burning sensation, Cold sweat, Cyanosis, Death, Depression, General physical health deterioration, Heavy menstrual bleeding, Hypokinesia, Left ventricular failure, Nasopharyngitis, Respiratory failure, Transient ischaemic attack, Urticaria, Wheezing (8 each), Abdominal discomfort, Amnesia, Arthritis, Brain natriuretic peptide increased, Bronchospasm, Cardio-respiratory arrest, Disease recurrence, Ear pain, Echocardiogram abnormal, Electrocardiogram ST segment depression, Herpes zoster, Hypersensitivity, Loss of consciousness, Menstrual disorder, Myocardial necrosis marker increased, Pallor, Thrombocytopenia, Visual impairment (7 each), Blood pressure abnormal, Body temperature increased, Bronchitis, Cardiac dysfunction, Cardiac failure acute, Depressed level of consciousness, Dysgeusia, Fall, Heart rate decreased, Mobility decreased, Night sweats, Pleuritic pain, Pruritus, Sepsis, Vaccination failure, Vaccination site swelling, Ventricular arrhythmia (6 each).

Fatal myocarditis cases in subjects aged ≥40 Years

There were 59 cases that reported 59 relevant events with fatal outcome in this age group. Of the 59 cases, 40 cases were medically confirmed and 19 were non-medically confirmed cases. There were 23 female and 36 male subjects. Subjects' ages ranged from 40 years to 96 years. The cases were reported from Japan (17), Germany (12), UK (7), Australia (5), Austria, France, Sweden (3 Each), New Zealand, Taiwan, Province of China (2 each), Hong Kong, Italy, Netherlands, Norway, and Switzerland (1 each).
The fatal events in these cases were coded to the PTs Abdominal pain upper, Acute coronary syndrome, Acute myocardial infarction, Amnesia, Aortic dissection, Aortic rupture, Aortitis, Arrhythmia, Arteriosclerosis coronary artery, Arteritis coronary, Arthralgia, Asthenia, Atrial fibrillation, Atrioventricular block complete, Back pain, Bacteraemia, Basal ganglia haemorrhage, Blood creatine phosphokinase increased, Blood creatinine increased, Blood lactic acid, Bradycardia, Brain injury, Cardiac arrest, Cardiac disorder, Cardiac dysfunction, Cardiac failure, Cardiac failure high output, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, Cardio-respiratory arrest, Cerebral haemorrhage, Chest pain, Chronic kidney disease, Circulatory collapse, Colitis, Coma, Coronary artery stenosis, C-reactive protein increased, Cytology abnormal, Death, Dizziness, Dyspnoea, Dyspnoea exertional, Electrocardiogram ST segment depression, Embolism, Encephalitis, Encephalomalacia, Endocarditis, Eosinophilic myocarditis, Fatigue, Haemorrhage, Haemosiderosis, Hepatotoxicity, Hyperhidrosis, Hypersensitivity myocarditis, Immunisation, Infection, Inflammation, Influenza like illness, Interchange of vaccine products, Internal haemorrhage, Intracranial pressure increased, Ischaemic cardiomyopathy, Malaise, Memory impairment, Multiple organ dysfunction syndrome, Myalgia, Myocardial fibrosis, Myocardial infarction, Myocardial necrosis, Myocarditis, Myopericarditis, Myositis, Obstruction, Off label use, Pain in extremity, Palpitations, Pericarditis, Peripheral coldness, pH body fluid, Pneumonia, Pneumonia aspiration, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary

hypertension, Pulmonary oedema, Pulseless electrical activity, Pyrexia, Respiration abnormal, Respiratory failure, Right ventricular failure, Sepsis, Spinal cord haemorrhage, Sudden death, Syncope, Tachycardia, Tachypnoea, Thrombocytopenia, Thrombosis, Troponin I, Troponin increased, Vasculitis, Vasculitis necrotising, Ventricular fibrillation, Ventricular hypokinesia, Viral myocarditis, Vomiting (1 each). Only 1 case reported a co-suspect medication (pembrolizumab). The most frequently reported (>1 occurrence) medical histories were coded to the PTs Hypertension (8), Cardiac failure, Diabetes mellitus, Obesity (4 each), Cardiac disorder (3), Cardiac failure chronic, Dyslipidaemia, and Type 2 diabetes mellitus (2 each). The most frequently reported (>2 occurrence) cause of death in these cases were coded to the PTs Myocarditis (47), Cardiac arrest (9), Death (7), Cardiac failure, Pericarditis (5 each), Cardio-respiratory arrest, Chest pain, Dyspnoea, Sudden death (4 each), Pneumonia, Syncope (3 each).

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

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

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	357	374	3
	No	565	437	16
Relevant PTs[a]	Myocarditis	791	716	19
	Myopericarditis	110	81	0
	Carditis	24	14	0
	Eosinophilic myocarditis	1	3	0
	Giant cell myocarditis	0	2	0
	Hypersensitivity myocarditis	0	1	0
Hospitalisation required/prolonged	Yes	331	350	4
	No	592	462	15
Relevant suspect dose	Dose 1	213	172	3
	Dose 2	273	250	9
	Dose 3	346	308	6
	Dose 4	8	4	0
	Unknown	83	77	1
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=958	≤24 hours	60	36	0
	1-5 days	167	166	1
	6-13 days	88	90	4
	14-21 days	58	56	1
	22-31 days	34	26	0
	32-60 days	40	42	0
	61-367 days	45	43	1
	Unknown	435	359	12

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

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Event Outcome	Fatal	23	36	0
	Not resolved	294	250	4
	Resolved	97	107	1
	Resolved with sequelae	33	32	2
	Resolving	143	147	0
	Unknown	337	245	12
Duration of event[b] n=89, median=34 days	Up to 3 days	2	9	0
	4-6 days	1	8	0
	7-25 days	7	9	0
	26-170 days	18	19	1
	171-822 days	10	5	0

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

Subjects with Unknown Age

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 441 (0.08 % of 507,683 cases of the total PM dataset, 0.7 % of the 60379 subjects with unknown age), compared to 732 cases (0.11%) retrieved in the PSUR #2.
- Country of incidence (≥10): UK (169), Canada (119), US (36), Germany (32), Australia (18), Israel, Japan (14 each). The remaining 39 cases were distributed among 17 countries.
- Subjects' age in years: Unknown
- Medical history (n = 125): the most frequently (>2 occurrence) reported medical conditions included Hypertension (16), Asthma (14), Anxiety, Attention deficit hyperactivity disorder, Diabetes mellitus, Drug hypersensitivity, Gastrooesophageal reflux disease, Tobacco user (7 each), Immunodeficiency, Steroid therapy (5 each), Depression, Fibromyalgia, Food allergy, Palpitations (4 each), Angina pectoris, Chest pain, Endometriosis, Hypothyroidism, Insomnia, Migraine, Nephrolithiasis, Obstructive sleep apnoea syndrome, Pregnancy, Rheumatoid arthritis (3 each).
- COVID-19 Medical history (n = 37): Suspected COVID-19 (23), COVID-19 (14)
- Co-suspect vaccine/medications: COVID-19 vaccine mRNA (MRNA 1273) (2), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), influenza vaccine, and JNJ 78436735 (1 each).

- Most frequently co-reported PTs (>5 occurrences): Chest pain (171), Pericarditis (132), Dyspnoea (124), Fatigue (122), Palpitations (113), Tachycardia (74), Immunisation (69), Off label use (55), Pyrexia (54), Interchange of vaccine products (51), Headache (37), Chest discomfort (36), Dizziness (26), Nausea (25), Pain in extremity (19), Arthralgia, Syncope (18 each), Pain (17), Asthenia, Malaise (16 each), Cough (14), Hypoaesthesia (13), Chills, Vomiting (12 each), Heart rate increased, Lymphadenopathy (11 each), Arrhythmia , COVID-19, Myalgia, Paraesthesia (10 each), Cardiac flutter , Diarrhoea, Drug ineffective, Feeling abnormal (9 each), Angina pectoris, Hyperhidrosis, Insomnia, Migraine, Peripheral swelling (8 each), Abdominal pain, Axillary pain, Inappropriate schedule of product administration, Troponin increased (7 each), Back pain, Decreased appetite, Heavy menstrual bleeding, Hypertension, Influenza like illness, Muscular weakness, Pericardial effusion, Pleuritic pain, Tremor (6 each).

Fatal myocarditis cases in subjects of unknown age (6 cases, medically confirmed; 2 cases non- medically confirmed)

A male subject from [redacted]:

- Medical history: Attention deficit hyperactivity disorder.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardiac arrest, Myocardial injury, Myocarditis, Toxic cardiomyopathy.
- Time to onset (myocarditis): Unknown days after dose 2.
- Causes of death: Cardiac arrest; Myocardial injury; Myocarditis; Toxic cardiomyopathy.
- Autopsy: Autopsy revealed stress cardiomyopathy.

A male subject from [redacted]:

- Medical history: Obesity.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocardial injury, Myocarditis, Stress cardiomyopathy, Toxic cardiomyopathy.
- Time to onset (myocarditis): Unknown days after dose 2.
- Causes of death: Myocardial injury; Myocarditis; Stress cardiomyopathy.
- Autopsy: The autopsy revealed biventricular dilatation (dilatation ventricular); pulmonary oedema (pulmonary oedema); global myocardial injury (myocardial injury); toxic cardiomyopathy (toxic cardiomyopathy).

A subject of unknown gender from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): Unknown days after unknown dose.
- Causes of death: Myocarditis.

- Autopsy: It was not reported if an autopsy was performed.

A male subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): Unknown days after unknown dose.
- Causes of death: Myocarditis.
- Autopsy: It was not reported if an autopsy was performed.

A male subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis.
- Time to onset (myocarditis): Unknown days after unknown dose.
- Causes of death: Myocarditis.
- Autopsy: It was not reported if an autopsy was performed.

A subject of unknown gender from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardio-respiratory arrest, Myocarditis.
- Time to onset (myocarditis): Unknown days after dose 3.
- Causes of death: Cardio-respiratory arrest; Myocarditis.
- Autopsy: It was not reported if an autopsy was performed.

A female subject from [redacted]:

- Medical history: None.
- Co-suspect medications: None.
- PTs with fatal outcome: Pneumonitis, Myocarditis.
- Time to onset (myocarditis): Unknown days after dose 2.
- Causes of death: Myocarditis; Pneumonitis.
- Autopsy: It was not reported if an autopsy was performed.

A subject of unknown gender from [redacted]:

- Medical history: None
- Co-suspect medications: None
- PTs with fatal outcome: Immunisation, Myocarditis, Colitis, Liver injury.
- Time to onset (myocarditis): Unknown days after unknown dose.
- Causes of death: Colitis; Liver injury; Myocarditis.

– Autopsy: It was not reported if an autopsy was performed.

Myocarditis relevant data in this subgroup of subjects are summarised in Table 43 below.

Table 43. Myocarditis in Subjects of Unknown Age (N=441)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	60	121	30
	No	97	92	41
Relevant PT[a]	Myocarditis	132	160	62
	Myopericarditis	28	51	7
	Carditis	0	6	3
Hospitalisation required/prolonged	Yes	37	84	8
	No	120	129	63
Relevant suspect dose	Dose 1	37	49	14
	Dose 2	53	92	11
	Dose 3	54	44	22
	Dose 4	0	1	0
	Unknown	13	27	24
		Female No. of Events	Male No. of Events	Unknown No. of Events
Time to Onset n=133	≤24 hours	9	10	0
	1-5 days	18	44	3
	6-13 days	3	16	2
	14-21 days	5	7	1
	22-31 days	1	3	1
	32-149 days	4	5	1
	Unknown	120	134	64
Event Outcome	Fatal	1	4	3
	Not resolved	47	55	8
	Resolved	26	55	8
	Resolved with sequelae	2	1	0
	Resolving	5	16	3
	Unknown	79	87	50
Duration of event[b] n=7, median=3 days	Up to 3 days	0	3	0
	4-6 days	1	0	0
	7146 days	1	1	1

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

Subjects with booster dose

Clinical Trial Data

- Number of cases: 1 case (0.15 % of 668 cases of the total CT dataset, 0.2 % of the 490 subjects who received a booster dose), compared to 2 cases (0.3%) in the PSUR #2.

- The case involved a 43-year-old male participant, who received homologous booster dose. Please see above the "Overall- All Ages" subsection for complete details.

Post-Authorisation Data

- Number of cases: 1682 (0.3 % of 507,683 cases of the total PM dataset, 1.4 % of the 117750 subjects who received a booster dose), compared to 381 cases (0.06%) in the PSUR #2.
- Country/region of incidence (≥10): UK (617), Germany (422), France (113), Austria (72), Italy (53), Japan (48), Israel (44), New Zealand (41), US (32), Greece, Sweden (21 each), Finland (19), Netherlands, Taiwan, Province of China (17 Each), Denmark (16), Australia, Hong Kong (15 each), Switzerland (13), Spain (12), Ireland (10); the remaining 64 cases were distributed among 19 countries.
- MC (702), NMC (980).
- Subjects' gender: female (656), male (988), and unknown (38).
- Subjects' age in years: n = 1552, range: 11 -94, mean: 39.3, median: 36.
- Medical history (n = 633): the medical conditions reported (>4 occurrence) included Hypertension (87), Asthma (46), Immunodeficiency (34), Tobacco user (31), Seasonal allergy (30), Hypothyroidism (28), Clinical trial participant (22), Myocarditis (21), Diabetes mellitus (20), Atrial fibrillation, Non-tobacco user (19), Obesity (18), Depression, Migraine (17 each), Steroid therapy (14), Food allergy (13), Anxiety, Dyslipidaemia (12 each), Drug hypersensitivity, Gastrooesophageal reflux disease, Interchange of vaccine products (11 each), Chest pain, Mite allergy, Overweight (10 each), Rheumatoid arthritis, Type 2 diabetes mellitus (9 each), Alcohol use, Chronic obstructive pulmonary disease, Dyspnoea, Fibromyalgia, Hyperlipidaemia, Myocardial infarction (8 each), Autoimmune thyroiditis, Cardiac disorder, Coronary artery disease, Ex-tobacco user, Nasopharyngitis (7 each), Cerebrovascular accident, Colitis ulcerative, Crohn's disease, Hypersensitivity, Inflammatory bowel disease, Insomnia, Mitral valve incompetence, Neoplasm, Nephrolithiasis, Nicotine dependence, Osteoarthritis, Pain, Pericarditis, Pneumonia, Pulmonary embolism, Sleep apnoea syndrome (6 each), Abstains from alcohol, Allergy to animal, Appendicectomy, Arteriosclerosis, Attention deficit hyperactivity disorder, Coeliac disease, Congestive cardiomyopathy, Contraception, Endometriosis, Epstein-Barr virus infection, Fatigue, Gastritis, Gout, Hodgkin's disease, Hormone replacement therapy, Menopause, Myopericarditis, Osteoporosis, Palpitations, Pregnancy, Radiotherapy, Supraventricular tachycardia, Surgery, Urinary tract infection (5 each).
- COVID-19 Medical history (n = 128[85]): Suspected COVID-19 (80), COVID-19 (49), Post-acute COVID-19 syndrome (4), SARS-CoV-2 test positive (2), and Asymptomatic COVID-19 (1).
- Co-suspect vaccines (n= 20) reported more than once: Influenza vaccine (5), pembrolizumab (2), amoxicillin, cisplatin, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), fluticasone, gabapentin, hepatitis A vaccine, infliximab, influenza vaccine

INACT SAG 3V, JNJ 78436735, paracetamol, propranolol, vinorelbine, zuclopenthixol (1 each).

- Number of relevant events: 1696.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Myocarditis (1458), Myopericarditis (211), Carditis (25), and Eosinophilic myocarditis (2).
- Relevant event outcome[78]: fatal (39), resolved/resolving (528); resolved with sequelae (29), not resolved (453), unknown (649).
- Most frequently co-reported PTs (>20 occurrence): Chest pain (691), Immunisation[43] (537), Fatigue (494), Pericarditis (467), Dyspnoea (466), Palpitations (443), Off label use (442), Interchange of vaccine products (379), Tachycardia (358), Pyrexia (311), Headache (174), Chest discomfort (163), Dizziness (111), Malaise , Pain (86 each), Pain in extremity (84), Nausea (77), Syncope (73), Arrhythmia (71), Chills , Heart rate increased (70 each), Angina pectoris (66), Myalgia (65), Asthenia (59), Arthralgia (58), Troponin increased (52), Lymphadenopathy (51), Vomiting (45), Dyspnoea exertional (43), Back pain, Pericardial effusion (41 each), Hypertension (38), Diarrhoea, Influenza like illness (37), Atrial fibrillation (36), Cough (35), Cardiac flutter, Hyperhidrosis (34 each), Cardiac failure, Vaccination site pain (30), COVID-19 (27), Oropharyngeal pain (26), C-reactive protein increased, Neck pain (24 each), Insomnia (23), Axillary pain, Hypoaesthesia, Paraesthesia (22 each), Cardiac disorder, Myocardial infarction (21 each), Blood pressure increased, Extrasystoles (20 each).

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

Table 44. Myocarditis in Subjects who Received a Booster dose

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

F=female; M=male; U=unknown

During the reporting period there were 1639 cases of medically confirmed myocarditis with a latency 21 days or less in subjects receiving booster dose. All cases were assessed as serious due to hospitalisation and/or medically significant (1002) or due to medically significant (637). In 1314 cases myocarditis occurred within 1 week post vaccine administration. In

most of these cases, the insufficient description of cardiovascular and/or non-cardiovascular medical history and the lack of diagnostic tests confirming the aetiologies of myocarditis preclude a clear causality assessment on an individual case basis.

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: No cases were retrieved during the current reporting period, compared to 1 case (0.14 %) retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 4156 (0.8% of 507,683 cases of the total PM dataset), compared to 5311 cases[86] (0.8%) retrieved in the PSUR #2.
- Country of incidence: Australia (1085), UK (903), France (580), Italy (281), Germany (271), Canada (174), New Zealand (111), Netherlands (97), Sweden (71), Japan (68). The remaining 515 cases were distributed among 44 countries.
- MC (2370), NMC (1786).
- Subjects' gender: female (2049), male (2017) and unknown (90).
- Subjects' age in years: n = 3847, range: 4 -98 years, mean: 39.8, median: 37.0.
- Medical history: (n = 1292) the most frequently (≥1%) reported relevant medical history included: Hypertension (154), Asthma (109), Pericarditis (95), Seasonal allergy (60), Drug hypersensitivity, Tobacco user (58 each), Immunodeficiency (54), Hypothyroidism (51), Obesity (46), Hypersensitivity, Non-tobacco user (40 each).
- COVID-19 Medical history (n = 321): COVID-19 (189), Suspected COVID-19 (130), Post-acute COVID-19 syndrome (7), SARS-CoV-2 test positive (5), COVID-19 pneumonia, Exposure to SARS-CoV-2 (2 each).
- Co-suspects (n=48 cases): frequently (?3 occurrences) reported relevant co-suspect vaccines/medications were COVID-19 vaccine mRNA (mRNA 1273), Influenza vaccine (8 each), COVID-19 vaccine, Influenza vaccine INACT SAG 3V, Influenza vaccine INACT SPLIT 4V (3 each).
- Number of relevant events: 4164.

[86] During the reporting period of PSUR #2 there were 5311 events of pericarditis [Pericarditis (5274), Pleuropericarditis (34), Pericarditis constrictive (11), Pericarditis adhesive (1)].

- Relevant event seriousness: serious (4164).
- Reported relevant PTs: Pericarditis (4133), Pleuropericarditis (26), Pericarditis constrictive (5).
- Relevant event outcome[78]: fatal (19), resolved/resolving (1311), resolved with sequelae (82), not resolved (1428), unknown (1325).

Age-stratified data[87]

Subjects aged less than 5 years

Clinical Trial Data

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

Post-Authorisation Data

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

Subjects aged 5 - 11 years

Clinical Trial Data

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

[87] Cases where the age was reported as Child (1 case), Adolescent (9 cases), Adult (62 cases) and Elderly (8 cases) are included in the subgroup of unknown age and in the overall.

Post-Authorisation Data

- Number of cases: 30 (0.006 % of 507,683 cases of the total PM dataset, 0.4 % of the 8375 subjects aged 5-11 years); 4 cases (0.0006%) were retrieved in the PSUR #2.
- Country of incidence: Australia (19), Canada (3), Italy, Japan (2 each), Germany, Israel, New Zealand, UK (1 each).
- Subjects' age in year: n = 30, range: 5 -11, mean: 9.4, median: 10.0.
- Medical history: Coeliac disease, Kawasaki's disease, Urinary tract infection viral (1 each).
- COVID-19 Medical history: COVID-19 (1)
- Co-suspects: none.
- Most frequently co-reported PTs (>2 occurrences): Chest pain (24), Dyspnoea (12), Electrocardiogram abnormal (7), Chest discomfort (6), Palpitations (5), Myocarditis (4), Pyrexia (3).

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

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

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

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

Subjects aged 12 - 15 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 118 (0.02 % of 507,683 cases of the total PM dataset, 0.9 % of the 13,366 subjects aged 12-15 years), compared to 215 cases (0.03%) retrieved in the PSUR #2.
- Country of incidence: Australia (31), UK (13), Taiwan, Province of China (11), France, Japan (8 each), Canada, Italy (7 each), Malaysia (6). The remaining 27 cases were distributed among 12 countries.
- Subjects' age in years: n = 118, range: 12.0 -15.3, mean: 13.7, median: 14.0.
- Medical history (n = 20): the medical conditions reported more than once included Adenotonsillectomy, Asthma, Glucose-6-phosphate dehydrogenase deficiency, and Hypersensitivity (2 each).
- COVID-19 Medical history (n = 5): COVID-19 (4), Suspected COVID-19 (1).
- Co-suspects: none.
- Most frequently co-reported PTs (≥2%): Chest pain (60), Myocarditis (34), Dyspnoea (25), Palpitations (23), Pyrexia (22), Chest discomfort, Fatigue (15 each), Headache, Tachycardia (9 each), Dizziness, Malaise (7 each), Asthenia, Inappropriate schedule of product administration (6 each), Cough, Heart rate increased, Nausea, Pain, Pericardial effusion (5 each), Dyspnoea exertional, Syncope, Vomiting (4 each), Arthralgia, Chills, COVID-19, Electrocardiogram abnormal, Electrocardiogram ST segment elevation, Troponin increased (3 each), Angina pectoris, Back pain, Drug ineffective, Electrocardiogram ambulatory abnormal, Exercise tolerance decreased, Immune system disorder, Lethargy, Musculoskeletal chest pain, Myalgia, Nasopharyngitis, Oropharyngeal pain, Pleural effusion, Pleuritic pain, and Sinus tachycardia (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 46.

Table 46. Pericarditis in Subjects aged 12-15 years (N=118)

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

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

Subjects aged 16 - 17 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 106 (0.02 % of 507,683 cases of the total PM dataset, 1.3 % of the 8313 subjects aged 16-17 years), compared to 174 cases (0.03%) retrieved in the PSUR #2.

- Country of incidence: Australia (25), UK (20), France (15), Italy (11), Germany (6), Taiwan, province of China (5). The remaining 24 cases were distributed among 14 countries.
- Subjects' age in years: n = 106, range: 16 -17, mean: 16.5, median: 16.0.
- Medical history (n = 17): the medical conditions reported more than once included the PTs Asthma, Food allergy, Pericarditis, Seasonal allergy (2 each).
- COVID-19 Medical history (n = 6): COVID-19 (5), Suspected COVID-19 (1).
- Co-suspects (n= 2 cases): COVID-19 vaccine MRNA (MRNA 1273), HPV vaccine VLP RL1 9V (yeast), Influenza vaccine INACT SPLIT 4V, Pneumococcal vaccine polysacch 23V (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (56), Dyspnoea (25), Myocarditis, Pyrexia (22 each), Fatigue, Palpitations (19 each), Tachycardia (15), Chest discomfort (14), Inappropriate schedule of product administration, Nausea, Pain (7 each), Headache, Pericardial effusion, Vomiting (6 each), Electrocardiogram abnormal, Malaise, Myopericarditis (5 each), Chills, Cough, Dizziness, Troponin increased, Abdominal pain upper, Influenza like illness, Lethargy, Pain in extremity (3 each), Asthenia, Back pain, Cellulitis, Cold sweat, C-reactive protein increased, Decreased appetite, Feeling hot, Heart rate irregular, Hyperhidrosis, Interchange of vaccine products, Myalgia, Off label use, Product use issue, Syncope, Vaccination site pain (2 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 47.

Table 47. Pericarditis in Subjects aged 16-17 years (N=106)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	20	50	1
	No	15	20	0
Relevant PT[a]	Pericarditis	35	70	1
Hospitalisation required/prolonged	Yes	7	21	0
	No	28	49	1
Relevant suspect dose	Dose 1	12	23	1
	Dose 2	20	26	0
	Dose 3	2	13	0
	Unknown	1	8	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=106	≤ 24 hours	1	6	0
	1-5 days	9	20	1
	6-13 days	3	5	0
	14-21 days	1	3	0
	22-31 days	2	3	0
	32-60 days	5	2	0
	61-180 days	2	3	0
	181-375 days	0	1	0
	Unknown	12	27	0
Event Outcome	Fatal	0	0	0
	Not resolved	11	17	1
	Resolved	4	19	0
	Resolved with sequelae	0	1	0
	Resolving	11	13	0
	Unknown	9	20	0
Duration of event[b] n=7, median: 10	Up to 3 days	1	2	0
	7-10 days	0	1	0
	11-26 days	0	1	0
	27-57 days	0	1	0
	58-180 days	0	1	0

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

Subjects aged 18 - 24 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 479 (0.09 % of 507,683 cases of the total PM dataset, 1.3% of the 38,293 subjects aged 18-24 years), compared to 659 cases (0.10%) retrieved in the PSUR #2.

- Country of incidence: Australia (135), France (79), UK (73), Germany (44), Italy (33), New Zealand (19), Japan (14), Netherlands, Sweden (12 each), Norway (11), US (6). The remaining 41 cases were distributed among 16 countries.
- Subjects' age in years: n = 479, range: 18 -24, mean: 21.2, median: 21.0.
- Medical history (n = 120): the medical conditions reported more than twice included Asthma (21), Immunodeficiency, Pericarditis (6 each), Attention deficit hyperactivity disorder, Mite allergy, Non-tobacco user, Obesity, Overweight, Tobacco user (5 each), Food allergy, Irritable bowel syndrome (4 each), Disease risk factor, Drug hypersensitivity, Endometriosis, Hospitalisation, Hypersensitivity, Hypothyroidism, Migraine, Seasonal allergy, and Substance use (3 each).
- COVID-19 Medical history (n = 37): COVID-19 (24), Suspected COVID-19 (12), SARS-CoV-2 test positive (1).
- Co-suspects (n= 8 cases): COVID-19 vaccine MRNA (MRNA 1273) (2), COVID-19 vaccine, dupilumab, Influenza vaccine INACT SPLIT 4V, insulin, levothyroxine, salbutamol, zuclopenthixol (1 each).
- Most frequently co-reported PTs (≥2%): Dyspnoea (141), Myocarditis (112), Palpitations (95), Fatigue (83), Chest discomfort (75), Pyrexia (66), Tachycardia (65), Headache, Pericardial effusion (35 each), Dizziness (33), Inappropriate schedule of product administration (26), Electrocardiogram abnormal (24), Pain (23), Immunisation, Myalgia (20 each), Malaise, Off label use (19 each), Interchange of vaccine products, Syncope (18 each), Asthenia (17), Pain in extremity (16), Nausea (15), Angina pectoris, Chills, Vomiting (14 each), Cough (13), C-reactive protein increased, Dyspnoea exertional, Hyperhidrosis, Lethargy (12 each), Anxiety, Sinus tachycardia (10 each), Arthralgia, Heart rate increased (9 each), Back pain, Electrocardiogram ST segment elevation, Paraesthesia, Troponin increased (8 each).
- Pericarditis events with fatal outcome (1).

Fatal pericarditis cases in adult (18-24 years of age) (1 case, medically confirmed)

A 22-year-old male subject from [redacted]:

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardiac tamponade, Multiple organ dysfunction syndrome, Pericardial effusion, Pericardial mass, Pericardial mesothelioma malignant, Pericarditis, Right ventricular dysfunction, Right ventricular failure.
- Time to onset (pericarditis): 31 days after dose 2.
- Causes of death: all the above events.

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 48.

Table 48. Pericarditis in Subjects aged 18-24 years (N=479)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	120	169	6
	No	72	110	2
Relevant PT[a]	Pericarditis	192	279	8
Hospitalisation required/prolonged	Yes	46	96	3
	No	146	183	5
Relevant suspect dose	Dose 1	79	102	4
	Dose 2	52	96	0
	Dose 3	49	60	0
	Dose 4	1	2	0
	Unknown	11	19	4
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=479	≤ 24 hours	27	18	0
	1-5 days	66	93	1
	6-13 days	22	34	2
	14-21 days	5	16	0
	22-31 days	5	9	0
	32-60 days	1	12	1
	61-180 days	7	10	0
	181-375 days	0	1	0
	Unknown	59	86	4
Event Outcome	Fatal	0	1	0
	Not resolved	74	97	2
	Resolved	20	33	2
	Resolved with sequelae	7	7	1
	Resolving	47	65	0
	Unknown	44	76	3
Duration of event[b] n=18, median: 21	Up to 3 days	1	2	0
	4-6 days	0	2	0
	7-10 days	0	3	0
	11-26 days	0	2	0
	27-57 days	3	3	1
	58-180 days	0	1	0

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

Subjects aged 25 - 29 years

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 417 (0.08 % of 507,683 cases of the total PM dataset, 1.0 % of the 43,518 subjects aged 25-29 years), compared to 614 cases (0.09%) retrieved in the PSUR #2.
- Country of incidence: Australia (136), UK (75), France (71), Germany (21), Italy, Netherlands (18 each), New Zealand (16), Sweden (8), Japan, Spain (7 each), Denmark (6), Canada (5). The remaining 29 cases were distributed among 17 countries.
- Subjects' age in years: n = 417, range: 25 -29, mean: 27.0, median: 27.0.
- Medical history (n = 87): the medical conditions reported more than twice included Asthma (10), Tobacco user (7), Obesity (6), Disease risk factor, Drug hypersensitivity, Non-tobacco user, Pericarditis (4 each), Abstains from alcohol, Contraception, Gastritis, Steroid therapy (3 each).
- COVID-19 Medical history (n = 31[88]): Suspected COVID-19 (17), COVID-19 (14), Post-acute COVID-19 syndrome (3), Exposure to SARS-CoV-2 (1).
- Co-suspects (n= 3 cases): COVID-19 vaccine (2), and Methylphenidate (1).
- Most frequently co-reported PTs (≥2%): Dyspnoea (137), Palpitations (101), Fatigue (94), Myocarditis (87), Tachycardia (67), Chest discomfort (60), Pyrexia (49), Headache (40), Dizziness, Immunisation (33 each), Nausea (22), Pain (21), Off label use (20), Interchange of vaccine products (19), Malaise, Pericardial effusion (17 each), Syncope (16), Electrocardiogram abnormal, Myalgia (14 each), Angina pectoris (13), Arthralgia, Asthenia, Heart rate increased (12 each), Dyspnoea exertional, Pain in extremity, Paraesthesia, Vaccination site pain (11 each), Lethargy, Lymphadenopathy (10 each), Inappropriate schedule of product administration (9), Troponin increased (8), Cardiac flutter, Diarrhoea, Vomiting (7 each).
- Pericarditis events with fatal outcome (1).

Fatal pericarditis cases in adult (25-29 years of age) (1 case, medically confirmed)

A 29-year-old male subject from [redacted]:

- Medical history: Hypoventilation, Obesity, Pulmonary fibrosis, Sleep apnoea syndrome, Still's disease
- Co-suspect medications: None
- PTs with fatal outcome: Acute kidney injury, Aortic dissection, Chest pain, Hypoventilation, Inflammatory marker increased, Multiple organ dysfunction syndrome, Pericardial disease, Pericarditis, Respiratory failure, Sepsis.
- Time to onset (pericarditis): 6 days after dose 3.
- Causes of death: Multiple organ dysfunction syndrome; Sepsis; Still's disease.

[88] In 4 cases, more than one COVID-19 history are reported.

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 49.

Table 49. Pericarditis in Subjects aged 25-29 years (N=417)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	102	146	2
	No	71	91	5
Relevant PT[a]	Pericarditis	171	237	7
	Pleuropericarditis	2	0	0
Hospitalisation required/prolonged	Yes	41	47	2
	No	132	190	5
Relevant suspect dose	Dose 1	68	100	4
	Dose 2	40	61	1
	Dose 3	50	58	2
	Dose 4	0	1	0
	Unknown	15	17	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=418	≤ 24 hours	15	21	0
	1-5 days	42	76	1
	6-13 days	23	21	0
	14-21 days	15	20	1
	22-31 days	6	7	0
	32-60 days	8	8	0
	61-180 days	11	12	1
	181-375 days	1	0	0
	Unknown	52	73	4
Event Outcome	Fatal	0	1	0
	Not resolved	78	84	1
	Resolved	12	37	2
	Resolved with sequelae	2	3	0
	Resolving	34	47	1
	Unknown	47	65	3
Duration of event[b] n=13, median: 13	Up to 3 days	0	3	0
	7-10 days	1	2	0
	11-26 days	1	2	1
	27-57 days	2	0	0
	58-180 days	0	1	0

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

Subjects aged 30 - 39 years

Clinical Trial Data

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

Post-Authorisation Data

- Number of cases: 940 (0.2 % of 507,683 cases of the total PM dataset; 1.0 % of the 97,870 subjects aged 30-39), compared to 1222 cases (0.2%) retrieved in the PSUR #2.
- Country/region of incidence: Australia (356), UK (217), France (114), Germany (46), Italy (39), New Zealand (26), Netherlands (21), Canada (18), Norway (16), Sweden (13), Belgium (9), Greece, US (8 each), Denmark, Japan (6 each), Austria, and Hong Kong (5 each). The remaining 27 cases were distributed among 17 different countries.
- Subjects' age in years: n = 940, range: 30 -39, mean: 34.3, median: 34.0.
- Medical history (n = 217): the medical conditions reported more than 5 times included the PTs Pericarditis (27), Asthma (20), Drug hypersensitivity (18), Seasonal allergy (13), Mite allergy, Non-tobacco user, Pregnancy, Tobacco user (11 each), Migraine (10), Chest pain, Hypothyroidism (8 each), Anxiety, Clinical trial participant, Immunodeficiency (7 each), Alcohol use, Eczema, Obesity (6 each).
- COVID-19 Medical history (n = 70): COVID-19 (43), Suspected COVID-19 (24), SARS-CoV-2 test positive (3).
- Co-suspect vaccines/medications (n=6): colchicine (2), amoxicillin, interferon Beta-1A, iron isomaltoside 1000, propranolol (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (547), Dyspnoea (345), Palpitations (260), Fatigue (239), Myocarditis (236), Tachycardia (179), Chest discomfort (125), Pyrexia (113), Headache (93), Dizziness (75), Immunisation (74), Malaise, Pain in extremity (54 each), Nausea, Paraesthesia (48 each), Arthralgia, Pain (46 each), Off label use (45), Myalgia (44), Inappropriate schedule of product administration (40), Heart rate increased, Interchange of vaccine products (39 each), Hypoaesthesia, Pericardial effusion (38 each), Asthenia (32), Hyperhidrosis, Syncope (29 each), Electrocardiogram abnormal, Influenza like illness (25 each), Cardiac flutter (24), Arrhythmia (23), Chills, Lethargy (21 each), Feeling abnormal, Vaccination site pain (20 each), Diarrhoea, Exercise tolerance decreased, Vomiting (18 each), Cough (17), Anxiety, Back pain, Dyspnoea exertional, Lymphadenopathy, Neck pain (16 each).

Pericarditis relevant data in this subgroup of subjects are summarised in below Table 50.

Table 50. Pericarditis in Subjects aged 30-39 years (N=940)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	277	284	5
	No	193	179	2
Relevant PT[a]	Pericarditis	470	462	7
	Pleuropericarditis	0	2	0
Hospitalisation required/prolonged	Yes	68	96	0
	No	402	367	7
Relevant suspect dose	Dose 1	223	243	3
	Dose 2	119	111	2
	Dose 3	108	85	2
	Unknown	20	24	0
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=941	≤ 24 hours	37	35	0
	1-5 days	105	120	0
	6-13 days	47	52	1
	14-21 days	27	20	0
	22-31 days	17	17	0
	32-60 days	17	20	0
	61-180 days	21	12	1
	181-375 days	5	1	0
	Unknown	194	187	5
Event Outcome	Fatal	0	0	0
	Not resolved	181	189	3
	Resolved	37	63	1
	Resolved with sequelae	6	3	0
	Resolving	80	65	0
	Unknown	166	144	3
Duration of event[b] n=27, median: 15	Up to 3 days	0	5	0
	4-6 days	1	2	0
	7-10 days	1	1	0
	11-26 days	5	4	0
	27-57 days	4	2	0
	58-180 days	1	1	0

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

Subjects aged ≥40 years

Clinical Trial Data

- Number of cases: none. One (1) case (0.14%) retrieved in the PSUR #2. Please see above the "Overall – All Ages" subsection.

Post-Authorisation Data

- Number of cases: 1756 (0.3 % of 507,683 cases of the total PM dataset, 0.7% of the 236,404 subjects ≥ 40 years), compared to 2059 cases (0.3%) retrieved in the PSUR #2.

- Country of incidence: UK (375), Australia (333), France (288), Italy (169), Germany (137), Canada (61), New Zealand (44), Netherlands (41), Greece (40), Sweden (35), Austria, Norway (28 each), Japan (25), Denmark (20). The remaining 132 cases were distributed among 25 different countries.

- Subjects' age in years: n = 1756, range: 40-98, mean: 54.6, median: 52.0.

- Medical history (n = 738): the medical conditions reported more than 10 times included PTs Hypertension (133), Pericarditis (47), Asthma (43), Immunodeficiency, Seasonal allergy (36 each), Hypothyroidism (34), Hypersensitivity (29), Obesity, Tobacco user, Type 2 diabetes mellitus (28 each), Diabetes mellitus (27), Drug hypersensitivity, Gastrooesophageal reflux disease (25 each), Depression (20), Atrial fibrillation (19), Dyslipidaemia, Rheumatoid arthritis (18 each), Anxiety (17), Breast cancer, Dyspnoea, Hypercholesterolaemia, Myocardial ischaemia, Non-tobacco user (16 each), Chronic kidney disease (15), Myocardial infarction (14), Chronic obstructive pulmonary disease, Food allergy, Gastritis (13 each), Autoimmune thyroiditis, Chest pain, Systemic lupus erythematosus (12 each), Overweight, Palpitations, Psoriasis, Steroid therapy (11 each).

- COVID-19 Medical history (n = 142): COVID-19 (89), Suspected COVID-19 (56), Post-acute COVID-19 syndrome (3), COVID-19 pneumonia (2), Exposure to SARS-CoV-2 (1).

- Co-suspect vaccines/medications (n= 24): Influenza vaccine (7), COVID-19 vaccine MRNA (MRNA 1273), Influenza vaccine INACT SAG 3V (3 each), Adalimumab, Apixaban, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Etanercept, Glyceryl trinitrate, Influenza vaccine INACT SPLIT 4V, Levetiracetam, Peginterferon alfa-2A, Pembrolizumab, Rivaroxaban, Sotrovimab (1 each).

- Most frequently co-reported PTs (≥2%): Chest pain (787), Dyspnoea (567), Fatigue (455), Myocarditis (396), Palpitations (372), Tachycardia (286), Off label use (272), Interchange of vaccine products (246), Immunisation (243), Pyrexia (223), Chest discomfort (199), Pericardial effusion (167), Headache (157), Dizziness (131), Malaise (87), Pain in extremity (83), Asthenia (82), Arthralgia (74), Nausea (73), Pain (71), Inappropriate schedule of product administration (70), Syncope (69), Myalgia (67), Angina pectoris, Paraesthesia (60 each), Arrhythmia, Cough (57 each), Lymphadenopathy (50), Heart rate increased (49), Chills (46), Hyperhidrosis (44), Electrocardiogram abnormal (43), Back pain (42), Hypertension (41), Lethargy (40), Pleural effusion, Vaccination site pain (39 each), Atrial fibrillation, Diarrhoea (38 each), Dyspnoea exertional (37), Influenza like illness (36), Myocardial infarction (33), Neck pain (32), Cardiac flutter, Condition aggravated (31 each), C-reactive protein increased, Vomiting (29 each).

- Pericarditis events with fatal outcome (17) occurred in subjects aged ≥40 years (n=17, ranged between 41 to 92 years of age).

Fatal Pericarditis cases in adult (40-50 years of age) (4 cases; 2 cases medically confirmed and 2 non-medically confirmed)

- 2 cases medically confirmed:

A 43-year-old male subject from [redacted].

- Medical history: Diabetes mellitus, Obesity.
- Co-suspect medications: None.
- PTs with fatal outcome: Myocarditis, Pericarditis, Sudden death.
- Time to onset (pericarditis and myocarditis): On the same day of receiving dose 3, the patient died.
- Cause of death: Myocarditis, Pericarditis, Sudden death.

A 48-year-old male subject from [redacted]

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Brain stem haemorrhage, Pericarditis.
- Time to onset (pericarditis): 17 days after dose 2.
- Cause of death: Both the above events.

- 2 cases non-medically confirmed:

A 41-year-old male subject from [redacted].

- Medical history: Congestive cardiomyopathy, Huntington's disease, Positive airway pressure therapy, Sleep apnoea syndrome, Type 2 diabetes mellitus.
- Co-suspect medications: None.
- PTs with fatal outcome: Interchange of vaccine products, Myocarditis, Off label use, Pericarditis, Sudden death.
- Time to onset (pericarditis and myocarditis): 11.5 hours after dose 3, the patient died.
- Cause of death: Myocarditis; Pericarditis; Sudden death.

A 49-year-old male subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Aortic rupture, Back pain, Cardiomegaly, Internal haemorrhage, Myocarditis, Pericarditis, Pyrexia, Syncope, Vomiting.
- Time to onset (pericarditis): ~50 days after dose 1, the patient died due to the above events.

- Cause of death: Cardiomegaly.

Fatal Pericarditis cases in adult (51-64 years of age) (7 cases; 5 cases medically confirmed and 2 non-medically confirmed)

- 5 cases medically confirmed:

A 56-year-old male subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Malaise, Pericarditis.
- Time to onset (pericarditis): On the same day of receiving dose 1.
- Cause of death: Both the above events.

A 57-year-old female subject from [redacted].

- Medical history: Thyroid cancer.
- Co-suspect medications: None.
- PTs with fatal outcome: Pericarditis.
- Time to onset (pericarditis): Unspecified days after dose 3.
- Cause of death: Pericarditis.

A 59-year-old female subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Atrial fibrillation, Atrioventricular block complete, Cardiac arrest, Chest pain, Electrocardiogram ST segment depression, Myocarditis, Pericarditis, Troponin increased.
- Time to onset (pericarditis): 67 days after dose 3.
- Cause of death: All the above events.

A 61-year-old female subject from [redacted].

- Medical history: Cerebrovascular accident, Syncope, Thymic carcinoma, Thymoma.
- Co-suspect medications: None.
- PTs with fatal outcome: Cardio-respiratory arrest, Coronary artery stenosis, Endocarditis, Myocarditis, Pericarditis, Right ventricular failure, Sudden death.
- Time to onset (pericarditis): 11 days after dose 3.
- Cause of death: All the above events.

A 62-year-old male subject from [redacted]

- Medical history: Unknown.

- Co-suspect medications: None.
- PTs with fatal outcome: Cardiac failure, Pericarditis.
- Time to onset (pericarditis): 14 days after dose 2.
- Cause of death: Both the above events.

- 2 cases non-medically confirmed:

A 53-year-old male subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Pericarditis.
- Time to onset (pericarditis): Within 7 days after dose 1.
- Cause of death: Pericarditis.

A 62-year-old male subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Abdominal pain upper, Cardiac arrest, Chest pain, Dizziness, Dyspnoea, Fatigue, Immunisation, Myocarditis, Pain in extremity, Palpitations, Pericarditis, Thrombosis.
- Time to onset (pericarditis): 6 days after dose 3.
- Cause of death: All the above clinical events.

Fatal Pericarditis cases in elderly (65-74 years of age) (2 cases, both non-medically confirmed)

A 69-year-old female subject from [redacted]

- Medical history: Arthralgia, Brain neoplasm, Hypertension.
- Co-suspect medications: None.
- PTs with fatal outcome: Amnesia, Death, Interchange of vaccine products, Memory impairment, Myocarditis, Off label use, Pericarditis.
- Time to onset (pericarditis and myocarditis): Unspecified days after the dose 3.
- Causes of death: Brain neoplasm.

A 71-year-old male subject from [redacted]

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Chest pain, Death, Dyspnoea, Fatigue, Myocarditis, Palpitations, Pericarditis, Pulmonary embolism, Thrombosis.
- Time to onset (pericarditis and myocarditis): Unspecified days after the dose 2.

- Causes of death: Death; Thrombosis.

Fatal Pericarditis cases in elderly (> 75 years of age –4 cases; 2 cases medically confirmed and 2 cases non-medically confirmed)

- 2 cases medically confirmed:

An 89-year-old female subject from [redacted].

- Medical history: Anaemia megaloblastic, Aphasia, Arthropathy, Atrial fibrillation, Benign tumour excision, Cardiac assistance device user, Cerebrovascular accident, Chronic gastritis, Cognitive disorder, Diverticulum, Dyslipidaemia, Hypertension, Neoplasm, Oropharyngeal surgery, Parotitis, Salivary gland neoplasm, Sinus node dysfunction, Type 2 diabetes mellitus.
- Co-suspect medications: Influenza vaccine INACT SAG 3V.
- PTs with fatal outcome: Pericarditis.
- Time to onset (pericarditis): 2 days after dose 3.
- Causes of death: Pericarditis

A 92-year-old male subject from [redacted].

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Aortic dissection, Cardiac failure, Cardiac tamponade, Pericarditis.
- Time to onset (pericarditis): Unspecified days after dose 3.
- Causes of death: All the above events.

- 2 cases not medically confirmed:

An 81-year-old male subject, from [redacted]

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Pericarditis.
- Time to onset (pericarditis): 60 days after dose 3.
- Causes of death: Pericarditis.

A 78-year-old male subject from [redacted]

- Medical history: Unknown.
- Co-suspect medications: None.
- PTs with fatal outcome: Multiple organ dysfunction syndrome, Myocardial infarction, Pericarditis.

- Time to onset (pericarditis): 8 days after dose 3.
- Causes of death: Due to all the above events.

Pericarditis relevant data in this subgroup of subjects are summarised in Table 51 below.

Table 51. Pericarditis in Subjects aged ≥ 40 years (N=1756)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	538	388	8
	No	474	338	10
Relevant PT[a]	Pericarditis	1001	720	17
	Pericarditis constrictive	2	3	0
	Pleuropericarditis	15	4	1
Hospitalisation required/prolonged	Yes	225	264	2
	No	789	462	16
Relevant suspect dose	Dose 1	296	224	5
	Dose 2	295	210	4
	Dose 3	348	241	6
	Dose 4	15	8	1
	Unknown	58	43	2
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=1763	≤ 24 hours	53	33	0
	1-5 days	190	122	2
	6-13 days	119	99	0
	14-21 days	77	74	0
	22-31 days	57	45	3
	32-60 days	64	44	0
	61-180 days	67	48	0
	181-375 days	17	5	0
	Unknown	374	257	13
Event Outcome[b]	Fatal	5	12	0
	Not resolved	355	207	2
	Resolved	114	121	2
	Resolved with sequelae	26	21	1
	Resolving	215	148	0
	Unknown	304	218	13
Duration of event[c] n= 87, median: 28	Up to 3 days	1	7	0
	4-6 days	6	2	0
	7-10 days	2	2	0
	11-26 days	11	11	0
	27-57 days	6	12	0
	58-180 days	16	8	0
	181-265 days	3	0	0

a. All serious occurrences.
b. Multiple episodes of the same PT event were reported with a different clinical outcome in one case hence the sum of the events outcome exceeds the total number of PT events.
c. For those cases where the event resolved or resolved with sequelae.

Subjects with Unknown Age

Clinical Trial Data

- Number of cases: none; no cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 309 (0.06 % of 507,683 cases of the total PM dataset, 0.5% of the 60,379 subjects with unknown age), compared to 363 (0.06%) cases retrieved in the PSUR #2.
- Country of incidence: UK (129), Canada (73), Australia (49), US (14), Germany (12), France, Greece (5 each). The remaining 22 cases were distributed among 13 countries.
- Subjects' age in years: Unknown.
- Medical history (n = 90): the medical conditions reported more than twice included the PTs Hypertension (12), Asthma (11), Pericarditis (8), Drug hypersensitivity, Tobacco user (7), Palpitations (5), Anxiety, Fibromyalgia, Hypothyroidism, Immunodeficiency, Seasonal allergy, Steroid therapy (4 each), Blood cholesterol increased, Depression, Gastrooesophageal reflux disease, Insomnia, Non-tobacco user, Pain, and Rheumatoid arthritis (3 each).
- COVID-19 Medical history (n = 29): Suspected COVID-19 (19), COVID-19 (9), Post-acute COVID-19 syndrome, SARS-CoV-2 test positive (1 each).
- Co-suspects (n= 5 cases): COVID-19 vaccine MRNA (MRNA 1273) (2), Clozapine, COBID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Influenza vaccine (1 each).
- Most frequently co-reported PTs (≥2%): Chest pain (167), Palpitations (120), Myocarditis (116), Dyspnoea (109), Fatigue (108), Tachycardia (72), Immunisation (46), Interchange of vaccine products, Off label use (44 each), Pyrexia (41), Chest discomfort (33), Headache (26), Dizziness (25), Myopericarditis, Syncope (17 each), Nausea, Pain in extremity (16 each), Malaise (15), Pain (14), Arthralgia, Asthenia, Pericardial effusion (12 each), Hypoaesthesia (11), Chills, COVID-19, Inappropriate schedule of product administration, Myalgia, Paraesthesia (10 each), Heart rate increased (9), Angina pectoris, Drug ineffective, Hyperhidrosis, Migraine (8 each), Back pain, Cardiac flutter, Cough, Influenza like illness, Loss of personal independence in daily activities (7 each), Arrhythmia, Axillary pain, Heart rate abnormal, Insomnia, Loss of consciousness, Lymphadenopathy, Muscular weakness, Musculoskeletal chest pain, Pleuritic pain (6 each), Condition aggravated, Discomfort, Gait disturbance, Oxygen saturation decreased, Tremor, Vaccination site pain, Vision blurred, and Vomiting (5 each).

Pericarditis relevant data in this subgroup of subjects are summarised in the below Table 52.

Table 52. Pericarditis in Subjects with Unknown Age (N=309)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
Medically Confirmed	Yes	46	79	14
	No	87	50	33
Relevant PT[a]	Pericarditis	132	129	47
	Pleuropericarditis	1	0	0
Hospitalisation required/prolonged	Yes	27	30	3
	No	106	99	44
Relevant suspect dose	Dose 1	38	50	13
	Dose 2	43	44	8
	Dose 3	47	25	11
	Unknown	5	10	15
		Female No. of Events	**Male No. of Events**	**Unknown No. of Events**
Time to Onset n=309	≤ 24 hours	4	7	1
	1-5 days	22	28	3
	6-13 days	2	9	2
	14-21 days	5	7	0
	22-31 days	1	2	1
	32-60 days	5	3	0
	61-180 days	3	1	1
	181-375 days	2	0	0
	Unknown	89	72	39
Event Outcome	Fatal	0	0	0
	Not resolved	35	44	4
	Resolved	6	19	4
	Resolved with sequelae	2	1	0
	Resolving	11	8	2
	Unknown	79	57	37
Duration of event[b] n=2, median: 34	4-6 days	0	0	1
	27-57 days	0	1	0

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

Subjects with booster dose

Clinical Trial Data

- Number of cases: none; one (1) case was retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 1216 (0.2% of 507,683 cases of the total PM dataset, 1.0% of the 117,750 subjects who received a booster dose), compared to 283 cases (0.04%) in the PSUR #2.

- Country of incidence: UK (474), France (202), Germany (94), Italy (93), Netherlands (46), New Zealand (38), Norway (32), Japan (30), Israel, Sweden (21 each); the remaining 165 cases were distributed among 24 countries.
- MC (500), NMC (716).
- Subjects' gender: female (661), male (531), and unknown (24).
- Subjects' age in year: n = 1130, range: 13 -93, mean: 45.1, median: 44.0
- Medical history (n = 566): the medical conditions reported more or equal to 10 times included the PTs Hypertension (79), Pericarditis (40), Asthma (38), Immunodeficiency (32), Hypothyroidism (29), Obesity (22), Diabetes mellitus, Drug hypersensitivity (19 each), Seasonal allergy (18), Depression, Steroid therapy, Tobacco user (15 each), Atrial fibrillation, Non-tobacco user, Type 2 diabetes mellitus (14 each), Anxiety, Dyslipidaemia, Gastrooesophageal reflux disease (13 each), Clinical trial participant, Disease risk factor, Migraine (12 each), Myocardial infarction, Rheumatoid arthritis (11 each), Chronic kidney disease, Food allergy (10 each).
- COVID-19 Medical history (n = 114[85]): Suspected COVID-19 (60), COVID-19 (55), Post-acute COVID-19 syndrome (3), Exposure to SARS-CoV-2, SARS-CoV-2 test positive (1 each).
- Co-suspects (n=20 cases): Influenza vaccine (6), Influenza vaccine INACT SAG 3V (3), Adalimumab, amoxicillin, Apixaban, Colchicine, COVID-19 vaccine, COVID-19 vaccine MRNA (MRNA 1273), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Etanercept, Propranolol, Salbutamol, Zuclopenthixol (1 each).
- Number of relevant events: 1220.
- Relevant event seriousness: all serious.
- Reported relevant PTs: Pericarditis (1212), Pleuropericarditis (8)
- Relevant event outcome[78]: fatal (12), resolved/resolving (414), resolved with sequelae (21), not resolved (296), unknown (478).
- Most frequently co-reported PTs (>3%): Chest pain (620), Myocarditis (461), Dyspnoea (448), Fatigue (427), Immunisation (418), Off label use (365), Palpitations (363), Interchange of vaccine products (332), Tachycardia (291), Pyrexia (218), Chest discomfort (151), Headache (124), Pericardial effusion (88), Malaise (87), Pain (82), Dizziness (74), Pain in extremity (66), Syncope (61), Arthralgia (58), Heart rate increased (57), Angina pectoris, Nausea (50 each), Asthenia (48), Arrhythmia (41), Chills, Lymphadenopathy, Myalgia (40 each), Back pain, Vaccination site pain (34 each), Cough (33).

The number of pericarditis cases occurred after a booster dose in each age group is reported in the below Table 53 by gender.

Table 53. Pericarditis in Subjects who Received a Booster Dose

Characteristics		Heterologous Booster dose No. of Cases			Homologous Booster dose No. of Cases			Unknown dose No. of cases		
		F	M	U	F	M	U	F	M	U
Age group	0 to 17 years	1	0	0	2	9	0	2	9	0
	18 to 24 years	4	13	0	24	32	0	25	22	0
	25 to 29 years	8	10	0	25	35	0	22	20	2
	30 to 39 years	23	15	0	62	50	2	32	24	0
	40 years and older	140	94	4	143	85	2	100	87	2
	Unknown	26	8	5	16	12	5	6	6	2
	Total	*202*	*140*	*9*	*272*	*223*	*9*	*187*	*168*	*6*

F=female; M=male; U=unknown

During the reporting period, of the 4156 cases reported, there were 1319 cases of medically confirmed pericarditis with a latency 21 days or less, of which in 975 cases pericarditis occurred within 1 week post vaccine administration. The majority (1255) of the cases were assessed as serious due to hospitalisation and/or medically significant. In 58 other cases, the seriousness criterion was reported as disability or life threatening, and in 6 cases, a fatal outcome was reported, which are reviewed above in the age-stratified sections.

Cumulatively, there were 9896 cases of pericarditis which constitute 0.7% of the overall PM dataset. During the current reporting period, there were 4156 cases reported which constitute 0.8% of 507,683 cases of the total PM dataset, and majority (~99%) of these cases were spontaneously reported, in which 43% of the cases were non-medically confirmed cases. Upon review of these 4156 cases, the majority of the cases (56.7%) were reported from adult population with the age group ranging from 30 to 64 years of age, where the female subjects (55.1%) were reported higher than the male subjects (44.1%). In the majority (66.2%) of the cases, the event of pericarditis was reported after the 1st dose (37.6%) or the 2nd dose (28.5%) and relatively less after the 3rd/booster dose (26.8%). Approximately 35% of the cases reported medical history such as hypertension, asthma and pericarditis, which might be attributed to the event of pericarditis. However, in the remaining cases, insufficient description of the cardiovascular and/or non-cardiovascular medical history and diagnostic to rule out other aetiologies in majority of the cases continues to preclude proper medical adjudication of causality assessment between administration of the vaccine and occurrence of pericarditis.

O/E Analysis

O/E analysis was performed for Myocarditis/Pericarditis (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Evaluation of Myocarditis and Pericarditis did not reveal any significant new safety information for this interval. Considering the accumulating data from post-authorisation use of the vaccine, including the consistent findings from passive and active surveillance

databases of increased occurrences of myocarditis and pericarditis following vaccination with BNT162b2, myocarditis and pericarditis have been added as ADRs in section 4.8, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022, after the DLP.

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.[89]

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.

[89] 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.

Of note, there were 9 cases reporting the PTs Vaccine associated enhanced disease, and Vaccine associated enhanced respiratory 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.

Post-Authorisation Data

Of the 1278 cases retrieved based on search strategy, 10 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- In 4 cases the PT indicative of lack of efficacy did not refer to BNT162b2 vaccine.
- In 3 cases, the subjects developed SARS-CoV-2 infection during the early days from the 1st dose (days 1 – 13); therefore, the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable, even if severe, cannot be considered a potential case of enhanced disease.
- In 3 cases the PT Drug ineffective was erroneously coded; upon review, none of them developed COVID-19 infection.

Overview

- Number of cases: 1268 (0.2% of 507,683 cases, the total PM dataset), compared to 1490 (0.2%) retrieved in the PSUR # 2. All cases are serious.
- MC cases (878), NMC cases (390).
- Country of incidence: France (346), Spain (142), UK (139), US (117), Italy (105), Estonia (94), Germany (66), Philippines (45), Australia, Canada (19 each), Switzerland (18), Portugal, (17), Netherlands (14), Austria (10); the remaining 117 cases originated from 117 different countries.
- Gender: female (636), male (604), and unknown (28).
- Age in years (n = 1215), range: 5 – 102, mean: 61.4, median: 65.0.
- Relevant event seriousness: 1295 serious, 406 non-serious.
- Reported relevant PTs by organ system:
    - Respiratory system PTs (1631): COVID-19 pneumonia (524), Dyspnoea (398), Respiratory failure (48), Acute respiratory distress syndrome (42), Pulmonary embolism (40), Hypoxia (28), and Tachypnoea (27).
    - Gastrointestinal/Hepatic system PTs (288): Diarrhoea (139), Vomiting (88), Abdominal pain (54), and Jaundice (7).
    - Cardiovascular system PTs (143): Myocarditis (85), Arrhythmia (32), Cardiac failure (18), Acute myocardial infarction (6), and Cardiogenic shock (2).

- Renal and urinary system PTs (39): Acute kidney injury (27), and Renal failure (12).
- Nervous system PTs (47): Seizure (21), Cerebrovascular accident (18), Encephalopathy (6), and Altered state of consciousness (2).
- Vascular system PTs (23): Deep vein thrombosis (12), Shock (6), Vasculitis (3), and Peripheral ischaemia (2).
- Blood and lymphatic system PTs (14): Thrombocytopenia (12), and Disseminated intravascular coagulation (2).
- Immune system PTs (30): Vaccine associated enhanced disease (12), and Multisystem inflammatory syndrome in children (9), and Vaccine associated enhanced respiratory disease (9 each).
- Other PTs (24): Multiple organ dysfunction syndrome (13), Chillblains (5), Meningitis (4), and Erythema multiforme (2).

- Case outcome: fatal (184), not resolved (329), resolved/resolving (582), resolved with sequelae (31), and unknown (142).

COVID-19 positivity and severity of events

- Suspected COVID-19 infection: 188 [no information on confirmatory tests performed or test negative; LOE coded to Drug ineffective (180 cases) or to Vaccination failure (8 cases, 2 of these cases also co-reported Vaccine associated enhance disease, Vaccine associated enhanced respiratory disease)]
- Confirmed COVID-19 infection: 1080 [test positive or implied COVID-19 infection; LOE coded to Drug ineffective (524 cases) or Vaccination failure (556 cases, 7 of these cases also co-reported Vaccine associated enhanced disease, or Vaccine associate enhanced respiratory disease)].
- Seriousness criteria for the total 1080 cases:
  - Medically significant: 325;
  - Hospitalisation required (non-fatal/non-life threatening): 521;
  - Life threatening: 60;
  - Death: 174.

Seriousness criteria: medically significant (450)

- In 325 of 450 cases where the seriousness criterion was "medically significant", the subjects had a confirmed COVID-19 infection after vaccination, while 125 subjects had suspected COVID-19 infection. These 125 subjects did not require hospitalisation.

- In the 325 confirmed COVID-19 cases, subjects' age ranged from 7 to 100 years (n = 304, mean: 47.0 years, median: 44.0 years) (14 paediatrics, 225 adults, 66 elderly, 20 unknown); gender was reported as female (212), male (101), and unknown (12).

- Time to event onset of the COVID 19 infection was reported for 250 of these 325 cases:
  - Day 13 to 344 after dose 1 (59 cases);
  - Day 0 to 492 after dose 2 (79 cases);
  - Day 0 to 329 after dose 3 (87 cases);
  - Day 6 to 95 after dose 4 (5 cases);
  - Day 12 to 431 after vaccination [dose number not reported] (20 cases).

- These 325 cases reported 419 relevant events.[90] The most commonly (≥17 occurrences) reported relevant PTs Dyspnoea (137), Diarrhoea (76), Myocarditis (45), Vomiting (38), Abdominal pain (33), and COVID-19 pneumonia (17).

- The outcome[78] of the COVID-19 infection related events reported in these 325 cases was: resolved/resolving (129), resolved with sequelae (2), not resolved (92), and unknown (197).

Seriousness criteria: hospitalisation (non-fatal, non-life threatening) (568)

- Hospitalisation occurred in 521 subjects, for 47 of them the COVID-19 infection was not confirmed.

- In the 521 COVID-19 confirmed cases, subjects' age (n = 515) ranged from 10 to 102 years, (mean: 69.2 years, median: 73.0 years) (6 paediatrics, 166 adults, 344 elderly, 5 unknown); gender was reported as female (235), male (279), and unknown (7).

- Time to event onset of the COVID-19 infection was reported for 464 of these 521 cases.
  - Day 13 to 264 after dose 1 (20 cases);
  - Day 3 to 424 days after dose 2 (223 cases);
  - Day 0 to 232 days after dose 3 (199 cases);
  - Day 2 to 71 days after dose 4 (15 cases);
  - Day 9 to 249 after vaccination [dose number not reported] (7 cases).

- These 521 cases reported 695 relevant events. The most commonly (≥27 occurrences) reported relevant PTs COVID-19 pneumonia (344), Dyspnoea (146), Respiratory failure (29), and Diarrhoea (27).

[90] PTs included in the search strategy excluding Drug ineffective and Vaccination failure.

- The outcome of the COVID-19 infection related events reported in these 521 cases was: resolved/resolving (402), not resolved (86), resolved with sequelae (7), and unknown (200).

Seriousness criteria: life-threatening (non-fatal) (66)

- In 60 of the 66 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 60 confirmed COVID-19 cases, subject's age ranged from 5 to 94 years (n = 59), (mean: 57.2 years, median: 60.0 years), (4 paediatrics, 30 adults, 25 elderly, 1 unknown); gender was reported as female (17), and male (43).

- Time to event onset of the COVID-19 infection was reported for 47 of these 60 cases.
  - Day 17 to 244 after dose 1 (8 cases);
  - Day 26 to 377 after dose 2 (25 cases);
  - Day 1 to 184 after dose 3 (13 cases);
  - Day 18 after vaccination [dose number not reported] (1 case).

- These 60 cases reported 85 relevant events. The most commonly (≥6 occurrences) reported relevant PTs COVID-19 pneumonia (24), Dyspnoea (9), Pulmonary embolism (8), Acute respiratory distress syndrome, and Myocarditis (6 each).

- The outcome of the COVID-19 infection related events reported in these 60 cases was: resolved/resolving (30), not resolved (11), resolved with sequelae (2), and unknown (42).

Seriousness criteria: Death (184 cases)

One-hundred and eighty-four (184) subjects died, of which COVID-19 was not confirmed in 10 cases; the remaining 174 confirmed cases are described below.

- Age: 11 to 99 years (n = 171), Mean = 77.6 years, Median = 80.0 years.

- Country of incidence: France (78), Spain (26), Estonia (21), Italy (7), Germany, Malaysia, Philippines, Switzerland (4 each), Hungary, Portugal (3 each), Bulgaria, Norway, Slovenia, South Africa, UK, US (2 each), Austria, Czech Republic, Greece, Iceland, Lithuania, Luxembourg, Netherlands, and Sweden (1 each).

- Gender: female (65), male (107), and unknown (2).

- Medical history (n = 153) included PTs in the following SOCs; Most frequently (≥4 occurrences) reported PTs by SOC are presented below:
  - Vascular disorders – 93 cases (60.8%): Hypertension (81), Deep vein thrombosis (6) Aortic aneurysm, Aortic stenosis, and Peripheral venous disease (4 each);
  - Metabolism and nutrition disorders - 74 cases (48.3%): Dyslipidaemia (28), Type 2 diabetes mellitus (23), Diabetes mellitus (13), Gout, Obesity (10 each), and Hypercholesterolaemia (5);
  - Cardiac disorders - 71 cases (46.4%): Atrial fibrillation (32), Myocardial ischaemia (17), Cardiac failure (15), Myocardial infarction (11), and Hypertensive heart disease (8);
  - Nervous system disorders - 52 cases (34.0%): Cognitive disorder (11), Cerebrovascular accident, Dementia Alzheimer's type (7 each), Ischaemic stroke (6), Parkinson's disease, and Transient ischaemic attack (4 each);
  - Surgical and medical procedures - 43 cases (28.1%): Cardiac pacemaker insertion, Hysterectomy, and Stent placement (4 each);
  - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - 42 cases (27.4%): Chronic lymphocytic leukaemia (6), Plasma cell myeloma, and Prostate cancer (5 each);
  - Respiratory, thoracic and mediastinal disorders - 31 cases (20.3%): Chronic obstructive pulmonary disease (8), Emphysema, Pulmonary embolism, and Sleep apnoea syndrome (4 each);
  - Other medical histories were reported under the following SOCs: Musculoskeletal and connective tissue disorders (28), Gastrointestinal disorders, Social circumstances (26 each), Infections and infestations (21), Psychiatric disorders (20), Endocrine disorders (16), Injury, poisoning and procedural complications (15), Eye disorders (11), Hepatobiliary disorders, Immune system disorders, Reproductive system and breast disorders (9 each), Ear and labyrinth disorders (8), Skin and subcutaneous tissue disorders (7), Blood and lymphatic system disorders, General disorders and administration site conditions (6 each), Congenital, familial and genetic disorders (5), Investigations (2).

- Latency of the COVID-19 occurrence was reported in 147 of the 174 cases:
  - Day 13 to 29 after dose 1 (7 cases);
  - Day 0 to 346 after dose 2 (64 cases);
  - Day 2 to 214 after dose 3 (63 cases);
  - Day 10 to 84 after dose 4 (3 cases);
  - Day 5 to 192 after vaccination [dose number not reported] (10 cases).

- The most frequently (>10 occurrences) reported causes of death in these 174 cases coded to the PTs COVID-19 pneumonia (112), COVID-19 (58), Vaccination failure (45), Drug ineffective (41), Acute respiratory distress syndrome, Dyspnoea (14), Multiple organ

dysfunction syndrome, and Respiratory failure (11 each). Of note, in 11 cases limited information regarding the cause of death was reported (PT Death).

- In 93 of the 174 fatal cases, vaccination failure was reported (cross referenced with Section 16.3.4.5 *Lack of Therapeutic Efficacy*).
- One hundred and fifty-two (152) of these 174 cases involved elderly subjects (aged 65 to 74 years [43] or ≥75 years [109]), including 138 subjects with underlying medical history of clinical significance.
- Among the remaining 22 cases; 15 of them had concurrent medical histories (less than or equal to 17 years [1], 18 to 30 years [1], 31 to 50 years [3], 51 to 64 years [9], and unknown [1]) that could impact the severity and evolution of the COVID-19 infection, including but not limited to cardiac history (carotid arteriosclerosis, hypertension, peripheral arterial occlusive disease, ventricular arrhythmia), renal disorders (chronic kidney disease) respiratory disorders (COVID-19, ex-tobacco user, tobacco user, acute respiratory distress syndrome, asphyxiating thoracic dystrophy, chronic respiratory failure, pleural thickening), and immunodeficient conditions (kidney transplant rejection, pulmonary mass, renal transplant, solid organ transplant).
- Of the remaining 7 cases where medical history was not reported, none of these 7 cases reported concomitant medications. The causes of death were reported as Dyspnoea (4), COVID-19 (2), Asthenia, Cerebral haemorrhage, Circulatory collapse, Cough, Hypoxia, Pain, Pyrexia, Vaccination failure, and Vomiting (1 each). Of note, in 1 case provided limited information regarding cause of death (PT Death). In 2 cases, the latency to onset of COVID-19 infection was not reported in the remaining 5 cases the latency was reported from dose 1 was 17 days, from dose 2 was: 59, 92, and 139 days, and from an unknown dose was reported as 5 days in 1 case.

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 that 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 categorised as important in which new information has become available during the reporting interval that allows further characterisation of a previously 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 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 the AESIs.

16.3.3.1.1. Anaphylactic AESIs

Please refer to the Risk 'Anaphylaxis' in Section 16.3.1 *Evaluation of Important Identified Risks*.

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: 27 (blinded therapy [6], and BNT162b2 [21]) (4.0 % of 668 cases, the total CT dataset) compared to 35 cases (4.9%) retrieved in the PSUR #2.
- Country of incidence: US (22), Argentina (3), Germany, South Africa (1 each).
- Subjects' gender: female (7), male (20).
- Subjects' age in years: (n = 27), range: 3-80, mean: 61.7, median: 64.
- Medical history (n = 23): the reported relevant medical conditions (>2 occurrences) included Hypertension (13), Type 2 diabetes mellitus (7), Hypercholesterolaemia, Hyperlipidaemia, Obesity (5 each), Coronary artery disease, Dyslipidaemia, Gastrooesophageal reflux disease (4 each), Anxiety, Depression, Osteoarthritis (3 each).
- COVID-19 medical history: None.
- Co-suspect medications: None.
- Reported relevant PTs: Myocardial infarction (9), Chest pain (8), Coronary artery disease (5), Acute myocardial infarction (4), Cardiac failure, Tachycardia (1 each).
- Relevant event outcome: fatal (2), resolved/resolving (21), resolved with sequelae (4), not resolved (1).
- None of the events were related BNT162b2 or blinded therapy.

Post-Authorisation Data

- Number of cases: 32,712 (6.4 % of 507,683 cases, the total PM dataset), compared to 29,486 (4.5%) cases retrieved in the PSUR #2.
- MC cases (11,952), NMC cases (20760).
- Country of incidence (>16 occurrences): Germany (11,180), Australia (4456), UK (3049), France (2612), Taiwan Province of China (1393), Italy (1334), Netherlands (810), Austria (677), Malaysia (591), Philippines (475), US (422), Japan (397), New Zealand (396), Norway (369), Finland (338), Sweden (333), Belgium (328), Canada (317), Poland (307), Iraq (298), Greece (275), Spain (271), Ireland (237), Romania (217), Czech Republic (198), Denmark (125), Switzerland (119), Brazil (118), Lithuania (110), Croatia (92), Estonia (88), Portugal (82), Egypt (77), Israel (74), Slovenia (70), Mexico (62), Iceland (52), Slovakia (51), Hungary (50), Singapore (35), South Africa (30), Georgia (24), Latvia (24), Luxembourg (22), Turkey (20), Bulgaria (18), Cyprus (17); the remaining 72 cases were distributed among 31 countries.
- Subjects' gender: female (19,730), male (12,424) and unknown (558).
- Subjects' age in years (n = 31,124), range: 2 months-99, mean: 40.3, median: 39.
- Medical history (n = 9348): the most frequently (>2%) reported relevant medical conditions included Hypertension (1349), Seasonal allergy (1121), Asthma (839), Drug hypersensitivity (758), Hypersensitivity (511), Food allergy (502), Mite allergy (387), Hypothyroidism (365), Tobacco user (290), Allergy to animal (285), Autoimmune thyroiditis (280), Diabetes mellitus (274), Obesity (253), Atrial fibrillation (232), Non-tobacco user (232), Arrhythmia (220), Allergy to metals (216), Migraine (214).
- COVID-19 Medical history (n = 1546): the medical conditions reported included COVID-19 (1021), Suspected COVID-19 (492), Post-acute COVID-19 syndrome (40), COVID-19 pneumonia (16), SARS-CoV-2 test positive (14), Coronavirus infection (7), Asymptomatic COVID-19 (6), Exposure to SARS-CoV-2 (4), and Coronavirus pneumonia (1).
- Co-suspects (n = 295 cases): the frequently (>12 occurrences) reported relevant co-suspect medications were COVID-19 vaccine mRNA (MRNA 1273) (66), COVID-19 vaccine (34), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (20), INFLUENZA VACCINE (19), adalimumab (13).
- Number of relevant events: 36,790.
- Relevant event seriousness[37]: serious (16,539), non-serious (20,268).
- Relevant PTs: Chest pain (17,945), Tachycardia (10,914), Arrhythmia (5627), Myocardial infarction (921), Cardiac failure (583), Acute myocardial infarction (364), Postural orthostatic tachycardia syndrome (149), Coronary artery disease (114), Cardiogenic shock (72), Cardiac failure acute (57), Stress cardiomyopathy (44).

- Time to event onset (n = 26,744 occurrences),[91] range: <24 hours to 382 days, median: 1 day.
  - <24 hours: 7337 events (19 fatal events);
  - 1 day: 5830 events (56 fatal events);
  - 2-7 days: 7426 events (83 fatal events);
  - 8-14 days: 2202 events (45 fatal events);
  - 15-30 days: 1887 events (42 fatal events);
  - 31-181 days: 1892 events (68 fatal events);
  - 182-382 days: 170 events (6 fatal events).

- Duration of relevant events (n = 8262 out of 8906 occurrences with outcome of resolved and resolved with sequalae), range: <24 hours to 430 days, median: 4 days.
  - <24 hours: 816 events;
  - 1 day: 681 events;
  - 2-7 days: 1379 events;
  - 8-14 days: 476 events;
  - 15-30 days: 487 events;
  - 31-181 days: 904 events;
  - 182-430 days: 158 events.

- Relevant event outcome[78]: fatal (496), resolved/resolving (13,937), resolved with sequelae (1321), not resolved (12,839), unknown (8437).

  In 449 cases (reporting 496 relevant events with fatal outcome), the reported causes of death (>10 occurrences) were coded to the PTs Myocardial infarction (147), Cardiac failure (94), Chest pain (55), Acute myocardial infarction (54), Dyspnoea (43), Cardiac arrest (42), Arrhythmia (34), Cardiac failure acute (26), Myocarditis (22), Cardiogenic shock, Cardio-respiratory arrest (20 each), Thrombosis (15), Malaise (13), Loss of consciousness, Pulmonary embolism, Pulmonary oedema, Tachycardia (12 each), Pneumonia, Respiratory failure (11 each). Of note, in 16 cases limited information regarding the cause of death was provided (PT Death [11]; PT Sudden death [1]; Unknown [4]). Most (250 of 449 cases) of the fatal cases involved elderly subjects. When the medical history was provided (253 cases), the most frequently (≥ 9 occurrences) relevant medical conditions included events coded to the PTs Hypertension (91), Diabetes mellitus (32), Atrial fibrillation (28), Obesity (24), Cardiac failure (23), Type 2 diabetes mellitus (16), Coronary artery disease (15), Dyslipidaemia, Myocardial infarction (13 each), Chronic kidney disease, Chronic obstructive pulmonary disease (12 each), Cardiac disorder, Tobacco user (11 each), Cardiac failure chronic, Hyperlipidaemia (10 each), Arteriosclerosis, Asthma, Cerebral infarction, Myocardial ischaemia (9 each).

[91] This number does not include 10,261 events for which partial administration or event onset dates were reported or events did not have a meaningful time to onset value provided in the reported information.

Analysis by age group

CT: Paediatric (1), Adults (14), and Elderly (12).

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

PM: Paediatric (2808), Adults (25850), Elderly (2996) and Unknown (1058).

- Higher reporting proportion of events coded to the PTs Arrhythmia [4.6% in paediatrics vs 18.2% in adults vs 24.3% in elderly], Cardiac failure [0.5% in paediatrics vs 0.8% in adults vs 11.5% in elderly], Myocardial infarction [0.3% in paediatrics vs 2.2% in adults vs 9.0% in elderly], Cardiogenic shock [0.1% in paediatrics vs 0.2% in adults vs 0.8% in elderly], Acute myocardial infarction [0.1% in paediatrics vs 0.8% in adults vs 4.8% in elderly], Cardiac failure acute [0.1% in paediatrics vs 0.1% in adults vs 0.8% in elderly], Stress cardiomyopathy [0.04% in paediatrics vs 0.1% in adults vs 0.7% in elderly], and Coronary artery disease [0% in paediatrics vs 0.3% in adults vs 1.5% in elderly] and was reported in elderly population when compared to adult and paediatric population. Higher reporting proportion of PT Chest pain [81.6% in paediatrics vs 53.5% in adults vs 36.3% in elderly] was reported in paediatrics compared to adults and elderly subjects. Higher reporting proportion of PT Tachycardia [19.6% in paediatrics vs 36.5% in adults vs 22.7% in elderly] was reported in adults compared to paediatrics and elderly subjects. The PT Postural orthostatic tachycardia syndrome was reported among the paediatric and adult subjects only (0.4% each).

Analysis by presence of comorbidities

Number of subjects with comorbidities: 3726 (0.7% of 507,683 cases, the total dataset).

No significant difference was observed in the reporting proportion of cardiovascular AESIs with fatal outcome in individuals with comorbid conditions (0.4% of events with fatal outcome) when compared to the reporting proportion observed in the individuals without comorbidities (0.9 % of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute myocardial infarction/Myocardial infarction; Arrhythmia; Coronary artery disease; Heart failure; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy (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[92] - HLTs (All Path) Leukopenias NEC; Neutropenias OR SMQ Haemorrhage terms (excl laboratory terms) OR PT Acquired haemophilia.

Clinical Trial Data

- Number of cases: 15 (BNT162b2 [12] and blinded therapy [3]) (2.2 % of 668 cases, the total CT dataset) compared to 19 cases (2.4%) retrieved in the PSUR #2[93].
- Country of incidence: US (11), Argentina, Brazil, China, and Germany (1 each).
- Subjects' gender: female (9), male (6).
- Subjects' age in years (n = 15), range: 14-79, mean: 51.5, median: 49.0.
- Medical history (n = 15): the relevant medical conditions reported more than twice were coded to the PTs Hypertension (6), Depression, Type 2 diabetes mellitus, and Hypercholesterolaemia (3 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Number of relevant events: 16.
- Reported relevant PTs (≥2 occurrences): Subdural haematoma (3), Haematoma, and Lower gastrointestinal haemorrhage (2 each). None of these SAEs were assessed as related to BNT162b2/blinded therapy.
- Relevant event outcome: fatal (1), resolved/resolving (13), resolved with sequelae (1), not resolved (1).

Post-Authorisation Data

- Number of relevant cases: 30,302 (5.9% of 507,683 cases, the total PM dataset), compared to 37,327 cases (5.7%) retrieved in the PSUR #2[93].
- MC cases (4952), NMC cases (25,350).

[92] The PT Acquired haemophilia has been added and PT Thrombocytopenia has been reassigned to Immune-mediated/autoimmune AESIs category.

[93] The change to the search criteria should be considered when comparing the cases retrieved in the current PSUR and in PSUR #2.

- Country of incidence: Germany (7802), Netherlands (6166), UK (3266), Norway (2930), France (2905), Australia (1010), Spain (626), Italy (579), Sweden (557), Belgium (438); the remaining 4023 cases were distributed among 63 countries.

- Subjects' age in years (n = 28,488), range: 5 months-100 years, mean: 38.9, median: 37.0.
- Medical history (n = 10,294): the most frequently (≥200 occurrences) reported relevant medical conditions were coded to the PTs Disease risk factor (957), Hypertension (648), Menopause (620), Asthma (508), Seasonal allergy (427), Drug hypersensitivity (419), Amenorrhoea (404), Hypersensitivity (379), Hypothyroidism (295), Endometriosis (225), Food allergy (223), Migraine (213), and Contraception (200).

- COVID-19 Medical history (n = 2397): Medical conditions reported more than once were coded to the PTs COVID-19 (1636), Suspected COVID-19 (730), Post-acute COVID-19 syndrome (12), SARS-CoV-2 test positive (8), COVID-19 pneumonia (5), Coronavirus infection, Exposure to SARS-CoV-2 (2 each), Asymptomatic COVID-19, and Coronavirus test positive (1 each).

- Co-suspects: the most frequently (≥10 occurrences) reported relevant co-suspect vaccines/medications were COVID-19 vaccine MRNA (97), adalimumab (43), Influenza vaccine (36), COVID-19 vaccine NRVV (31), levonorgestrel (24), and COVID-19 vaccine (19).

- Number of relevant events: 33,677.

- Relevant event seriousness: serious (8090) and non-serious (25,587).

- Most frequently reported relevant PTs (≥2%): Heavy menstrual bleeding (12,905), Intermenstrual bleeding (6088), Vaginal haemorrhage (1759), Epistaxis (1645), Contusion (1450), Vaccination site haematoma (1137), Postmenopausal haemorrhage (1137), Haematoma (944), and Haemorrhage (677).

- Time to event onset (n = 24,005 events),[94] range: <24 hours to 7337 days, median: 3 days.

  - <24 hours: 4020 events (7 of which had a fatal outcome);
  - 1 day: 3680 events (10 of which had a fatal outcome);
  - 2-7 days: 6477 events (23 of which had a fatal outcome);
  - 8-14 days: 3113 events (15 of which had a fatal outcome);
  - 15-30 days: 3566 events (15 of which had a fatal outcome);
  - 31-181 days: 3003 events (24 of which had a fatal outcome);
  - ≥182 days: 146 events (5 of which had a fatal outcome).

[94] This number does not include 45 events for which partial administration or event onset dates were reported or events did not have a meaningful time to onset value provided in the reports.

- Duration of relevant events (n = 240 out of 572 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 21,170 days.
  - 1 day: 512 events;
  - 2-7 days: 1767 events;
  - 8-14 days: 522 events;
  - 15-30 days: 352 events;
  - 31-181 days: 1311 events;
  - 182-235 days: 64 events;
  - >235 days: 30 events.

- Relevant event outcome: fatal (146), resolved/resolving (11,605), resolved with sequelae (571), not resolved (13,999), and unknown (7480).
  - In the 174 fatal cases (including 146 relevant events with fatal outcome, reported in 114 cases), the reported causes of death (>8 occurrences) were coded to the PTs Haemorrhage (12), Gastrointestinal haemorrhage, Haematemesis, and Pericardial haemorrhage (9 each). Of note, in 19 cases limited information regarding the cause of death was provided (PT Death). Most (122 of 174 cases) of the fatal cases involved elderly subjects. When the medical history was provided (114 cases), the most frequently (≥ 10 occurrences) relevant medical conditions included the PTs Hypertension (44), Cardiac arrest (16), Myocardial infarction (14), Cardiac failure, Cardio-respiratory arrest, Haemorrhage, and Myocardial ischaemia (10 each).

Analysis by age group

- CT: Adults (9) and Elderly (5).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

- PM: Paediatric (1044), Adults (26,592), Elderly (1731) and Unknown (935).
  - A significantly higher reporting proportion of events coded to the PTs Heavy menstrual bleeding and Intermenstrual bleeding was observed in paediatric and adult population when compared to elderly population (Heavy menstrual bleeding [33.9 % in paediatrics vs 45.7% in adults vs 0.2 % in elderly] and Intermenstrual bleeding [8.3% in paediatrics vs 22.1 % in adults vs 1.2 % in elderly]). The reporting proportion of the PT Epistaxis was significantly higher in paediatric and elderly population when compared to adult population (21.3 % in paediatrics vs 14.3 % in elderly vs 4.2 % in adults). The reporting proportion of PT Haematoma was higher in elderly population (12.1 %) when compared to paediatrics (1.2 %) and adult (2.0 %) population. The comparative differences in reporting proportions are not unexpected given the generally expected medical issues affecting each age group (paediatrics, adults, elderly).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 2542 (8.4% of the CT and PM cases reporting haematological AESIs).
- The reporting proportion of haematological AESIs with fatal outcome (1.6%) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (0.3%).

O/E Analysis

O/E analysis was performed for Acquired haemophilia and Haemorrhage (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Acquired haemophilia was evaluated during this reporting period (please refer to Section 15 *Overview of Signals: New, Ongoing, or Closed* and to Appendix 6A.2 for cumulative review of cases indicative of acquired haemophilia). No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.4. COVID-19 AESIs

Search criteria – SMQ COVID-19 (Narrow and Broad) OR PTs: Ageusia; Anosmia; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease.[95]

Cases reporting long COVID (PT: Post-acute COVID-19 syndrome) are reviewed in this section. Please refer also to Section 18.1 *Benefit-Risk Context – Medical Need and Important Alternatives (Complications of COVID-19 and Post-acute COVID).*

Clinical Trial Data

- Number of cases: 7 (blinded therapy [3] and BNT162b2 [4]) (1.0 % of 668 cases, the total CT dataset) compared to 3 cases (0.4%) retrieved in the PSUR #2[93].
- Country of incidence: US (3), Argentina, Dominican Republic, South Africa and Spain (1 each).
- Subjects' gender: female (5), male (2).
- Subjects' age in years: (n = 6), range: 2-77, mean: 38.0, median: 33.0

[95] The PTs Vaccine associated enhanced disease and Vaccine associated enhanced respiratory disease are evaluated in Section 16.3.2. *Evaluation of Important Potential Risks*, as overlapping terms with the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD).

- Medical history (n = 7): the reported relevant medical conditions included the PTs Asthma, Hypothyroidism (2 each), Abscess, Anxiety disorder, Basal cell carcinoma, Bipolar disorder, Catheterisation cardiac, Concussion, Coronary arterial stent insertion, Depression, Epilepsy, Ex-alcohol user, Glucose tolerance impaired, Headache, Heart transplant, Hypercholesterolaemia, Hyperlipidaemia, Hypertension, Hypocalcaemia, Medical procedure, Migraine, Non-tobacco user, Pain, Palpitations, Pulmonary valve stenosis, Seasonal allergy, Sinus bradycardia, Stress, Surgery, Varicella (1 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PTs: COVID-19 (6), COVID-19 pneumonia (1). None of the events were related to BNT162b2 or blinded therapy.
- Relevant event outcome: fatal (1), resolved/resolving (6).

Post-Authorisation Data

- Number of relevant cases: 54,335 (10.7% of 507,683 cases, the total PM dataset), compared to 25,453 cases (3.9%) retrieved in the PSUR #2[93]. The increase in the number of cases reported during the current PSUR is attributed to the increase in cases reported from Austria (9068 cases in the PSUR #2 vs 31,769 cases in the current PSUR #3) due to active solicitation of LOE cases from the Austrian BoH.
- MC cases (40,416); NMC cases (13,919).
- Country of incidence (≥ 2%): Austria (31,769), US (4874), UK (2725), Germany (2386), France (1934), Netherlands (1495); the remaining 9152 cases were distributed among 77 countries.
- Subjects' gender: female (29,370), male (22,867) and unknown (2098).
- Subjects' age in years: (n = 51,267), range: 6 months – 107 years, mean: 47.1, median: 46.0.
- Medical history (n = 8328): the most frequently (≥2%) reported relevant medical conditions included Hypertension (1429), Asthma (766), Drug hypersensitivity (617).
- COVID-19 Medical history: COVID-19 (1018), Suspected COVID-19 (361), Exposure to SARS-CoV-2 (49), Post-acute COVID-19 syndrome (48), COVID-19 pneumonia (10), SARS-CoV-2 test positive (9), Asymptomatic COVID-19, Coronavirus infection (3 each), Coronavirus test positive, Occupational exposure to SARS-CoV-2 (2 each).
- Co-suspects (n = 3995 cases): the most frequently (≥10) reported relevant co-suspect vaccines/medications were COVID-19 vaccine (1861), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (798), COVID-19 vaccine MRNA (MRNA 1273) (768), Adalimumab (256), JNJ 78436735 (100), Ocrelizumab (35), Influenza vaccine (34),

Upadacitinib (31), COVID-19 vaccine INACT (VERO) CZ02 (25), Risankizumab (21), Prednisone (18), Casirivimab/Imdevimab, Rituximab (13 each), Mycophenolate (10).

- Number of relevant events: 55,437.
- Relevant event seriousness: serious (52,185), non-serious (3254).
- Most frequently reported relevant PTs (≥2%): COVID-19 (47,981) Suspected COVID-19 (3002), and Ageusia (1094).
- Time to event onset (n = 46,269[96]), range: <24 hours to 564 days, median: 117 days.
  - <24 hours: 828 events (7 fatal events);
  - 1 day: 598 events (2 fatal events);
  - 2-7 days: 2061 events (24 fatal events);
  - 8-14 days: 1832 events (36 fatal events);
  - 15-30 days: 1812 events (35 fatal events);
  - 31-181 days: 36339 events (256 fatal events);
  - ≥ 182 days: 2799 events (53 fatal events).
- Duration of relevant events (n = 1968 out of 4800 occurrences with outcome of resolved/resolved with sequelae), range: 24 hours to 373 days, median: 9 days:
  - <24 hours: 71 events
  - 1 day: 46 events
  - 2-7 days: 631 events
  - 8-14 days: 848 events
  - 15-30 days: 275 events
  - 31-181 days: 76 events
  - ≥ 182 days: 9 events
- Relevant event outcome[78]: fatal (506), resolved/resolving (7289), resolved with sequelae (296), not resolved (3281), unknown (44071).
  - In 493 cases (reporting 543 relevant events of which 506 relevant events reported a fatal outcome), the reported causes of death (>20 occurrences) were coded to the PTs COVID-19 (297), Vaccination failure (143), Drug ineffective (131), COVID-19 pneumonia (127), Death (46), Dyspnoea (21). Of note, in 39 cases limited information regarding the cause of death was provided (PT Death [38] and Sudden death [1]). Most (406 of 493 cases) of the fatal cases involved elderly subjects. When the medical history was provided (272 cases), the most frequently (≥ 20 occurrences) relevant medical conditions included the PTs Hypertension (117), Atrial

[96] This number does not include 28 events for which a meaningful time to onset value was not provided in the reported information.

fibrillation (53), Chronic kidney disease, Dyslipidaemia (33 each), Type 2 diabetes mellitus (29), Myocardial ischaemia (25), Cardiac failure (24), COVID-19 (22), and Diabetes mellitus (21).

Analysis by age group

- CT: Paediatric (1), Adults (5), Elderly (1).
  - Due to low volume of paediatric cases, a meaningful comparison of the same with the other age groups is not possible.
- PM: Paediatric (2158), Adults (39,726), Elderly (9566).
  - No significant difference was observed in the reporting proportion of the most frequently reported COVID-19 AEs (≥2%) between adult, elderly and paediatric population.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3846 (0.8% of 507,683 cases, the total dataset).

  The reporting proportion of COVID-19 AESIs with fatal outcome (5.6% [230 of 4093 events]) is higher in subjects with comorbid conditions, compared to the reporting proportion observed in the individuals without comorbidities (0.5% [276 of 51,344 cases] of fatal events).

LONG COVID

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

Clinical Trial Data

- Number of cases: none.

Post-Authorisation Data

- Number of relevant cases: 200 (0.04% of 507,683 cases, the total PM dataset), compared to 72 cases (0.3% of 25,453 cases) retrieved in the PSUR #2.
- MC cases (62); NMC cases (138).
- Country of incidence: Germany (106), France (15), UK (14), Austria (13), Sweden (9), Australia, Finland (8 each), Netherlands (6), Italy (4), Ireland, US (3 each), Belgium, Hungary, New Zealand, Spain (2 each), Brazil, Greece and Luxembourg (1 each).
- Subjects' gender: female (151), male (46) and unknown (3).
- Subjects' age in years: (n = 174), range: 9 – 85 years, mean: 43.6, median: 45.0. Of these 174 subjects, there were 10 paediatric, 156 adults, and 8 elderly subjects.

- Medical history (n = 104): the most frequently (≥2%) reported medical conditions included Asthma, Drug hypersensitivity (8 each), and Seasonal allergy (7).

- COVID-19 Medical history: COVID-19 (38), Post-acute COVID-19 syndrome (33), Suspected COVID-19 (10).

Analysis by presence of co-morbidities:

- Number of subjects with comorbidities: 33 (16.5% of the 200 cases).

- Co-suspects (n = 9 cases): the reported co-suspect vaccines/medications were COVID-19 vaccine (5), COVID-19 vaccine MRNA (MRNA 1273) (3), Rupatadine (1).

- Co-reported events (≥20 occurrences): Fatigue (82), Headache (46), Condition aggravated (35), Dyspnoea (33), Disturbance in attention, Pyrexia (31 each), Drug ineffective (29), Asthenia (28), Myalgia (26), Palpitations (24), and Chest pain (20).

- Relevant event seriousness: serious (93), non-serious (107).

- Relevant event outcome: Resolved/resolving (22), Resolved with sequelae (9), Not resolved (98), Unknown (70) and Fatal (1).

  The case reporting the fatal outcome was spontaneously reported, that involved an 83-year-old female patient with co-morbid conditions (such as angina pectoris, macular degeneration, mitral valve incompetence, myalgia, pneumonia bacterial, respiratory failure) who received 2 doses of Comirnaty (on 27 January 2021 and on 05 March 2021) for immunisation and reported multiple serious events coded to the PTs Post-acute COVID-19 syndrome, Cough, Pneumonia, Hypoxia, Myocardial infarction, Acute myocardial infarction, Angina pectoris, and Cardiac failure. In this case all the above fatal events were likely attributable to the patient's medical history and an individual contributory role of Comirnaty cannot be established.

- Time to event onset (n = 95), range: <24 hours to 251 days, median: 2 days.

  - <24 hours: 25 events;
  - 1 day: 18 events;
  - 2-7 days: 20 events;
  - 8-14 days: 7 events;
  - 15-30 days: 15 events;
  - 31-181 days: 9 events;
  - ≥ 182 days: 1 event.

- Duration of relevant events (n = 7 out of 20 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 209 days, median: 4 days:

  - 1 day: 1 event
  - 8-14 days: 1 event

- 31-181 days: 4 events
- ≥ 182 days: 1 event

O/E Analysis

O/E analysis was performed for Ageusia/anosmia (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Loss of/Altered Taste and Smell was evaluated as signal during the reporting period and determined not to be a risk (please refer to Section 16.2.1 *Evaluation of Closed Signals*).

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 #2.

Post-Authorisation Data

- Number of cases: 284 (0.06% of 507,683 cases, the total PM dataset), compared to 339 (0.05%) cases retrieved in the PSUR #2.
- MC cases (158), NMC cases (126).
- Country of incidence: France (72), Germany (38), UK (25), Italy (24), Singapore (18), Japan, Poland (11 each), the Netherlands, US (9 each), Australia (8), Belgium (7), Canada, New Zealand, Spain (6 each); the remaining 34 cases were distributed among 18 countries.
- Subjects' gender: female (182), male (93) and unknown (9).
- Subjects' age in years: (n = 269), range: 7-89, mean: 46.4, median: 46.
- Medical history (n = 102): the most frequently (≥ 4 occurrences) reported relevant medical conditions included Hypertension (16), COVID-19 (12), Asthma (8), Drug hypersensitivity, Suspected COVID-19 (6 each), Diabetes mellitus (5), Cerebrovascular accident, Food allergy, Herpes simplex, Hypothyroidism, Type 2 diabetes mellitus (4 each).
- COVID-19 Medical history (n = 17): COVID-19 (12), Suspected COVID-19 (6), and Post-acute COVID-19 syndrome (1).

- Co-suspects (n = 4 cases): Acetylcysteine/benzalkoniumchloride/tuaminoheptane sulfate, Albendazole, Dextromethorphan, Ibuprofen, Ketoprofen, Ocrelizumab, Prednisolone metasulfobenzoate sodium, Sulfasalazine (1 each).

- Number of events: 284.

- Relevant event seriousness: serious (206), non-serious (78).

- Reported relevant PTs: Erythema multiforme (181), Chillblains (103).

- Time to event onset (n = 72), range: <24 hours to 262 days, median: 4 days.

  - <24 hours: 26 events;
  - 1 day: 35 events;
  - 2-7 days: 69 events;
  - 8-14 days: 31 events;
  - 15-30 days: 26 events;
  - 31-180 days: 24 events.

- Duration of relevant events (n = 14 out of 53 occurrences with outcome of resolved/resolved with sequelae), range: 0 days to 67 days, median: 20.5 days:

  - 1-7 days: 2 events;
  - 8-14 days: 2 events;
  - 15-30 days: 5 events;
  - 31-180 days: 3 events.

- Relevant event outcome: resolved/resolving (108), resolved with sequelae (8), not resolved (118), unknown (50). No fatal events were reported.

Analysis by age group

- PM: Paediatric (31), Adults (183), Elderly (60) and Unknown (10).

  - Due to low volume of paediatric cases a meaningful comparison of the same with the other age groups is not possible. No significant difference observed in the reporting proportion of events chillblains and erythema multiforme between adult and elderly population.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 53 (18.7 % of the cases reporting dermatological AESIs). A higher reporting proportion of dermatological AESIs was reported in subjects without significant comorbidities (81.3 %) when compared to subjects with significant comorbidities.

O/E Analysis

O/E analysis was performed for Chillblains and Erythema multiforme (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

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

- Number of cases: 1 (BNT162b2 [1]) (0.1% of 668 cases, the total CT dataset) compared to no cases retrieved in the PSUR #2.
- Country of incidence: US (1).
- Subject's gender: female (1).
- Subject's age: 75 years (1).
- Medical history (n = 1): Blood cholesterol increased, Cataract, Dyspepsia, Foot fracture, Gastrooesophageal reflux disease, Headache, Hypermetropia, Hypertension, Hypertonic bladder, Myopia, Overweight, and Squamous cell carcinoma of skin (1 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PT: Bell's palsy (1), not related to BNT162b2.
- Relevant event outcome: resolved (1).

Post-Authorisation Data

- Number of cases: 2589 (0.5% of 507,683 cases, the total PM dataset), compared to 4515 cases (0.7%) retrieved in the PSUR #2.
- MC cases (1105), NMC cases (1484).
- Country/region of incidence: Germany (714), France (387), UK (229), Australia (184), Italy (112), Austria (97), Sweden (87), Hong Kong (70), Taiwan, Province of China (69), US (54); the remaining 586 cases were distributed among 40 countries.
- Subjects' gender: female (1487), male (1060), and unknown (42).

- Subjects' age in years: (n = 2473), range: 1.42 – 99, mean 47.3, median 47.0.

- Medical history (n = 934): the most frequently (>2%) reported relevant medical conditions were coded to the PTs Hypertension (185), Asthma (89), Seasonal allergy (85), Drug hypersensitivity (63), Hypersensitivity (57), Diabetes mellitus (55), Type 2 diabetes mellitus (40), Obesity (35), Food allergy (34), Hypothyroidism (32), Facial paralysis, Mite allergy (28 each), Allergy to animal (26), Bell's palsy (25), Hypercholesterolaemia (24), Chronic obstructive pulmonary disease, Tobacco user (23 each), Migraine (20), and Coronary artery disease (19).

- COVID-19 Medical history (n = 133): reported medical conditions were coded to the PTs COVID-19 (100), Suspected COVID-19 (31), Post-acute COVID-19 syndrome (4), SARS-CoV-2 test positive (2), Asymptomatic COVID-19, Coronavirus infection, and COVID-19 pneumonia (1 each).

- Co-suspects (n = 33): the relevant co-suspect vaccines/medications were diphtheria vaccine toxoid/ polio vaccine inact 3V (vero)/ tetanus vaccine toxoid and meningococcal group C tetanus toxoid conjugate vaccine (1 each).

- Number of relevant events: 2706.

- Relevant event seriousness:[42] serious (2431) and non-serious (543).

- Reported relevant PTs: Facial paralysis (1428), Bell's palsy (733), Facial paresis (543), and Oculofacial paralysis (2).

- Time to event onset (n = 2152 events),[97] range: <24 hours to 389 days, median 7 days.

  - <24 hours: 351 events (none of which had a fatal outcome);
  - 1 day: 233 events (1 of which had a fatal outcome);
  - 2-7 days: 529 events (1 of which had a fatal outcome);
  - 8-14 days: 265 events (none of which had a fatal outcome);
  - 15-30 days: 332 events (2 of which had a fatal outcome);
  - 31-181 days: 414 events (1 of which had a fatal outcome);
  - 182-389 days: 27 events (none of which had a fatal outcome).

- Duration of relevant events (n = 286 out of 613 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 246 days, median: 6 days.

  - <24 hours: 48 events;
  - 1 day: 32 events:
  - 2-7 days: 69 events;
  - 8-14 days: 18 events;

[97] This number does not include 2 events for which partial administration and/or event onset date was reported.

- 15-30 days: 41 events;
- 31-181 days: 71 events.
- 182-246 days: 7 events.

- Relevant event outcome: fatal (6), resolved/resolving (999), resolved with sequelae (111), not resolved at the time of reporting (1063), and unknown (534).

  In 6 cases (reporting 6 relevant events with a fatal outcome), the causes of death (≥2 occurrences) were coded to the PTs Facial paralysis (3), Cerebrovascular accident and Death (2 each). Of note, in 2 cases limited information regarding the cause of death was provided (PT Death). All of the patients were >60 years of age (range 61 to 99 years). When the medical history was provided (4 cases), significant medical conditions reported Arthralgia, Cerebral infarction, Diverticulitis, Lung adenocarcinoma, Neoplasm malignant, Pemphigoid, and Pulmonary embolism (1 each).

Analysis by age group

- PM: Paediatric (146), Adults (1914), Elderly (420), and Unknown (109).
  - There was no significant difference observed in the reporting proportion of facial paralysis events between age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 407 (15.7% of the CT and PM cases reporting facial paralysis).

- The reporting proportion of cases reporting a facial paralysis events with a fatal outcome is higher in subjects with comorbid conditions (0.74%) when compared to the reporting proportion observed in the subjects without comorbidities (0.14%).

O/E Analysis

O/E analysis was performed for Bell's palsy (PTs: Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis) (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.

16.3.3.1.7. Hepatic AESIs

Search criteria - SMQ Liver related investigations, signs and symptoms (Narrow and Broad) OR PTs Autoimmune hepatitis[98] , Liver injury.

Upon review, 2 cases were determined to be non-contributory and were not included in the discussion since these cases involved exposure to the vaccine during the mother's pregnancy or through breastfeeding[99].

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported, compared to 2 cases (0.28%) retrieved in the PSUR #2[93].

Post-Authorisation Data

- Number of relevant cases: 1091 (0.2 % of 507,683 cases, the total PM dataset), compared to 1393 cases (0.2%) retrieved in the PSUR #2[93].
- MC cases (560), NMC cases (531).
- Country of incidence: Germany (276), Japan (157), France (152), UK (71), Australia (66), US (55), Italy (44), Austria (35), Spain (29), Taiwan, province of China (26), Netherlands (17), Sweden (15), Belgium, Finland (14 each), New Zealand (13), Greece (11), Canada (10), Denmark (9), Czech Republic (8), Norway, Poland (6 each), Croatia, Ireland, Romania (5 each), Switzerland (4), Brazil, Latvia, Philippines, Portugal, Slovakia, Slovenia (3 each), Estonia, Hungary, Lithuania, Malaysia, Mexico (2 each); the remaining 10 cases were distributed among 10 countries.
- Subjects' gender: female (661), male (406) and unknown (24).
- Subjects' age in years (n = 1017), range: 5 - 94, mean: 49.3, median: 51.0.
- Medical history (n = 518): the most frequently reported relevant medical conditions (≥ 5 occurrences) included Hypertension (80), Drug hypersensitivity (38), Hypothyroidism, Seasonal allergy (33), Asthma (32), Food allergy (23), Autoimmune thyroiditis, Type 2 diabetes mellitus (21 each), Allergy to animal (20), Allergy to metals, Dyslipidaemia (19 each), Mite allergy (17), Atrial fibrillation (16), Diabetes mellitus, Hepatic steatosis, Tobacco user (15 each), Obesity (14), Hypercholesterolaemia, Hypersensitivity (13 each), Gastrooesophageal reflux disease, Rheumatoid arthritis (12 each), Breast cancer, Mycotic allergy, Non-tobacco user, Tonsillectomy (11 each), Autoimmune hepatitis, Depression, Ovarian cystectomy (10 each), Interchange of vaccine products, Osteoporosis, Salivary gland operation (9 each), Cardiac failure, Cholecystectomy, Liver disorder, Migraine (8

[98] The PT Autoimmune hepatitis has been added, compared to search criteria used in PSUR #2 (cross-referenced with Section 15 *Overview Of Signals: New, Ongoing, Or Closed*).

[99] These cases are included in Section 16.3.5.3 *Use in Pregnant/Lactating Women.*

each), Abstains from alcohol, Alcohol use, Allergy to plants, Anxiety, Arrhythmia, Epstein-Barr virus infection, Headache, Hysterectomy, Pyrexia, Type 1 diabetes mellitus (7 each), Coeliac disease, Disease risk factor, Hepatic cirrhosis, Hyperuricaemia, Thyroid disorder, Weight decreased (6 each), Colon cancer, Dermatitis contact, Diverticulum intestinal, Epilepsy, Hepatic function abnormal, Hepatitis, Hyperlipidaemia, Immunodeficiency, Insomnia, Nephrolithiasis, Neuropathy peripheral, Pericarditis, Primary biliary cholangitis, Sinus operation, Sjogren's syndrome, Sleep apnoea syndrome, and Thyroid cancer (5 each).

- COVID-19 Medical history (n = 46): the medical conditions reported included COVID-19 (34), Post-acute COVID-19 syndrome, Suspected COVID-19, (5 each), Asymptomatic COVID-19, and COVID-19 pneumonia (1 each).

- Co-suspects (n = 58): the relevant co-suspect medications reported were adalimumab (10), upadacitinib (3), atorvastatin, hepatitis A vaccine, methotrexate, paracetamol (2 each), amlodipine, amoxicillin, cabozantinib, cefuroxime, certolizumab, clopidogrel, clozapine, colchicine, drospirenone ethinylestradiol, ebastine, ethinylestradiol gestodene, exemestane, fingolimod, ibuprofen, ipilimumab, lanreotide, nitrofurantoin, nivolumab, paclitaxel, ribociclib, rosuvastatin, sorafenib, spironolactone, teriflunomide, torasemide, and valsartan (1 each).

- Number of relevant events: 1422.

- Relevant event seriousness: serious (676) and non-serious (746).

- Most frequently reported relevant PTs (≥50 occurrences): Hepatic enzyme increased (131), Alanine aminotransferase increased (126), Hepatic function abnormal (124), Liver function test abnormal (119), Aspartate aminotransferase increased (110), Autoimmune hepatitis (99), Hepatic pain (98), Gamma-glutamyltransferase increased (86), Liver function test increased (79), Transaminases increased (72), Ascites (60).

- Time to event onset (n = 876 events)[100], range: <24 hours to 177 days, median: 7 days.

  - <24 hours: 83 events (of which 1 had a fatal outcome);
  - 1 day: 77 events;
  - 2-7 days: 290 events (of which 3 had a fatal outcome);
  - 8-14 days: 133 events (of which 4 had a fatal outcome);
  - 15-30 days: 132 events (of which 2 had a fatal outcome);
  - 31-180 days: 161 events (of which 2 had a fatal outcome.

[100] This number is not including 546 events for which partial administration and/or event onset dates were reported or events did not have a meaningful time to onset value provided in the reported information.

- Duration of relevant events (n = 120 out of 1425 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 210 days, median: 23 days.

  - <24 hours: 4 events
  - 1 day: 2 events;
  - 2-7 days: 24 events;
  - 8-14 days: 18 events;
  - 15-30 days: 22 events;
  - 31-180 days: 49 events;
  - >180 days: 1 event.

- Relevant event outcome[78]: fatal (23), resolved/resolving (426), resolved with sequelae (46), not resolved at the time of reporting (343), and unknown (586).

  In 22 cases with fatal outcome (reporting 23 relevant events with fatal outcome), the reported causes of death were coded to Ascites (5), Congestive hepatopathy, Hepatic function abnormal, Hepatic pain, Hypertransaminasaemia (2 each), Alanine aminotransferase increased, Autoimmune hepatitis, Blood bilirubin increased, Hepatic enzyme increased, Hepatic mass, Hepatomegaly, Hepatosplenomegaly, Hypoalbuminaemia, Liver function test abnormal, and Liver injury (1 each). Of note, in 6 cases limited information regarding the cause of death was provided (Alanine aminotransferase increased, Ascites, Hepatic mass, Hepatic pain, Hypertransaminasaemia, Liver injury (1 each). Most (13 of 22 cases) of the fatal cases involved subjects who were ≥60 years of age.

  When the medical history was provided (13 cases), the relevant medical conditions included Hepatic steatosis, Type 2 diabetes mellitus (3 each), Diabetes mellitus (2), Autoimmune hepatitis, and Hepatic function abnormal (1 each).

Analysis by age group

- PM: Paediatric (66), Adults (712), Elderly (243) and No data (70).

  - Among the frequently (≥2%) reported relevant hepatic events, Hepatic pain was reported significantly higher in the adult population when compared to elderly population (25.5% in adult vs 6.3% in elderly). Upon further review, the majority of the events of hepatic pain were assessed as non-serious in the adult population (63 of 84 events).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 265 (24.3% of the CT and PM cases reporting hepatic AESIs).

- The reporting proportion of hepatic AESIs with fatal outcome (2.1%) is slightly higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (1.4%)

O/E Analysis

O/E analysis was performed for Acute liver injury/Liver injury and Autoimmune hepatitis (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

A cumulative review of Autoimmune hepatitis has been performed (please refer to Section 15 *Overview of Signals: New, Ongoing, or Closed* and to Appendix 6A.5 for a cumulative review of cases indicative of autoimmune hepatitis). 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[101] - SMQ Immune-mediated/autoimmune disorders (Narrow and Broad) OR HLGT (All Path) Autoimmune disorders OR PTs Cytokine storm; Hypersensitivity; Thyroiditis subacute; Thrombocytopenia.

Clinical Trial Data

- Number of cases: 19 (BNT162b2 [17] and blinded therapy [2] (2.8% of 668 cases, the total CT dataset) compared to 20 cases (2.8%) retrieved in the PSUR #2[93].
- Country of incidence: US (14), Brazil (3), Argentina and China (1 each).
- Subjects' gender: female (7) and male (12).
- Subjects' age in years (n = 19), range: 6 – 79, mean 39.8, median 45.0.
- Medical history (n = 18): the relevant medical conditions reported more than once were coded to the PTs Dermatomyositis, Diabetes mellitus, Hypothyroidism, Seasonal allergy, and Type 1 diabetes mellitus (2 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Number of relevant events: 19.

[101] The PTs indicative of myocarditis and pericarditis have been moved from Immune-mediated/autoimmune AESIs to the newly added Section 16.3.3.1.11 *Myocarditis and Pericarditis AESIs* that is cross-referenced to Section 16.3.1.2 *Important Identified Risks - Myocarditis and Pericarditis*. The PT Thrombocytopenia has been reassigned from Haematological AESIs to Immune-mediated/autoimmune AESIs category.

- Reported relevant PTs (≥2 occurrences): Colitis (5), Diabetic ketoacidosis (3), Dermatomyositis, and Pancreatitis (2 each). All SAEs were assessed as not related to BNT162b2 or blinded therapy.

- Relevant event outcome: resolved/resolving (15), resolved with sequelae (1), not resolved (3).

Post-Authorisation Data

Number of cases: 11,729. Upon review, 3 cases were determined to be non-contributory and were not included in the discussion since these 3 cases involved exposures to the vaccine during the mothers' pregnancy or through breastfeeding.[99]

- Number of cases: 11,726 (2.3% of 507,683 cases of the total PM dataset), compared to 21,994 cases (3.3%) retrieved in the PSUR #2[93].

- MC cases (4822), NMC cases (6904).

- Country of incidence: Germany (3094), France (1474), UK (1038), US (718), Italy (582), Japan (490), Australia (461), Netherlands (370), Austria (362), Sweden (250), Belgium (237), Norway (230), Greece (229), Finland (216), Poland, Spain (184 each), Taiwan, Province of China (156), Canada (145), New Zealand (125); the remaining 1181 cases were distributed among 64 countries.

- Subjects' gender: female (7678), male (3661), and unknown (387).

- Subjects' age in years (n = 10,827), range: 5 – 98, mean: 47.5, median: 47.0.

- Medical history (n = 4887): the most frequently (≥150 occurrences) reported relevant medical conditions were coded to the PTs Seasonal allergy (400), Asthma (378), Drug hypersensitivity (317), Hypersensitivity (306), Psoriasis (269), Hypothyroidism (252), Autoimmune thyroiditis (237), Food allergy (235), Diabetes mellitus (186), and Colitis ulcerative (158).

- COVID-19 Medical history (n = 507): the reported medical conditions were coded to the PTs COVID-19 (382), Suspected COVID-19 (115), COVID-19 pneumonia (11), Post-acute COVID-19 syndrome (6), Coronavirus infection (4), SARS-CoV-2 test positive (3), and Asymptomatic COVID-19 (2).

- Co-suspects (n = 460): the most frequently (≥10 occurrences) reported relevant co-suspects were adalimumab (168), COVID-19 vaccine MRNA (MRNA 1273) (36), influenza vaccine (26), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (19), influenza vaccine inact split 4V, and Risankizumab (13 each).

- Number of relevant events: 12,795.

- Relevant event seriousness:[42] serious (8445) and non-serious (4356).

- Most frequently reported relevant PTs (≥2%): Hypersensitivity (2393), Psoriasis (660), Thrombocytopenia (487), Polymyalgia rheumatica (431), Dermatitis (305), Rheumatic disorder (286), and Alopecia areata (281).

- Time to event onset (n = 7591), [102] range: <24 hours to 499 days, median: 6 days.

  - <24 hours: 1451 events (5 of which had a fatal outcome);
  - 1 day: 847 events (1 of which had a fatal outcome);
  - 2-7 days: 1845 events (20 of which had a fatal outcome);
  - 8-14 days: 924 events (9 of which had a fatal outcome);
  - 15-30 days: 1032 events (18 of which had a fatal outcome);
  - 31-181 days: 1348 events (23 of which had a fatal outcome);
    182-499 days: 144 events (3 of which had a fatal outcome).

- Duration of relevant events (n = 969 out of 2334 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 419 days, median 14 days.

  - <24 hours: 145 events;
  - 1 day: 68 events;
  - 2-7 days: 186 events;
  - 8-14 days: 90 events;
  - 15-30 days: 106 events;
  - 31-181 days: 311 events;
  - 182-419 days: 63 events.

- Relevant event outcome: fatal (133), resolved/resolving (3786), resolved with sequelae (664), not resolved at the time of reporting (4934), and unknown (3304).

  - In 112 cases (reporting 133 relevant events with a fatal outcome), the reported causes of death (≥5 occurrences) were coded to the PTs Thrombocytopenia (19), Death, Interstitial lung disease (13 each), Haemophagocytic lymphohistiocytosis, Immune thrombocytopenia (8 each), Cerebral haemorrhage, Encephalitis, Multiple organ dysfunction syndrome, Renal failure (7 each), Pneumonia, Respiratory failure (6 each), and Pulmonary embolism (5). Of note, in 13 cases limited information regarding the cause of death was provided (PT Death). Most (78 of 104 cases that provided age) of the fatal cases involved elderly subjects. When the medical history was provided (67 cases), significant medical conditions reported in more than 3 cases included Hypertension (23), Atrial fibrillation (9), Osteoporosis (7), Dyslipidaemia (6), Diabetes mellitus, Hyperlipidemia, Type 2 diabetes mellitus (5 each), Hypothyroidism, Myocardial infarction, Radiotherapy, and Thrombocytopenia (4 each).

[102] This number does not include 23 events for which partial administration and/or event onset dates were reported.

Analysis by age group

- CT: Paediatric (5), Adults (11), and Elderly (3).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (591), Adults (8319), Elderly (2125) and Unknown (691).
  - Among the frequently (>2%) reported immune mediated/autoimmune AESIs, a higher reporting proportion of events coded to the PT Polymyalgia rheumatica were observed in the elderly population when compared to paediatric and adult populations (none in paediatrics vs 1.7% in adults vs 12.9% in elderly). A higher reporting proportion of events coded to the PTs Hypersensitivity and Alopecia areata were observed in the paediatric and adult populations when compared to the elderly population (Hypersensitivity [24.2% in paediatrics vs 20.8% in adults vs 11.8% in elderly], Alopecia areata [3.6% in paediatrics vs 2.7% in adults vs 0.9% in elderly]). A higher reporting proportion of events coded to the PTs Psoriasis and Rheumatic disorder were observed in the adult and elderly populations when compared to the paediatric population (Psoriasis [2.2% in paediatrics vs 5.8% in adults vs 5.9% in elderly], Rheumatic disorder [0.5% in paediatrics vs 2.3% in adults vs 3.4% in elderly]). A higher reporting proportion of events coded to the PT Thrombocytopenia were observed in the paediatric and elderly populations when compared to the adult population (8.8% in paediatrics vs 3.3% in adults vs 6.3% in elderly).

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3199 (27.2% of the CT and PM cases reporting immune mediated/autoimmune AESIs).

The reporting proportion of immune mediated/autoimmune AESIs with a fatal outcome (2.6%) is higher in subjects with comorbid conditions when compared to the reporting proportion observed in the subjects without comorbidities (0.6% of events with fatal outcome).

O/E Analysis

O/E analysis was performed for Acute disseminated encephalomyelitis (ADEM), ADEM and encephalitis, Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Polymyalgia rheumatica, Uveitis and Subacute Thyroiditis (SAT) were evaluated as signals in the reporting period and determined not to be risks (please refer to Section 16.2.1- *Evaluation of Closed Signals).*

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

Search Criteria[103]: PTs Cytokine release syndrome; Distributive shock; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome; Multisystem inflammatory syndrome in adults; Multisystem inflammatory syndrome in children; Systemic inflammatory response syndrome.

Clinical Trial Data

- During the reporting period, no serious cases from the CT dataset were reported. For comparison, 2 cases (0.3%) were retrieved in the PSUR #2[93].

Post-Authorisation Data

- Number of relevant cases: 207 (0.04% of 507,683 cases in the total PM dataset), compared to 438 (0.07%) retrieved in PSUR #2[93].
- MC cases (170), NMC cases (37).
- Country of incidence (≥5 occurrences): France (55), Germany (27), UK (18), Australia (15), US (14), Japan (12), Norway (6), Spain (5); the remaining 55 cases were distributed among 30 countries.
- Subjects' gender: female (92), male (109), unknown (6).
- Subjects' age in years (n = 196), range: 3 – 95, mean: 46.6, median: 50.
- Medical history (n = 132): the most frequently (≥5 occurrences) reported medical conditions included the PTs Hypertension (40), Obesity (11), Diabetes mellitus (9), Ex-tobacco user, Hypothyroidism (8 each), Atrial fibrillation, Tobacco user, Type 2 diabetes mellitus (7 each), Alcohol use, Osteoporosis, Pyrexia, Sleep apnoea syndrome (6 each), Asthma, Non-tobacco user, Prostate cancer, and Rheumatoid arthritis (5 each).

[103] The MAH proposed to consider the PTs Cytokine release syndrome, Distributive shock, Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome as search strategy for the identification of potential cases of MIS-C/A going forward was endorsed by the PRAC as per EMA PRAC Assessment for the SBSR 2 (Product No. EMEA/H/C/005735/MEA/002.12). The other PTs included in the TME List and previously reviewed under the MIS-C/A AESIs category (Autoinflammatory disease, Cytokine storm, Haemophagocytic lymphohistiocytosis, Hypotensive crisis, Kawasaki's disease, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease) were re-assigned and are reviewed under a different AESIs category based on their clinical relevance; the remaining PTs previously reviewed under the MIS-C/A AESIs category but not included in the TME List (Macrophage activation, Macrophages increased, Septic shock, Toxic shock syndrome) will no longer be reviewed in the AESIs review.

- COVID-19 medical history (n = 19): PTs COVID-19 (15), Suspected COVID-19 (3), Asymptomatic COVID-19 (1).

- Co-suspects (n = 16 cases): COVID-19 vaccine mRNA (mRNA 1273) (2), carboplatin, cefotaxime, ciclosporin, colchicine, COVID-19 vaccine, eltrombopag, enoxaparin, everolimus, mesalazine, methotrexate, pembrolizumab, pemetrexed, rituximab, treprostinil (1 each).

- Number of relevant events: 210.

- Relevant event seriousness: serious (210).

- Relevant PTs: Multiple organ dysfunction syndrome (82), Multisystem inflammatory syndrome (43), Multisystem inflammatory syndrome in children (38), Systemic inflammatory response syndrome (32), Multisystem inflammatory syndrome in adults (10), Cytokine release syndrome (5).

- Time to event onset (n = 115),[104] range: <24 hours to 234 days, median: 15 days.

  - <24 hours: 8 events (2 of which had a fatal outcome);
  - 1 day: 5 events (1 of which had a fatal outcome);
  - 2-7 days: 27 events (7 of which had a fatal outcome);
  - 8-14 days: 13 events (2 of which had a fatal outcome);
  - 15-30 days: 27 events (8 of which had a fatal outcome);
  - 31-180 days: 33 events (11 of which had a fatal outcome);
  - >180 days: 2 events.

- Duration of relevant events (n = 12 out of 39 occurrences with outcome of resolved or resolved with sequelae), range: 3 days to 57 days, median: 16 days.

  - 2-7 days: 5 events;
  - 8-14 days: 1 event;
  - 15-30 days: 2 events;
  - 31-180 days: 4 events.

- Relevant event outcome:[105] fatal (57), resolved/resolving (61), resolved with sequelae (3), not resolved (20), unknown (72).

---

[104] This number does not include 98 events for which administration and/or event onset dates were not provided or were incomplete. Please note, multiple episodes of the same PT event were reported with different latencies within some cases hence the sum of latencies exceeds the total number of PT events.

[105] 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.

- In 56 cases (reporting 57 relevant events with fatal outcome), the reported causes of death (≥5 occurrences) were coded to Multiple organ dysfunction syndrome (55), Septic shock (10), Renal failure (9), Immunisation, Sepsis (8 each), Pneumonia (7), Acute respiratory distress syndrome (6), Acute kidney injury, Cardiac arrest, COVID-19, COVID-19 pneumonia, Drug ineffective, Hepatic failure, Respiratory failure, and Vaccination failure (5 each).[106] Most (35 of 56 cases) of the fatal cases involved elderly subjects. When the medical history was provided (43 cases), the most frequently (≥3 occurrences) medical conditions included Hypertension (19), Diabetes mellitus, Obesity (6 each), COVID-19 (5), Atrial fibrillation, Ex-tobacco user, Hypothyroidism, Osteoarthritis, Renal transplant, and Tobacco user (3 each).

Analysis by age group

- PM: Paediatric (46 [16 Child, 30 Adolescent]), Adult (84), Elderly (69), Unknown (8).
  - Among the relevant multisystem inflammatory syndrome events, it was observed that:
    - PT Multiple organ dysfunction syndrome was reported at a higher frequency in the elderly population compared to the adult and paediatric populations (62.3% of the elderly population vs 39.3% of the adult population and 4.3% of the paediatric population).
    - PT Multisystem inflammatory syndrome was reported at a higher frequency in the adult population compared to the elderly and paediatric populations (29.8% of the adult population vs 14.5% of the elderly population and 15.2% of the paediatric population).
    - PT Multisystem inflammatory syndrome in children was reported, as expected, primarily in the paediatric population (80.4% were in the paediatric population).
    - PT Systemic inflammatory response syndrome was reported at similar frequency in the adults and the elderly population (21.4% of the adult population vs 18.8% of the elderly population; no cases in paediatric population).
    - PT Multisystem inflammatory syndrome in adults was reported, as expected, primarily in the adult population and elderly population (9.5% of the adult population and 2.9% of the elderly population; no cases in paediatric population).
    - PT Cytokine release syndrome was observed only in the adult and elderly populations (2.4% in the adult population and 1.4% in the elderly population; no cases in paediatric population).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 73 (35.3% of the 207 cases reporting Multisystem Inflammatory Syndrome AESIs).

[106] A case may report multiple causes of death (i.e., other causes of death in addition to the fatal relevant PT[s]).

- Of the PM cases that reported medical histories, the percentage of cases with a fatal Multisystem Inflammatory Syndrome AESI is higher in subjects with comorbid conditions (60.5%) when compared to the percentage of cases with a fatal Multisystem Inflammatory Syndrome AESI in subjects without comorbidities (39.5%).

- Upon review of the relevant events in PM cases that recorded medical histories, no Multisystem Inflammatory Syndrome AESIs had a significant proportional reporting ratio of >3:1 in subjects with comorbidities compared to subjects without comorbidities.

O/E Analysis

O/E analysis was performed for Multisystem inflammatory syndrome (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*). As in the most recent SBSR #3, the 21-24 years age group using the 21-day risk window meets the signal criteria with an O/E ratio >1, however, the result if not statistically significant as the 95% CI includes 1.

Conclusion

Cases of potential MIS in adults (MIS-A) and children (MIS-C) reported during this interval period are assessed in Appendix 6A.4).
During the reporting period, an article including important safety information on MIS-C was reviewed. Please refer to Section 11 *Literature* for details.

No new safety signals have emerged based on a review of these cases, literature or of the O/E analysis. The MAH will continue to monitor MIS.

16.3.3.1.10. Musculoskeletal AESIs

Search Criteria: PTs Arthralgia; Arthritis; Chronic fatigue syndrome; Juvenile idiopathic arthritis[107]; Polyarthritis; Post viral fatigue syndrome; Rhabdomyolysis; Rheumatoid arthritis.

Clinical Trial Data

- Number of cases: 6 (BNT162b2) (0.9% of 668 cases, the total CT dataset) compared to 4 cases (0.6%) retrieved in the PSUR #2[93].

- Country of incidence: US (6).

- Subjects' gender: female (3), male (3).

- Subjects' age in years (n = 6), range: 50-79, mean: 70.8, median: 74.0.

[107] The PT Juvenile idiopathic arthritis has been moved from Immune-mediated/autoimmune AESIs to Muscoloskeletal AESIs category.

- Medical history (n=6): the most frequently (>1 occurrence) reported medical conditions included Hypertension (4), Insomnia (3), Anaemia (2), Arthritis (2), Gastroesophageal reflux disease (2), and Hyperlipidaemia (2).

- COVID-19 Medical history: None.

- Co-suspects: None.

- Reported relevant PTs (6): Arthralgia (3), Arthritis (1), Rhabdomyolysis (1) and Rheumatoid arthritis (1), not related to BNT162b2.

- Relevant event outcome: resolved/resolving (5), not resolved (1).

Post-Authorisation Data

- Number of relevant cases: 31,012 (6.1% of 507,683 cases, the total PM dataset), compared to 58,250 cases (8.9 %) retrieved in the PSUR #2[93].

- MC cases (8400), NMC cases (22,612).

- Country of incidence (≥105 occurrences): Netherlands (6107), Germany (4444), UK (2391), Belgium (1821), France (1733), Australia (1498), Iraq (1334), Austria (1248), Sweden (1114), Italy (986), Japan (893), Poland (722), US (653), Romania (620), Slovenia (613), Norway (606), Czech Republic (474), Finland (425), Spain (364), Denmark (358), Malaysia (296), Ireland (269), Portugal (215), Philippines (211), Canada (168), New Zealand (153), Lithuania (119), Taiwan, Province Of China (105); the remaining 1072 cases were distributed among 51 countries.

- Subjects' gender: female (22,130), male (8359) and unknown (523).

- Subjects' age in years (n = 29,340), range: 0.08-97 years, mean: 44.9, median: 44.

- Medical history (n = 7884 cases): the most frequently (≥ 100 occurrences) reported medical conditions included Disease risk factor (1020), Hypertension (874), Asthma (620), Seasonal allergy (479), Drug hypersensitivity (461), Hypersensitivity (389), Rheumatoid arthritis (323), Hypothyroidism (308), Food allergy (255), Diabetes mellitus (249), Fibromyalgia (213), Arthralgia (190), Depression (187), Migraine (183), Osteoarthritis (177), Pain (173), Autoimmune thyroiditis (164), Immunodeficiency (157), Arthritis (154), Mite allergy (138), Type 2 diabetes mellitus (132), Non-tobacco user (126), Tobacco user (113), Anxiety (110), Psoriasis (109), Gastroesophageal reflux disease (104), Allergy to animal (103), Interchange of vaccine products (103), Hypercholesterolaemia (101).

- COVID-19 medical history (n = 2567 cases): COVID-19 (1760) Suspected COVID-19 (782), Post-acute COVID-19 syndrome (42), COVID-19 pneumonia (14), Coronavirus infection (8), SARS-CoV-2 test positive (8), Asymptomatic COVID-19 (4), Exposure to SARS-CoV-2 (4), SARS-CoV-2 antibody test positive (1).

- Co-suspects (n = 478 cases): the frequently (>5 occurrences) reported co-suspect vaccines/medications included adalimumab (119), influenza vaccine (48), COVID-19 vaccine mRNA (mRNA 1273) (44), upadacitinib (38), COVID-19 vaccine NRVV AD (Chadox1 NCOV-19) (25), COVID-19 vaccine (15), influenza vaccine inact split 3v (14), pneumococcal vaccine polysacch 23v (11), etanercept (8), tocilizumab (8), influenza vaccine inact split 4v (7), ocrelizumab (7), influenza vaccine inact sag 4v (6).

- Number of relevant events: 31,633.

- Relevant event seriousness:[42] serious (6164), non-serious (25,510).

- Relevant PTs: Arthralgia (29,429), Arthritis (996), Rheumatoid arthritis (660), Chronic fatigue syndrome (219), Polyarthritis (145), Post viral fatigue syndrome (92), Rhabdomyolysis (78), Juvenile idiopathic arthritis (14).

- Time to event onset (n = 24,700[108]), range: <24 hours to 3654 days, median: 0 days.

  - <24 hours: 8655 events (1 of which had a fatal outcome;
  - 1 day: 8837 events;
  - 2-7 days: 4004 events;
  - 8-14 days: 1105 events;
  - 15-30 days: 959 events;
  - 31-180 days: 1044 events;
  - 181-3654 days: 96 events.

- Duration of relevant events (n = 5620 out of 31,633 occurrences with outcome of resolved/resolved with sequelae), range: < 24 hours to 353 days, median 1 day.

  - <24 hours: 394 events;
  - 1 day: 1656 events;
  - 2 - 7 days: 2840 events;
  - 8-14 days: 211 events;
  - 15-31 days: 157 events;
  - 32-181 days: 286 event;
  - 182-353 days: 89 events.

- Relevant event outcome (31,815): fatal (22), resolved/resolving (14,443), resolved with sequelae (512), not resolved (12,142), unknown (4696).

  In 22 cases (reporting 22 relevant events with fatal outcome), the reported causes of death were coded to the PTs Arthralgia (14), Rhabdomyolysis (5), Pyrexia (2), Arthritis (1), Inflammation (1), Polyarthritis (1), and Rheumatoid arthritis (1). Most (14 of 22 cases) of

[108] This number does not include 40 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

the fatal cases involved elderly subjects. When the medical history was provided (18 cases), the most frequently (≥ 2 occurrences) relevant medical conditions included Hypertension (9), Parkinson's disease (3), Cerebrovascular accident (2), Coronary arterial stent insertion (2), Diabetes mellitus (2), Myocardial infarction (2), Osteoarthritis (2).

Analysis by age group

- CT: Adult (1) and Elderly (5).
- PM: Paediatric (664), Adult (25,307), Elderly (3469), Unknown (1572).
  - Higher reporting proportion of events coded to the PT Rheumatoid arthritis was reported in the elderly population when compared to adult and paediatric population ([1.8 % in adults vs 0.8% in paediatrics vs 4.6 % in elderly]).

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 3193 (10.3% of the cases reporting musculoskeletal AESIs).
- A higher reporting proportion of musculoskeletal AESIs was reported in subjects without significant comorbidities 27,825 (89.7%) when compared to subjects with significant comorbidities.
- The reporting proportion of musculoskeletal AESIs with outcome resolved (91.4%) is higher in subjects without comorbid conditions when compared to the reporting proportion observed in the subjects with comorbidities (8.6% of events with resolved).

O/E Analysis

O/E analysis was performed for Chronic fatigue syndrome/ME/PVFS, Rhabdomyolysis, Rheumatoid arthritis, polyarthritis, juvenile idiopathic arthritis (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. The majority of the events reported in this category are arthralgia which is considered to be an adverse reaction for the vaccine and is labelled as such. Arthralgia will be removed from the search strategy in the next PSUR. Safety surveillance will continue.

16.3.3.1.11. Myocarditis and Pericarditis AESIs[109]

Please refer to the Risk 'Myocarditis and Pericarditis' in Section 16.3.1.2 *Important Identified Risks – Myocarditis*.

16.3.3.1.12. Neurological AESIs (including demyelination)

Search Criteria[110]: SMQ Generalised convulsive seizures following immunisation (Narrow) OR SMQ Demyelination (Narrow and Broad) OR PTs Ataxia; Cataplexy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Narcolepsy; Neuropathy peripheral; Polyneuropathy.

Clinical Trial Data

- Number of cases: 15 cases (BNT162b2 [11], blinded therapy [4]; 2.2% of 668 cases in the total CT dataset) compared to 7 cases (0.97%) retrieved in the PSUR #2[93].
- Country of incidence: US (10), Brazil, Poland (2 each), Argentina (1).
- Subjects' gender: female (7), male (8).
- Subjects' age in years (n = 15), range: 0.58 – 79, mean: 36.1, median: 43.
- Medical history (n = 9): medical conditions reported more than once were coded to the PTs Insomnia (3), Blood cholesterol increased, Hypertension, and Seizure (2 each).
- COVID-19 medical history: None.
- Co-suspects: None.
- Reported relevant PTs: Seizure (6), Febrile convulsion (5), Meningitis, Myelitis transverse, Optic neuritis, Polyneuropathy, Toxic leukoencephalopathy (1 each). However, none of these SAEs were assessed as related to BNT162b2/blinded therapy.
- Relevant event outcome: resolved/resolving (12), resolved with sequelae (2), not resolved (2).

Post-Authorisation Data

- Number of relevant cases: 5111 (1.0% of 507,683 cases in the total PM dataset), compared to 7197 cases (1.1%) retrieved in the PSUR #2[93].

---

[109] The PTs indicative of myocarditis and pericarditis have been moved from Immune-mediated/autoimmune AESIs to this newly added AESIs.

[110] The SMQ Convulsions (Narrow and Broad) has been replaced with the SMQ Generalized convulsive seizures following immunisation (Narrow) to be more vaccine-focused.

- MC cases (2245), NMC cases (2866).

- Country of incidence (> 56 occurrences): Germany (1258), France (552), UK (455), Italy (288), US (248), Australia (240), Japan (227), Austria (178), Poland (177), Netherlands (158), Finland (96), Norway (92), Sweden (81), Canada (79), Philippines (78), New Zealand (76), Spain (74), Greece (65), Taiwan (64), Belgium, Ireland (60 each), Czech Republic (57); the remaining 448 cases were distributed among 51 countries.

- Subjects' gender: female (3163), male (1810), unknown (138).

- Subjects' age in years (n = 4811), range: 2.33 – 100, mean: 44.0, median: 44.

- Medical history (n = 2493): the most frequently (>51 occurrences) reported medical conditions included the PTs Hypertension (333), Epilepsy (253), Multiple sclerosis (241), Seasonal allergy (172), Drug hypersensitivity (160), Fibromyalgia (156), Asthma (150), Depression (98), Hypothyroidism (92), Food allergy, Hypersensitivity (91 each), Seizure (82), Diabetes mellitus (81), Migraine (62), Mite allergy (61), Obesity (60), Type 2 diabetes mellitus (54), and Pain (52).

- COVID-19 Medical history (n = 267): COVID-19 (206), Suspected COVID-19 (59), COVID-19 pneumonia (5), Post-acute COVID-19 syndrome (3), Coronavirus infection, SARS-CoV-2 test positive (2 each), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (1 each).

- Co-suspects (n = 150 cases): the reported co-suspect medications (≥3 occurrence) were ocrelizumab (15), COVID-19 vaccine mRNA (mRNA 1273) (12), adalimumab (11), COVID-19 vaccine NRVV AD, influenza vaccine INACT SPLIT 4V (10 each), influenza vaccine (9), COVID-19 vaccine (6), apixaban, levetiracetam, teriflunomide (4 each), cannabidiol/dronabinol, lamotrigine, and natalizumab (3 each).

- Number of relevant events: 5501.

- Relevant event seriousness:[42] serious (4973), non-serious (530).

- Most frequently (>58 occurrences) reported relevant PTs: Seizure (1282), Epilepsy (540), Neuropathy peripheral (528), Guillain-Barre syndrome (524), Trigeminal neuralgia (341), Fibromyalgia (314), Multiple sclerosis (265), Polyneuropathy (250), Multiple sclerosis relapse (199), Optic neuritis (182), Generalised tonic-clonic seizure (175), Ataxia (127), Myelitis transverse (90), Meningitis (79), Febrile convulsion (76), Demyelination, Intracranial pressure increased (59 each).

- Time to event onset (n = 3717),[111] range: <24 hours to 391 days, median: 3 days.
  - <24 hours: 883 events (7 of which had a fatal outcome);
  - 1 day: 579 events (5 of which had a fatal outcome);
  - 2-7 days: 862 events (12 of which had a fatal outcome);
  - 8-14 days: 383 events (7 of which had a fatal outcome);
  - 15-30 days: 414 events (6 of which had a fatal outcome);
  - 31-180 days: 557 events (12 of which had a fatal outcome);
  - >180 days: 39 events.

- Duration of relevant events (n = 619 out of 1404 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 330 days, median 1 day.
  - <24 hours: 269 events;
  - 1 day: 60 events;
  - 2-7 days: 102 events;
  - 8-14 days: 42 events;
  - 15-30 days: 43 events;
  - 31-180 days: 88 events;
  - >180 days: 15 events.

- Relevant event outcome:[78] fatal (67), resolved/resolving (1890), resolved with sequelae (306), not resolved (1839), unknown (1418).

- In 61 cases (reporting 67 relevant events with fatal outcome), the reported causes of death (>3 occurrences) were coded to the PTs Seizure (34), Guillain-Barre syndrome (11), Headache (8), Cardiac arrest, Off label use (7 each), Epilepsy (6), Dyspnoea, Interchange of vaccine products, Pneumonia (5 each), Intracranial pressure increased, Loss of consciousness, Pyrexia, and Sudden death (4 each).[106] Over half (31 of 61 cases) of the fatal cases involved elderly subjects. When the medical history was provided (33 cases), the most frequent (≥3 occurrences) medical conditions included the PTs Hypertension (14), Cardiac failure, COVID-19, Diabetes mellitus (4 each), Atrial fibrillation, Chronic obstructive pulmonary disease, and Seizure (3 each).

Analysis by age group

- CT: Paediatric (Infant [2], Child [4]), Adult (6), Elderly (3).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

[111] This number does not include 1808 events for which administration and/or event onset dates were not provided or were incomplete; or events without a meaningful time to onset value as per reported information. Please note, multiple episodes of the same PT event were reported with different latencies within some cases hence the sum of latencies exceeds the total number of PT events.

- PM: Paediatric (523 [162 Child, 361 Adolescent]), Adult (3574), Elderly (787), Unknown (227).

  - Among the most frequently (>50 occurrences) reported relevant neurological events, it was observed that:

    - The PTs Seizure, Generalised tonic-clonic seizure, and Febrile convulsion were reported at higher frequencies in the paediatric population compared to the adult population and the elderly population (57.9%, 7.5%, and 6.1% of the paediatric population vs 22.0%, 3.2%, and 0.8% of the adult population, and 15.5%, 2.2%, and 1.7% of the elderly population, respectively). This pattern is consistent with the known epidemiology of seizures and epilepsy.
    - The PTs Guillain-Barre syndrome, Polyneuropathy, and Ataxia were reported at higher frequencies in the elderly population compared to the paediatric population and the adult population (17.2%, 8.4%, and 4.7% of the elderly population vs 7.1%, 1.3%, and 1.1% of the paediatric population, and 9.0%, 4.7%, and 2.3% of the adult population, respectively).
    - The PTs Neuropathy peripheral, Trigeminal neuralgia, and Fibromyalgia were reported at higher frequencies in the adult population and the elderly population compared to the paediatric population (11.3%, 7.9%, and 7.2% of the adult population and 11.3%, 5.8%, and 5.3% of the elderly population vs 1.3%, 0.0%, and 0.4% of the paediatric population, respectively).
    - The PTs Multiple sclerosis, Multiple sclerosis relapse, and Optic neuritis were reported at higher frequencies in the adult population compared to the paediatric population and the elderly population (6.4%, 4.8%, and 4.4% of the adult population vs 1.0%, 0.6%, and 2.3% of the paediatric population, and 1.8%, 2.0%, and 1.4% of the elderly population, respectively).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 1201 (23.5% of the 5111 cases reporting Neurological AESIs).

- Of the PM cases that reported medical histories, the percentage of cases with a fatal Neurological AESI is higher in subjects with comorbid conditions (71.9%) when compared to the percentage of cases with a fatal Neurological AESI in subjects without comorbidities (28.1%).

Upon review of the most frequent (≥50 occurrences) relevant events in PM cases that recorded medical histories, the PTs Multiple sclerosis and Multiple sclerosis relapse were the only PTs that had a significant proportional reporting ratio of >3:1 in subjects with comorbidities compared to subjects without comorbidities.

O/E Analysis

O/E analysis was performed for Generalized convulsive, Fibromyalgia, Guillain-Barré syndrome, Meningitis, Narcolepsy, Multiple sclerosis (MS) and Polyneuropathy (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.

16.3.3.1.13. Other AESIs

Search Criteria[112]: HLT (All Path) Herpes viral infections OR PTs Adverse event following immunisation; Appendicectomy; Appendicitis; Appendiceal abscess; Appendicitis perforated; Complicated appendicitis; Deafness; Deafness bilateral; Deafness neurosensory; Deafness permanent; Deafness transitory; Deafness unilateral; Hypoacusis; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Occupational exposure to communicable disease; Patient isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive; Sudden hearing loss.

Upon review, 245 PM cases were determined to be non-contributory and were not included in the discussion since these 245 cases involved exposures to the vaccine during the mother's pregnancy or through breastfeeding.[99]

Clinical Trial Data

- Number of cases: 26 (BNT162b2 [22], blinded therapy [3] and placebo [1]) (3.9% of 668 cases, the total CT dataset) compared to 2 cases (0.28%) retrieved in the PSUR #2[93].
- Country of incidence: US (14), Argentina (5), Germany (3), Brazil, China, Finland, and Poland (1 each).
- Subjects' gender: female (14), male (12).
- Subjects' age in years (n = 26), range: 23 months – 79 years, mean: 25.5, median: 22.0
- Relevant Medical history: Appendicectomy (2) and Wiskott-Aldrich syndrome (1)

---

[112] The PTs Appendicectomy; Appendicitis; Appendiceal abscess; Appendicitis perforated; Complicated appendicitis; Deafness; Deafness bilateral; Deafness neurosensory; Deafness permanent; Deafness transitory; Deafness unilateral; Hypoacusis; Sudden hearing loss have been added. Hearing loss and Appendicitis were reviewed as signals during the reporting period (see Appendix 6A.3 and Section 15).

- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported relevant PTs: Appendicitis (14), Pyrexia (6), Deafness neurosensory (2), Complicated appendicitis, Exanthema subitem, Herpes zoster, and Sudden hearing loss (1 each). None of the SAEs were assessed as related to BNT162b2 or blinded therapy or placebo.
- Relevant event outcome: resolved/resolving (23), not resolved (3).

Post-Authorisation Data

- Number of cases: 68,548 (13.5% of 507,683 cases, the total PM dataset), compared to 118,843 cases (18.1%) retrieved in the PSUR #2[93].
- MC cases (25,353), NMC cases (43,195).
- Country of incidence (≥100 occurrences): Germany (14,740), Netherlands (5318), Iraq (4917), Japan (3834), UK (3392), Spain (2839), France (2686), Australia (2634), Poland (2374), Italy (2362), Sweden (2297), Philippines (2234), Belgium (2144), Romania (1847), Austria (1829), Malaysia (1620), Egypt (1468), US (1282), Norway (1013), Finland (833), Denmark (747), Czech Republic (640), Taiwan, Province of China (634), Ireland (538), Lithuania (445), Greece (377), Portugal (375), Croatia (347), Canada (313), Switzerland (298), Georgia (285), New Zealand (279), Brazil (276), Estonia (193), Mexico (138), and Hungary (107); the remaining 893 cases were distributed among 50 countries.
- Subjects' gender: female (45,066), male (21,639) and unknown (1843).
- Subjects' age in years (n = 63640), range: 2 days -104 years, mean: 41.1, median: 39.
- Medical history (n = 15037): the most frequently (≥50 occurrences) relevant medical conditions included Immunodeficiency (242), Herpes zoster (176), Breast cancer (155), Neoplasm malignant (70).
- COVID-19 Medical history (n =3,535): the most frequently (≥10 occurrences) reported medical conditions included COVID-19 (2452), Suspected COVID-19 (938), Post-acute COVID-19 syndrome (59), COVID-19 pneumonia (33), Coronavirus infection (24), Asymptomatic COVID-19, SARS-CoV-2 test positive (10 each), Exposure to SARS-CoV-2 (6), Coronavirus test positive, Occupational exposure to SARS-CoV-2, and SARS-CoV-2 antibody test positive (1 each).
- Co-suspects (n = 677): the reported relevant co-suspect medications were Adalimumab (64), Methotrexate (5) Apixaban (4), Etanercept (3), Rituximab (2), Infliximab (1).
- Number of relevant events: 69,859.

- Relevant event seriousness: serious (10,676), non-serious (59,208).

- Most frequently reported relevant PTs (≥ 50 occurrences): Pyrexia (57,474), Herpes zoster (6216), Inflammation (1585), Oral herpes (794), Hypoacusis (744), Deafness (488), Sudden hearing loss (370), Herpes virus infection (297), Appendicitis (254), Deafness unilateral, Ophthalmic herpes zoster (222 each), Herpes simplex (206), Adverse event following immunisation (188), Genital herpes (163), Herpes ophthalmic (70), Deafness neurosensory (63), Herpes zoster oticus (61), Herpes zoster reactivation, and Varicella (59 each).

- Time to event onset (n = 55,778),[113] range: <24 hours to 180 days, median: 1 day.

  - <24 hours: 21,103 events (17 of which had a fatal outcome;
  - 1 day: 20491 events (25 of which had a fatal outcome);
  - 2-7 days: 6833 events (27 of which had a fatal outcome);
  - 8-14 days: 2154 events (14 of which had a fatal outcome);
  - 15-30 days: 2229 events (8 of which had a fatal outcome);
  - 31-180 days: 2968 events (20 of which had a fatal outcome).

- Duration of relevant events (n = 19,717 out of 70,158 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 179 days, median 1 day.

  - <24 hours: 2487 events;
  - 1 day: 7397 events;
  - 2 - 7 days: 8026 events;
  - 8-14 days: 724 events;
  - 15-31 days: 547 events;
  - 32-181 days: 536 events.

- Relevant event outcome:[78] fatal (166), resolved/resolving (43,472), resolved with sequelae (855), not resolved (13,677), unknown (11,880).

  - In 164 cases (reporting 166 relevant events with fatal outcome), the reported causes of death (>10 occurrences) were coded to the PTs Pyrexia (118), Adverse event following immunisation (27), and Inflammation (11). Most (82 of 164 cases) of the fatal cases involved elderly subjects. When the medical history was provided (151 cases), the most frequently (≥ 20 occurrences) relevant medical conditions included Hypertension (52) and Diabetes mellitus (27).

[113] This number does not include 13,972 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

Analysis by age group

CT: Adult (14), Paediatric (10), Elderly (2).

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

PM: Paediatric (5092), Adult (53,918), Elderly (6771), and Unknown (2767).

- Among the frequently (≥2%) reported relevant Other AESI events, PTs Herpes zoster and Inflammation were reported significantly higher in elderly population when compared to adult population (Herpes zoster [37% in adults vs 58.7% in elderly], Inflammation [0.9% in adult vs 2.7% in elderly]). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 5215 (7.6 % of the cases reporting other AESI). A higher reporting proportion of other AESIs was reported in population without significant comorbidities (92.4 %) when compared to population with significant comorbidities.

- The reporting proportion of other AESIs with fatal outcome (0.9 %) 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).

O/E Analysis

O/E analysis was performed on Appendicitis, Herpes zoster and Sudden hearing loss (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Hearing loss was evaluated as a signal during the reporting period (please refer to Appendix 6A.3 for cumulative review of cases indicative of hearing loss).

Appendicitis was evaluated as signal during the reporting period (please refer to Section 16.2.1 *Evaluation of Closed Signals*).

No other safety signals than those mentioned have emerged based on the review of these cases, or from the O/E analysis. No risks have been identified following the evaluations of appendicitis and hearing loss. Safety surveillance will continue.

16.3.3.1.14. 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.*

16.3.3.1.15. Glomerulonephritis and Nephrotic Syndrome AESIs[114]

Search criteria - HLT Glomerulonephritis and nephrotic syndrome.

Upon review, 2 cases were determined to be noncontributory and were not included in the discussion since these cases involved exposures to the vaccine during the mother's pregnancy or through breastfeeding.[99]

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported. No comparison with PSUR #2 is possible due to the change in the search criteria.

Post-Authorisation Data

- Number of cases: 276 (0.05% of 507,683 cases, the total PM dataset). No comparison with PSUR #2 is possible.
- MC cases (172), NMC cases (104).
- Country of incidence: Germany (74), Japan (50), France (29), Australia (13), Italy, UK (11 each); the remaining 88 cases were distributed among 28 countries.
- Subjects' gender: female (150), male (124) and unknown (2).
- Subjects' age in years (n = 270), range: 5 – 88, mean: 44.2, median: 43.0.
- Medical history (n = 148): the most frequently (≥5 occurrences) reported relevant medical conditions included Hypertension (25), Nephrotic syndrome (12), Hypercholesterolaemia (8), Dyslipidaemia, Glomerulonephritis, Haematuria, IgA nephropathy (7 each), Proteinuria (6).
- COVID-19 Medical history (n = 10): COVID-19 (7), Suspected COVID-19 (2), COVID-19 pneumonia (1).
- Co-suspects (n= 3 cases): the reported relevant co-suspect medications included Hepatitis A vaccine, Influenza vaccine, and Tocilizumab (1 each).
- Number of relevant events: 323
- Relevant event seriousness: serious (318), non-serious (5).

---

[114] The PTs Acute kidney injury and Renal failure have been removed from the search criteria and replaced with a more focused search of glomerulonephritis and nephrotic syndrome based on the evolving pharmacovigilance and medical literature. An evaluation of IgA nephropathy, as requested by EMA in the PSUR 2 assessment report is ongoing and will be provided to EMA under separate cover from the PSUR.

- Most frequently reported relevant PTs: Nephrotic syndrome (99), IgA nephropathy (47), Glomerulonephritis (46), Glomerulonephritis minimal lesion (25), Granulomatosis with polyangiitis (22), Microscopic polyangiitis (14), Glomerulonephritis membranous (12), Focal segmental glomerulosclerosis, and Glomerulonephritis rapidly progressive (10 each).
- Time to event onset (n = 172),[115] range: <24 hours to 172 days, median: 12 days.
  - <24 hours: 7 events;
  - 1 day: 22 events;
  - 2-7 days: 43 events (1 of which had a fatal outcome);
  - 8-14 days: 23 events;
  - 15-30 days: 32 events;
  - 31-180 days: 45 events (1 of which had a fatal outcome).
- Duration of relevant events (n = 12 out of 323 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 137 days, median 48 days.
  - <24 hours: 1 event;
  - 1 day: 0 events;
  - 2 - 7 days: 1 event;
  - 8-14 days: 0 events;
  - 15-31 days: 1 event;
  - 32-181 days: 9 events.
- Relevant event outcome: fatal (2), resolved/resolving (95), resolved with sequelae (23), not resolved (111), unknown (92).
- In 2 cases (reporting 2 relevant events with fatal outcome), the reported causes of death were coded to Glomerulonephritis and Granulomatosis with polyangiitis (1 each). Both fatal cases involved elderly subjects. Medical history was provided in both cases and included Autoimmune hypothyroidism, Hypertension and Obesity (1 each).

Analysis by age group

PM: Paediatric (33), Adult (177), Elderly (62) and Unknown (4).

- Among the frequently (≥2%) reported relevant events Glomerulonephritis and Nephrotic Syndrome AESIs, the PT Renal failure was reported significantly higher in elderly population when compared to adult population (2.8% in adults vs 8.4% in elderly). A higher reporting proportion of events coded to the PTs Haematuria and IgA nephropathy were observed in the adult population when compared to the elderly population (Haematuria [10.4% in adults vs 2.1% in elderly] and IgA nephropathy

[115] This number does not include 151 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[11.1% in adults vs 1.1% in elderly]). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 14 (5.1% of the cases reporting Glomerulonephritis and nephrotic syndrome AESIs).
- The reporting proportion of Glomerulonephritis and nephrotic syndrome AESIs with fatal outcome is 0.4 % in subjects without comorbid conditions. There were no fatal outcomes in the subjects with comorbidities.

O/E Analysis

O/E analysis was performed for Glomerulonephritis/nephrotic syndrome (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Please refer to Section 15 *Overview of Signals: New, Ongoing, or Closed* and to Appendix 6A for the response to the PRAC request (EMA/PRAC/416198/2021 – EPITT 19722).

No safety signals have emerged based on the review of these cases, or from the O/E analysis. The ongoing evaluation of IgA nephropathy will be submitted separately from the PSUR. Safety surveillance will continue.

16.3.3.1.16. 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.

Upon review, 4 cases were determined to be non-contributory and were not included in the discussion since these cases involved exposures to the vaccine during the mother's pregnancy or through breastfeeding.[99]

Clinical Trial Data

- Number of cases: 33 (Blinded therapy [10], BNT162b2 [23]) (4.9 % of 668 cases, the total CT dataset) compared to 38 cases (5.3%) retrieved in the PSUR #2.
- Country of incidence: US (24), Argentina (4), Poland, Spain (2 each), and Brazil (1).
- Subjects' gender: female (15), male (18).
- Subjects' age in years (n = 33), range: 17 months – 81 years, mean: 49.3, median: 63.0.

- Medical history (n = 25): the relevant medical conditions included Chronic obstructive pulmonary disease (4), Seasonal allergy (3), Asthma, Bronchitis chronic, Lung neoplasm malignant, and Upper respiratory tract infection (1 each).
- COVID-19 medical history (n = 1): COVID-19 (1).
- Co-suspects: None.
- Reported relevant PTs (35): Pneumonia (15), Acute respiratory failure (6), Bronchitis (4), Hypoxia (3), Lower respiratory tract infection, Metapneumovirus infection (2 each), Cardio-respiratory arrest, Respiratory failure, and Respiratory syncytial virus bronchitis (1 each).
- Relevant event outcome: fatal (4), resolved/resolving (30), not resolved (1).
- Of the above SAEs, all were assessed as not related to BNT162B2 or Blinded therapy.

Post-Authorisation Data

- Number of cases: 2188 (0.4% of 507,683 cases, the total PM dataset), compared to 3356 cases (0.51%) retrieved in the PSUR #2.
- MC cases (1186), NMC cases (1002).
- Country of incidence: Germany (374), France (311), UK (193), Japan (156), Australia (145), Belgium (108), US (106), Italy (102), Austria (82), Spain (66), Philippines (58); the remaining 487 cases were distributed among 43 countries.
- Subjects' gender: female (1189), male (948) and unknown (51).
- Subjects' age in years (n = 2064), range: 5 - 106, mean: 56.4, median: 58.0
- Medical history (n = 1168): the most frequently (≥5 occurrences) reported medical conditions included Asthma (140), Chronic obstructive pulmonary disease (70), Seasonal allergy (42), Pneumonia (29), Pulmonary embolism (20), Sleep apnoea syndrome (14), Bronchitis, Emphysema (11 each), Chronic respiratory failure, Lung disorder (8 each), Bronchiectasis, Lower respiratory tract infection, Obstructive sleep apnoea syndrome, Pulmonary fibrosis (7 each), Bronchitis chronic, and Respiratory disorder (6 each).
- COVID-19 Medical history (n = 123): the most frequently reported medical conditions included COVID-19 (88), Suspected COVID-19 (24), COVID-19 pneumonia (6), Post-acute COVID-19 syndrome (2), Coronavirus infection, Exposure to SARS-CoV-2, SARS-CoV-2 test positive (1 each).
- Co-suspects (n = 138 cases): the reported relevant co-suspect medications included Adalimumab (25), Rituximab (3), Casirivimab, Imdevimab (2), Atenolol, Bromazepam, Durvalumab, Methotrexate, Salbutamol, and Terbutaline (1 each).
- Number of relevant events: 2383.
- Relevant event seriousness: serious (1873), non-serious (510).

- Most frequently reported relevant PTs (≥ 100 occurrences): Pneumonia (809), Respiratory disorder (325), Bronchitis (303), Respiratory failure (213), Lower respiratory tract infection (175), Cardio-respiratory arrest (140), and Hypoxia (133).
- Time to event onset (n = 1422),[116] range: <24 hours to 437 days, median: 5 days.
  - <24 hours: 216 events (21 of which had a fatal outcome);
  - 1 day: 230 events (52 of which had a fatal outcome);
  - 2-7 days: 330 events (50 of which had a fatal outcome);
  - 8-14 days: 170 events (29 of which had a fatal outcome);
  - 15-30 days: 146 events (27 of which had a fatal outcome);
  - 31-180 days: 272 events (44 of which had a fatal outcome)
  - 181-437 days: 58 events (10 of which had a fatal outcome).
- Duration of relevant events (n = 176 out of 2395 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 288 days, median 7 days.
  - <24 hours: 26 events;
  - 1 day: 24 events;
  - 2 - 7 days: 43 events;
  - 8-14 days: 29 events;
  - 15-30 days: 29 events
  - 31-180 days: 21 events;
  - 181-288 days: 4 events.
- Relevant event outcome:[78] fatal (363), resolved/resolving (694), resolved with sequelae (53), not resolved (544), unknown (738).
  - In 318 cases (reporting 363 relevant events with fatal outcome), the reported causes of death (>20 occurrences) were coded to the PTs Cardio-respiratory arrest (99), Pneumonia (74), Respiratory failure (63), Acute respiratory failure (31), Hypoxia (26), and Acute respiratory distress syndrome (22). Most (235 of 318 cases) of the fatal cases involved elderly subjects. When the medical history was provided (234 cases), the most frequently (≥ 20 occurrences) relevant medical conditions included Hypertension (104), Atrial fibrillation (39), Diabetes mellitus (27), Type 2 diabetes mellitus (25), Chronic obstructive pulmonary disease, and Dyslipidaemia (23 each).

[116] This number does not include 973 events for which partial administration and/or event onset dates were reported or events with a not meaningful time to onset value as per reported information.

Analysis by age group

- CT: Paediatric (8), Adult (12) and Elderly (13).
    - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (83), Adult (1168), Elderly (836) and Unknown (101).
    - A higher reporting proportion of events coded to the PTs Acute respiratory distress syndrome and Respiratory failure was observed in elderly population when compared to the adult population (Acute respiratory distress syndrome [5.7% vs 1.3%], Respiratory failure [12.7% vs 4.6%]. Additionally, a higher reporting proportion of events coded to the PTs Cardio-respiratory arrest and Respiratory disorder was observed in the adult population when compared to elderly (Cardio-respiratory arrest 10% vs 1.4% and Respiratory disorder 15.2% vs 5.6%). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis by presence of comorbidities

- Number of subjects reporting comorbidities: 113 (5.16 % of the cases reporting respiratory AESIs).
- The reporting proportion of respiratory events with a fatal outcome (17.4 %) is higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (15.1 % of events with resolved).

O/E Analysis

O/E analysis was performed for Acute respiratory distress syndrome (ARDS) (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. Respiratory events were originally included in the AESI list in order to capture potential cases of respiratory failure that may occur in cases of severe COVID-19. The search strategy will be amended to focus on acute respiratory distress syndrome and respiratory failure for the next PSUR.

16.3.3.1.17. Stroke

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

Clinical Trial Data

- Number of cases: 19 cases (BNT162b2 [18], blinded therapy [1]; 2.8% of 668 cases in the total CT dataset) compared to 19 cases (2.6%) retrieved in the PSUR #2.
- Country of incidence: US (15), Argentina (2), Brazil, China (1 each).
- Subjects' gender: female (5), male (14).
- Subjects' age in years (n = 19), range: 36 – 85, mean: 67.4, median: 71.
- Medical history (n = 18): medical conditions reported more than twice were coded to the PTs Hypertension (12), Type 2 diabetes mellitus (5), Hypercholesterolaemia (4), Obesity, and Osteoarthritis (3 each).
- COVID-19 Medical history: None.
- Co-suspects (n= 1 case): amlodipine, metoprolol (1 each).
- Reported relevant PTs: Cerebrovascular accident (13), Ischaemic stroke (3), Cerebral infarction, Embolic stroke, Haemorrhagic stroke (1 each). However, none of these SAEs were assessed as related to BNT162b2/blinded therapy.
- Relevant event outcome: fatal (1), resolved/resolving (12), resolved with sequelae (6).

Post-Authorisation Data

- Number of cases: 3091 (0.6% of 507,683 cases in the total PM dataset), compared to 4834 cases (0.7%) retrieved in the PSUR #2.
- MC cases (1418), NMC cases (1673).
- Country of incidence (>50 occurrences): Germany (1011), France (353), UK (219), Japan (143), Austria (138), Australia (127), US (116), Italy (108), Sweden (89), Taiwan (83), Netherlands (81), Poland (57), Denmark (51); the remaining 515 cases were distributed among 40 countries.
- Subjects' gender: female (1555), male (1467), unknown (69).
- Subjects' age in years (n = 2915), range: 5 – 101, mean: 60.8, median: 62.
- Medical history (n = 1593): the most frequently (>55 occurrences) reported medical conditions were coded to the PTs Hypertension (590), Diabetes mellitus (119), Atrial fibrillation (111), Tobacco user (98), Type 2 diabetes mellitus (96), Obesity (86), Cerebrovascular accident (83), Dyslipidaemia, Seasonal allergy (74 each), Non-tobacco user (71), Hypercholesterolaemia (63), Asthma (58), Drug hypersensitivity, and Hypothyroidism (56 each).
- COVID-19 medical history (n = 101): PTs COVID-19 (80), Suspected COVID-19 (20), COVID-19 pneumonia (6).
- Co-suspects (n = 96 cases): Most frequently (≥3 occurrences) reported co-suspect medications were COVID-19 vaccine mRNA (mRNA 1273) (10), influenza vaccine, influenza vaccine INACT SPLIT 4V (7 each), adalimumab, apixaban (6 each), COVID-

19 vaccine, ethinylestradiol/levonorgestrel (4 each), acetylsalicylic acid, clopidogrel, COVID-19 vaccine NRVV AD, and rivaroxaban (3 each).

- Number of relevant events: 3532.
- Relevant event seriousness: serious (3532).
- Most frequently (>25 occurrences) reported relevant PTs: Cerebrovascular accident (1363), Cerebral infarction (416), Ischaemic stroke (367), Cerebral haemorrhage (306), Cerebral venous sinus thrombosis (166), Cerebral thrombosis (93), Cerebral ischaemia (76), Subarachnoid haemorrhage (72), Cerebral venous thrombosis (68), Cerebellar infarction (42), Brain stem infarction, Haemorrhage intracranial (35 each), Ischaemic cerebral infarction (33), Embolic stroke (31), Haemorrhagic stroke (29), Thalamic infarction (26).
- Time to event onset (n = 2626),[117] range: <24 hours to 402 days, median: 12 days.
  - <24 hours: 183 events (18 of which had a fatal outcome);
  - 1 day: 212 events (23 of which had a fatal outcome);
  - 2-7 days: 649 events (67 of which had a fatal outcome);
  - 8-14 days: 388 events (34 of which had a fatal outcome);
  - 15-30 days: 508 events (37 of which had a fatal outcome);
  - 31-180 days: 625 events (53 of which had a fatal outcome);
  - >180 days: 61 events (6 of which had a fatal outcome).
- Duration of relevant events (n = 201 out of 833 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 350 days, median 5 days.
  - <24 hours: 50 events;
  - 1 day: 16 events;
  - 2-7 days: 50 events;
  - 8-14 days: 16 events;
  - 15-30 days: 18 events;
  - 31-181 days: 41 events;
  - >180 days: 10 events.
- Relevant event outcome:[78] fatal (314), resolved/resolving (1013), resolved with sequelae (504), not resolved (804), unknown (910).
- In 267 cases (reporting 314 relevant events with fatal outcome), the reported causes of death (≥10 occurrences) were coded to the PTs Cerebrovascular accident (94), Cerebral haemorrhage (77), Cerebral infarction (36), Immunisation (27), Off label use (26), Interchange of vaccine products (23), Ischaemic stroke (18), Headache (17), Death,

[117] This number does not include 923 events for which administration and/or event onset dates were not provided or were incomplete; or events without a meaningful time to onset value as per reported information. Please note, multiple episodes of the same PT event were reported with different latencies within some cases hence the sum of latencies exceeds the total number of PT events.

Subarachnoid haemorrhage (16 each), Thrombosis (14), Myocardial infarction (13), Brain oedema, Cerebral thrombosis, Loss of consciousness (12 each), and Cardiac arrest (10).[106] Most (183 of 267 cases) of the fatal cases involved elderly subjects. When the medical history was provided (162 cases), the most frequently (>5 occurrences) medical conditions included the PTs Hypertension (59), Diabetes mellitus (19), Atrial fibrillation (18), Cerebrovascular accident (12), COVID-19 (9), Cardiac failure, Cerebral infarction, Dyslipidaemia, Type 2 diabetes mellitus (8 each), Tobacco user (7), Chronic obstructive pulmonary disease, Cognitive disorder, Depression, Obesity, and Pulmonary embolism (6 each).

Analysis by age group

- CT: Adult (6), Elderly (13).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (33 [9 Child, 24 Adolescent]), Adult (1575), Elderly (1352), Unknown (131).
  - Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible. Among the most frequently (>25 occurrences) reported relevant stroke-related events, the PTs Cerebral venous sinus thrombosis and Cerebral venous thrombosis had a greater than 3-fold reporting proportion in the adult population (8.2% and 3.7%, respectively) when compared to the elderly population (1.6% and 0.6%, respectively). Conversely, among the most frequently reported relevant stroke-related events, the PT Haemorrhagic stroke had a greater than 3-fold reporting proportion in the elderly population (1.7%) when compared to the adult population (0.4%).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 719 (23.3% of the 3091 cases reporting stroke-related events).
- Of the PM cases that reported medical histories, the percentage of cases with a fatal stroke-related event is higher in subjects with comorbid conditions (55.6%) when compared to the percentage of cases with a fatal stroke-related event in subjects without comorbidities (44.4%).
- Upon review of the most frequent (>25 occurrences) relevant events in PM cases that recorded medical histories, no relevant stroke-related events had a significant proportional reporting ratio of >3:1 in subjects with comorbidities compared to subjects without comorbidities.

O/E Analysis

O/E analysis was performed for Cerebral venous sinus thrombosis, Ischemic stroke and Hemorrhagic stroke (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*). For CVST, some age groups had O/E greater than 1 when the low background rate was used in the analysis. However, the 95% CIs did not all include 1 (indicating non statistical significance). The O/E were similar to the most recent SBSR #3. Using the mid-range background rate, all stratifications have an O/E ratio less than 1.

Conclusion

Cerebral venous sinus thrombosis (CVST) and Cerebrovascular Accident (CVA)/Stroke were evaluated as signals during the reporting period and were not determined to be risks causally associated with the vaccine (please refer to Section 16.2.1 *Evaluation of Closed Signals*).

No additional safety signals other than those mentioned above have emerged based on the review of these cases, or from the O/E analysis. Safety surveillance will continue.

16.3.3.1.18. Sudden Death

Search criteria - PT Sudden Death.

Please refer to Section 16.3.4.1 *Death*.

16.3.3.1.19. Thromboembolic AESIs

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

Clinical Trial Data

- Number of cases: 17 (BNT162b2 [16], blinded therapy [1]; 2.5% of 668 cases in the total CT dataset) compared to 15 cases (2.1%) retrieved in the PSUR #2.
- Country of incidence: US (13), Argentina (3), Brazil (1).
- Subjects' gender: female (10), male (7).
- Subjects' age in years (n = 17), range: 18 – 81, mean: 56.4, median: 55.
- Medical history (n = 14): medical conditions reported more than once were coded to the PTs: Obesity (6), Hypertension (4), Depression (3), Anxiety, Cholecystectomy, Deep vein thrombosis, Gastrooesophageal reflux disease, Hyperlipidaemia, Hypothyroidism, Osteoarthritis, Type 2 diabetes mellitus, and Vasectomy (2 each).
- COVID-19 medical history: None.
- Co-suspects: None.
- Reported relevant PTs: Pulmonary embolism (8), Deep vein thrombosis (6), Thrombosis (2), Coagulopathy, Embolism, Peripheral artery thrombosis, Portal vein

thrombosis (1 each). However, none of these SAEs were assessed as related to BNT162b2/blinded therapy.

- Relevant event outcome: fatal (1), resolved/resolving (13), resolved with sequelae (1), not resolved (5).

Post-Authorisation Data

- Number of cases: 6102 (1.2 % of 507,683 cases in the total PM dataset), compared to 6507 cases (1.0%) retrieved in the PSUR #2.
- MC cases (2944), NMC cases (3158).
- Country of incidence (>50 occurrences): Germany (1882), France (910), UK (499), Australia (314), Italy (294), Sweden (278), Austria (264), US (200), Netherlands (129), Japan (109), New Zealand, Poland (93 each), Greece, Spain (90 each), Finland (86), Czech Republic (85), Belgium (82), Norway (78), Denmark (72), Taiwan (52); the remaining 402 cases were distributed among 41 countries.
- Subjects' gender: female (3322), male (2682), unknown (98).
- Subjects' age in years (n = 5794), range: 5 – 102, mean: 55.0, median: 55.
- Medical history (n = 3054): the most frequently (>100 occurrences) reported medical conditions were coded to the PTs Hypertension (738), Non-tobacco user (203), Obesity (199), Asthma (184), Seasonal allergy (173), Deep vein thrombosis, Drug hypersensitivity (151 each), Tobacco user (137), Hypothyroidism (135), Pulmonary embolism (119), Type 2 diabetes mellitus (115), and Diabetes mellitus (113).
- COVID-19 Medical history (n = 261): COVID-19 (193), Suspected COVID-19 (65), COVID-19 pneumonia (7), Post-acute COVID-19 syndrome (2), Asymptomatic COVID-19, Coronavirus infection, SARS-CoV-2 antibody test positive (1 each).
- Co-suspects (n = 162 cases): the most frequently (≥3 occurrences) reported co-suspect medications were ethinylestradiol/levonorgestrel (14), COVID-19 vaccine mRNA (mRNA 1273) (13), adalimumab (12), COVID-19 vaccine, influenza vaccine INACT SPLIT 4V (11 each), apixaban, influenza vaccine (9 each), COVID-19 vaccine NRVV AD, JNJ 78436735 (6 each), rivaroxaban (5), influenza vaccine INACT SAG 4V (4), enoxaparin, ethinylestradiol/etonogestrel, and ethinylestradiol/gestodene (3 each).
- Number of relevant events: 7194.
- Relevant event seriousness: serious (6724), non-serious (470).
- Most frequently (≥50 occurrences) reported relevant PTs: Pulmonary embolism (2068), Thrombosis (1461), Deep vein thrombosis (1321), Thrombophlebitis (285), Venous thrombosis limb (276), Superficial vein thrombosis (258), Venous thrombosis (173), Coagulopathy (164), Retinal vein occlusion (127), Embolism (103), Pulmonary thrombosis (77), Ophthalmic vein thrombosis (74), Retinal vein thrombosis (54), Retinal artery occlusion (52), Portal vein thrombosis (50).

- Time to event onset (n = 5217),[118] range: < 24 hours to 375 days, median: 12 days.

  - <24 hours: 321 events (14 of which had a fatal outcome);
  - 1 day: 368 events (12 of which had a fatal outcome);
  - 2-7 days: 1358 events (37 of which had a fatal outcome);
  - 8-14 days: 810 events (36 of which had a fatal outcome);
  - 15-30 days: 1007 events (19 of which had a fatal outcome);
  - 31-180 days: 1243 events (37 of which had a fatal outcome);
  - >180 days: 110 events (6 of which had a fatal outcome).

- Duration of relevant events (n = 442 out of 1325 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 329 days, median 24.5 days.

  - <24 hours: 25 events;
  - 1 day: 11 events;
  - 2-7 days: 92 events;
  - 8-14 days: 51 events;
  - 15-30 days: 61 events;
  - 31-180 days: 165 events;
  - >180 days: 37 events.

- Relevant event outcome:[78] fatal (265), resolved/resolving (2521), resolved with sequelae (506), not resolved (2148), unknown (1774).

- In 236 cases (reporting 265 relevant events with fatal outcome), the reported causes of death (>10 occurrences) were coded to the PTs Pulmonary embolism (116), Thrombosis (62), Cardiac arrest (27), Immunisation (26), Dyspnoea (24), Off label use (19), Myocardial infarction (18), Interchange of vaccine products (17), Deep vein thrombosis (15), Cardio-respiratory arrest, Cerebrovascular accident (14 each), Embolism (13), and Loss of consciousness (11).[106] Most (153 of 236 cases) of the fatal cases involved elderly subjects. When the medical history was provided (153 cases), the most frequently (>5 occurrences) medical conditions included the PTs Hypertension (51), Diabetes mellitus (13), Atrial fibrillation, Obesity (12 each), Chronic obstructive pulmonary disease, Osteoporosis, Type 2 diabetes mellitus (9 each), Arteriosclerosis, Tobacco user (8 each), Asthma, Cholecystectomy, COVID-19, Deep vein thrombosis, Hypothyroidism, Myocardial infarction, Pulmonary embolism (7 each), Cerebral infarction, Dementia, Depression, Ex-tobacco user, Hospitalisation, Hypercholesterolaemia, Osteoarthritis, Overweight, and Surgery (6 each).

[118] This number does not include 2001 events for which administration and/or event onset dates were not provided or were incomplete; or events without a meaningful time to onset value as per reported information. Please note, multiple episodes of the same PT event were reported with different latencies within some cases hence the sum of latencies exceeds the total number of PT events.

Analysis by age group

- CT: Adults (12), Elderly (5).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM: Paediatric (79 [7 Child, 72 Adolescent]), Adults (3833), Elderly (1966), Unknown (224).
  - Except for the PT Coagulopathy, no significant difference was observed in the reporting proportion of the most frequently (≥50 occurrences) reported thromboembolic AESIs, between the paediatric, adult and elderly populations. The reporting proportion of the PT Coagulopathy was significantly higher in the paediatric population (11.4%) when compared to the adult and elderly populations (2.7% and 2.1%, respectively).

Analysis by presence of comorbidities

- Number of PM subjects reporting comorbidities: 1356 (22.2% of the 6102 cases reporting thromboembolic AESIs).
- Of the PM cases that reported medical histories, the percentage of cases with a fatal thromboembolic AESI is higher in subjects with comorbid conditions (65.4%) when compared to the percentage of cases with a fatal thromboembolic AESI in subjects without comorbidities (34.6%).
- Upon review of the most frequent (≥50 occurrences) relevant events in cases that recorded medical histories, no thromboembolic AESIs had a significant proportional reporting ratio of >3:1 in subjects with comorbidities compared to subjects without comorbidities.

O/E Analysis

O/E analysis was performed for Arterial thromboembolism, Deep vein thrombosis, Disseminated intravascular coagulation, Thrombotic thrombocytopenia syndrome and Venous thromboembolism (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.

16.3.3.1.20. Vasculitic events

Search criteria - HLT (All Path) Vasculitides OR PTs Microangiopathy; Peripheral ischaemia.

Clinical Trial Data

- During the reporting period no serious cases from the CT dataset were reported; no cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 612 (0.12% of 507,683 cases, the total PM dataset), compared to 854 cases (0.13%) retrieved in the PSUR #2.
- MC cases (375), NMC cases (237).
- Country of incidence: Germany (154), France (112), Japan (57), UK (34), Italy (28), Australia (26), US (20), Austria (19), Netherlands (16), Taiwan, Province of China (15), Denmark, Greece, Norway (11 each); the remaining 98 cases were distributed among 31 countries.
- Subjects' gender: female (363), male (234) and unknown (15).
- Subjects' age in years (n = 576), range: 2 – 97, mean: 53.3, median: 58.0.
- Medical history (n = 332): the most frequently (≥ 5 occurrences) reported relevant medical conditions included Hypertension (78), Tobacco user (22), Type 2 diabetes mellitus (19), Diabetes mellitus (16), Obesity (13), Hypercholesterolaemia (12), Giant cell arteritis, Vasculitis (11 each), Dyslipidaemia, Henoch-Schonlein purpura (10), Autoimmune thyroiditis, Hyperlipidaemia, Hypersensitivity, Rheumatoid arthritis (9 each), Drug hypersensitivity (8), Raynaud's phenomenon (7), Autoimmune disorder (6), Polymyalgia rheumatica, Pulmonary embolism, Tobacco abuse, and Uveitis (5 each).
- COVID-19 Medical history (n = 27): COVID-19 (20), Suspected COVID-19 (4), Asymptomatic COVID-19, Coronavirus infection, and Post-acute COVID-19 syndrome (1 each).
- Co-suspects (n = 20 cases): relevant co-suspect included Adalimumab (3).
- Number of events: 648.
- Relevant event seriousness: serious (455) and nonserious (193).
- Most frequently reported relevant PTs (≥20 occurrences): Vasculitis (267), Giant cell arteritis (102), Henoch-Schonlein purpura (66), Peripheral ischaemia (60).
- Time to event onset (n = 390),[119] range: range: <24 hours to 178 days, median: 10 days.
  - <24 hours: 33 events (1 of which had a fatal outcome);
  - 1 day: 43 events;
  - 2-7 days: 105 events (2 of which had a fatal outcome);
  - 8-14 days: 51 events (1 of which had a fatal outcome);
  - 15-30 days: 63 events (1 of which had a fatal outcome);

[119] This number does not include 259 events for which partial administration or event onset date was reported.

- 31-180 days: 95 events (6 of which had a fatal outcome).

- Duration of relevant events (n = 49 out of 649 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 172 days, median 25 days.
  - <24 hours: 2 events;
  - 1 day: 1 event;
  - 2 - 7 days: 11 events;
  - 8-14 days: 5 events;
  - 15-30 days: 9 events;
  - 31-180 days: 21 events.

- Relevant event outcome: fatal (17), resolved/resolving (218), resolved with sequelae (53), not resolved (195), unknown (165).

- In 17 cases (reporting 17 relevant events with fatal outcome), the reported causes of death (>2 occurrences) were coded to Vasculitis (7), Eosinophilic granulomatosis with polyangiitis, Peripheral ischaemia (2 each). Most (13 of 17 cases) of the fatal cases involved elderly subjects. When the medical history was provided (14 cases), the most frequently (≥ 2 occurrences) relevant medical conditions included Hypertension (3), Diabetes mellitus and Obesity (2 each).

Analysis by age group

- PM: Paediatric (62), Adults (317), Elderly (208) and Unknown (25).
  - Among the frequently (≥2%) reported relevant PT, the reporting proportion of PT Anti-neutrophil cytoplasmic antibody positive vasculitis was higher in elderly population when compared to adult population (47.1% in elderly vs 38.5% in adult). No paediatric cases reported PT Anti-neutrophil cytoplasmic antibody positive vasculitis which is consistent with the known epidemiology.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 224 (36.6 % 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 (2.2 % for fatal outcome).

O/E Analysis

O/E analysis was performed for Behcet's syndrome, Giant cell arteritis, Henoch-Schonlein purpura, Limb ischaemia, and Vasculitis (see Appendix 6B *Observed versus Expected Analyses for Adverse Events of Special Interest*).

Conclusion

Vasculitis was evaluated as signal during the reporting period and was determined to not be a risk (please refer to Section 16.2.1 *Evaluation of Closed Signals*).

No new significant safety information was identified based on a review of these cases or of the O/E analysis. Safety surveillance will continue.

16.3.3.1.21. AESIs in subjects with Malnutrition; HIV infection

As part of the approval letter for the emergency use of Tozinameran - COVID-19 mRNA vaccine (nucleoside modified) - COMIRNATY®, the WHO requested the MAH to provide additional data on vaccine immunogenicity, effectiveness and safety on population groups represented in Low- and Middle-Income Countries (LMICs) including individuals with conditions such as malnutrition and populations with existing co-morbidities such as tuberculosis, human immunodeficiency virus (HIV) infection and other high prevalent infectious diseases.

Search criteria - PT Decode (History): Acute HIV infection; Asymptomatic HIV infection; Congenital HIV infection; HIV infection; HIV infection CDC Group I; HIV infection CDC Group II; HIV infection CDC Group III; HIV infection CDC Group IV subgroup A; HIV infection CDC Group IV subgroup B; HIV infection CDC Group IV subgroup C1; HIV infection CDC Group IV subgroup C2; HIV infection CDC Group IV subgroup D; HIV infection CDC Group IV subgroup E; HIV infection CDC category A; HIV infection CDC category B; HIV infection CDC category C; HIV infection CDC group IV; HIV infection WHO clinical stage I; HIV infection WHO clinical stage II; HIV infection WHO clinical stage III; HIV infection WHO clinical stage IV; Malnutrition; Perinatal HIV infection; Prophylaxis against HIV infection; Tuberculosis.

Clinical Trial Data

- Number of cases: 11 (blinded therapy [2], BNT162b2 [9]) (1.6% of 668 cases, the total CT dataset, compared to 7 cases (1.0%) retrieved in the PSUR #2.
- Country of incidence: US (4), Brazil, Germany, South Africa (2 each), and Argentina (1).
- Subjects' gender: female (2), male (9).
- Subjects' age in years (n = 11), range: 6 – 71, mean: 40, median: 39.
- Medical history (n = 11): HIV infection (7), Malnutrition, Tuberculosis (2 each).
- COVID-19 Medical history: None.
- Co-suspects: None.
- Reported PTs (16): Condition aggravated, Maternal exposure during pregnancy[120], Mental disorder (2 each), Atrial fibrillation, Cephalo-pelvic disproportion, Constipation,

[120] Maternal cases with no exposure *in-utero* reported.

Craniocerebral injury, Failed trial of labour, Headache, Intestinal obstruction, Lumbar spinal stenosis, Prostate cancer, and Spinal claudication (1 each). None of the events were related to BNT162b2 or blinded therapy.

- Relevant event outcome: resolved/resolving (14), resolved with sequelae (2).

Post-Authorisation Data

- Number of cases: 197 (0.04% of 507,683 cases, the total PM dataset), compared to 393 cases (0.06%) retrieved in the PSUR #2.

Patients with pre-existing HIV Infection: 107 (0.02% of 507,683 cases, the total PM dataset).

- MC cases (50), NMC cases (57).
- Country of incidence[121]: France (29), Italy (21), Germany (17), US (12), UK (7), Brazil, Netherlands (3 each), Mexico, Romania, and Sweden (2 each); the remaining 9 cases were distributed among 9 countries.
- Subjects' gender: female (19), male (79) and unknown (9).
- Subjects' age in years (n = 98), range: 16 – 81, mean: 50.2, median: 51.
- COVID-19 Medical history (n = 8): COVID-19 (7), COVID-19 pneumonia (1).
- Co-suspect vaccines/medications (3): COVID-19 vaccine (unspecified), dolutegravir sodium/rilpivirine hydrochloride, influenza vaccine inactive Split 3V (1 each).
- Of the 107 cases reporting a pre-existing HIV condition, 6 subjects reported cardiac disorders. The events (10) in these cases were coded to the PTs Myocarditis, Pericarditis, Tachycardia (2 each), Arrhythmia, Cardiovascular disorder, Endocarditis fibroplastica, and Palpitations (1 each). Of the 10 events, 8 were assessed as serious and 2 events were non-serious. Outcome of the events[122] was reported as resolved/resolving (3), not resolved (2), and unknown (6).
- Of the 107 cases, 35 subjects reported nervous system disorders. The events (49) reported more than once in these cases were coded to the PTs Headache (15), Dizziness (7), Facial paralysis (3), Bell's palsy, Cerebrovascular accident, Disturbance in attention, Hypoaesthesia, Paraesthesia, and Speech disorder (2 each); Of the 49 events, 23 were assessed as serious and 26 events as non-serious. Outcome was reported as resolved/resolving (21), not resolved (17), and unknown (11).
- Of the 107 cases, 30 subjects reported infectious events. The events (30) in these cases were coded to PTs COVID-19 (16), Herpes zoster (2), Arthritis bacterial, Asymptomatic COVID-19, Bacterial sepsis, Encephalitis, Fungal infection, Herpes simplex encephalitis,

[121] There were 7 cases reported from low- and middle-income countries (Brazil [3], Mexico [2], Serbia, South Africa [1 each]).

[122] One event reported more than 1 outcome.

Herpes zoster reactivation, HIV peripheral neuropathy, Myelitis, Oral fungal infection, Post viral fatigue syndrome, Virologic failure (1 each). Of the 30 events, 25 were assessed as serious and 5 events were non-serious. Outcome of the events was reported as resolved with sequelae (1), resolved/resolving (8), not resolved (6), and unknown (15).

- Time to event onset (n = 175[123]), range: <24 hours to 255 days, median: 2 days (no events with a fatal outcome).
  - <24 hours: 47 events;
  - 1 day: 26 events;
  - 2-7 days: 45 events;
  - 8-14 days: 14 events;
  - 15-30 days: 8 events;
  - 31-90 days: 6 events;
  - 91-255 days: 19 events.

- Duration of relevant events (n = 22[124], of which 21 events reported an outcome of resolved/resolving/resolved with sequelae), range: 2 hours to 288 days, median: 2 days.
  - <24 hours: 1 event;
  - 1 day: 3 events;
  - 2 - 7 days: 10 events;
  - 8-14 days: 3 event;
  - 15-31 days: 4 events;
  - 288 days: 1 events.

- 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 107 cases, 88 cases involved adults, 9 cases involved elderly and in 9 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: 67 (0.01% of 507,683 cases, the total PM dataset).

- MC cases (37), NMC cases (30).

[123] This number does not include events which occurred prior to vaccine administration.

[124] 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.

- Country of incidence[125]: France (35), UK (7), Germany, Brazil, US (4 each), Canada, Netherlands, South Africa, Taiwan (Province of China) (2 each), Bulgaria, Japan, New Zealand, Philippines, Sweden (1 each).
- Subjects' gender: female (46), male (21).
- Subjects' age in years (n = 66), range: 8 – 94, mean: 59.3, median: 62.
- COVID-19 Medical history (n = 6): COVID-19 (4), Coronavirus infection, and Suspected COVID-19 (1 each).
- Co-suspect vaccines/medications (7): COVID-19 vaccine (unspecified), COVID-19 MRNA 1273, COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Influenza vaccine, Influenza vaccine INACT SPLIT 4V, Ranibizumab, varicella zoster vaccine live (OKA/Merck) (1 each).
- Of the 67 cases reporting pre-existing tuberculosis, 13 subjects reported cardiac disorders. The events (21) in these cases were coded to the PTs Pericarditis (4), Myopericarditis, Palpitations (2 each), Arrhythmia, Atrioventricular block, Bradycardia, Cardiac arrest, Cardiac failure, Cardiac failure acute, Cardiovascular disorder, Early repolarisation syndrome, Myocarditis, Pericardial effusion, Pericardial fibrosis, Tachycardia, and Ventricular hypokinesia (1 each). Of the 21 events, 19 were assessed as serious and 2 events were non-serious. Outcome of the events[78] was reported as fatal (1), resolved with sequelae (1), resolved/resolving (8), not resolved (5), and unknown (7).
- Of the 67 cases, 19 subjects reported nervous system disorders. The events (32) in these cases were coded to PTs Headache (7), Dizziness, Somnolence (3 each), Hypoaesthesia, Speech disorder (2 each), Aphasia, Burning sensation, Cerebral infarction, Dysstasia, Head discomfort, Hypokinesia, Irregular sleep wake rhythm disorder, Ischaemic stroke, Loss of consciousness, Migraine, Neuralgia, Paraesthesia, Sensory disturbance, Sensory loss, and Syncope (1 each). Of the 32 events, 14 were assessed as serious and 18 events were non-serious. Outcome of the events was reported as fatal (1), resolved/resolving (11), not resolved (6), resolved with sequelae (1), and unknown (13).
- Of the 67 cases, 13 subjects reported infectious events. The events (15) in these cases were coded to the PTs COVID-19 (4), Influenza, Nasopharyngitis (2 each), Bronchitis, Chorioretinitis, COVID-19 pneumonia, Herpes virus infection, Herpes zoster, Pancreatic abscess, Tuberculosis (1 each). Of the 15 events, 9 were assessed as serious and 6 events were non-serious. Outcome of the events was reported as resolved with sequelae (1), resolved/resolving (4), not resolved (1), and unknown (9).
- Time to event onset (n = 235), range: <24 hours to 377 days, median: 2 days.
  - <24 hours: 70 events (none of which had a fatal outcome);
  - 1 day: 22 events (1 of which had a fatal outcome);
  - 2-7 days: 55 events (none of which had a fatal outcome);
  - 8-14 days: 12 events (none of which had a fatal outcome);

[125] There were 8 cases reported from low- and middle-income countries (Brazil [4], South Africa [2], Bulgaria, and Philippines [1 each]).

- 15-30 days: 27 events (1 of which had a fatal outcome);
- 31-180 days: 44 events (4 of which had a fatal outcome);
- 181-377 days: 5 events (none of which had a fatal outcome).

- Duration of relevant events (n = 13[126], out of which 12 occurrences were reported with outcome of resolved/resolved with sequelae/resolving), range: 2 to 300 days, median 12 days.

  - 2 - 7 days: 5 events;
  - 8-14 days: 3 events;
  - 15-31 days: 2 events;
  - 32-300 days: 3 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 67 cases, 36 cases involved adults, and 29 cases involved elderly, and the age group was not reported in 1 case. The reporting proportion of cases involving infectious events was higher in adult population (14.9%) when compared to the elderly (4.5%); and more adult subjects reported cases involving nervous system disorders as compared to the elderly (17.9% in adults vs 10.4% in elderly). No significant difference was observed in the reporting proportion of cases involving cardiac events (10.4% in adults vs 9.0% in elderly) between the elderly and adult population.

Patients with pre-existing malnutrition: 23 (<0.01% of 507,683 cases, the total PM dataset).

- MC cases (13), NMC cases (10).
- Country of incidence[127]: France (8), Germany (5), Sweden, Switzerland (3 each), Finland, Japan, Latvia, and US (1 each).
- Subjects' gender: female (13), male (10).
- Subjects' age in years (n = 21), range: 17 – 94, mean: 61.2, median: 62.
- COVID-19 Medical history (n = 2): COVID-19, COVID-19 pneumonia (1 each).
- Co-suspect medications (2): bevacizumab, and COVID-19 vaccine MRNA (MRNA 1273) (1 each).
- In these 23 cases, the most frequently reported events (119, ≥3 occurrences) were coded to the PTs General physical health deterioration (5), Headache, Inappropriate schedule of

[126] This number does not include events for which event onset dates or event cessation dates were not reported or events without a meaningful time to event cessation value as per reported information.

[127] There was 1 case reported from a low- and middle-income country (Latvia).

product administration, Interchange of vaccine products, Off label use, Pyrexia (4 each), Condition aggravated, Fatigue, Vaccination site pain (3 each).

- Of the 23 cases reporting pre-existing malnutrition, 9 subjects reported PTs General physical health deterioration (5), Condition aggravated, Fatigue (3 each), Anaemia, Asthenia, Dehydration, and Marasmus (1 each). Of the total 15 events, 7 events were assessed as serious, and 8 events were non-serious. Outcome of the events was reported as fatal (1), resolved/resolving (4), not resolved (4), and unknown (6).
- Time to event onset (n = 81), range: <24 hours to 107 days, median: 1 day.
  - <24 hours: 38 events (3 of which had a fatal outcome);
  - 1 day: 7 events (none of which had a fatal outcome);
  - 2-7 days: 10 events (1 of which had a fatal outcome);
  - 8-14 days: 9 events (2 of which had a fatal outcome);
  - 15-30 days: 10 events (3 of which had a fatal outcome);
  - 31-107 days: 7 events (2 of which had a fatal outcome).
- Duration of relevant events (n = 9[128] all occurrences with outcome of resolved), range: <24 hours to 3 days, median 1 day.
  - <24 hours: 1 event;
  - 1 day: 7 events;
  - 3 days: 1 event;

Of the 23 cases, 10 were reported in elderly and 11 cases involved adults, the age group was not reported in 1 case. Due to the low volume of cases (1 case) reporting cardiac disorders, it was not possible to make a meaningful comparison between the adults and elderly patient population. The reporting proportion of cases involving infectious events was higher in the elderly population (13.0%) when compared to adults (4.3%). No significant difference was observed in the reporting proportion of cases involving nervous system disorders between the elderly (21.7%) and adult population (17.4%). Generally, there was a low volume of cases reporting malnutrition in the current dataset.

Conclusion

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

[128] This number does not include events for which event onset dates or event cessation dates were not reported or events without a meaningful time to event cessation value as per reported information.

16.3.3.2. Clinical Reactogenicity Data on Individuals Previously exposed or not to SARS-COV-2

Data are available from 3 analyses: children 2 to <5 years and children 6 months to <2 years receiving up to 3 primary doses of BNT162b2 3 µg, and adults 18-55 years receiving a fourth dose booster of either the current vaccine or a monovalent Omicron-modified vaccine, both at 30 µg.

Children 6 months to <2 years (from C4591007)

Subgroups of Phase 2/3 pediatric participants 6 months to <2 years of age had similar reactogenicity, with regard to local reactions, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution. There were no meaningful differences in the overall patterns of local reactions across these subgroups.

There were 88 BNT162b2 participants with baseline positive SARS-CoV-2 status and 1078 BNT162b2 participants with baseline negative SARS-CoV-2 status who reported e-diary data in the 6 months to <2 years of age group. The frequencies of local reactions reported after any dose of BNT162b2 in the SARS-CoV-2 baseline status subgroups were:

- Tenderness: baseline positive: 28.4%, baseline negative: 26.3%
- Redness: baseline positive: 13.6%, baseline negative: 18.0%
- Swelling: baseline positive: 6.8%, baseline negative: 7.4%.

After any of three doses of BNT162b2 3-µg in the 6 months to <2 years of age group, the frequency and pattern of local reactions in baseline positive children was similar to those who were baseline negative and did not suggest any clinically meaningful difference based on prior infection status.

Subgroups of Phase 2/3 pediatric participants 6 months to <2 years of age had similar reactogenicity, with regard to systemic events, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS-CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution. There were no meaningful differences in the overall patterns of systemic events across these subgroups.

The frequencies of systemic events reported after any dose of BNT162b2 in the SARS-CoV-2 baseline status (positive or negative) subgroups were:

- Irritability: baseline positive: 63.6%, baseline negative: 68.6%
- Drowsiness: baseline positive: 47.7%, baseline negative: 40.9%
- Appetite: baseline positive: 46.6%, baseline negative: 37.9%
- Fever: baseline positive: 14.8%, baseline negative: 14.2%.

After any of three doses of BNT162b2 3-µg in the 6 months to <2 years of age group, the frequency and pattern of systemic events in baseline positive children was similar to those

who were baseline negative and did not suggest any clinically meaningful difference based on prior infection status.

The reactogenicity data for participant subgroups based on their baseline SARS-CoV-2 positive or negative status are shown as tabular summary data for local reactions (Appendix 6D -Table 5 and Table 6) and systemic events (Appendix 6D -Table 7 and Table 8).

Children 2 to <5 years (from C4591007)

Subgroups of Phase 2/3 pediatric participants 2 to <5 years of age had similar reactogenicity, with regard to local reactions, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution. There were no meaningful differences in the overall patterns of local reactions across these subgroups.

There were 231 BNT162b2 participants with baseline positive SARS-CoV-2 status and 1597 BNT162b2 participants with baseline negative SARS-CoV-2 status who reported e-diary data in the 2 to <5 years of age group. The frequencies of local reactions reported after any dose of BNT162b2 in the SARS-CoV-2 baseline status subgroups were:

- Pain: baseline positive: 45.9%, baseline negative: 47.2%
- Redness: baseline positive: 15.2%, baseline negative: 19.4%
- Swelling: baseline positive: 9.1%, baseline negative: 8.3%.

After any of three doses of BNT162b2 3-µg, the frequency and pattern of local reactions in baseline positive children was similar to those who were baseline negative and did not suggest any clinically meaningful difference based on prior infection status.

Subgroups of Phase 2/3 pediatric participants 2 to <5 years of age had similar reactogenicity, with regard to systemic events, across the BNT162b2 and placebo groups when evaluated by baseline SARS-CoV-2 status. The subgroup of baseline SARS-CoV-2 status (positive) included a limited number of participants, and results should be interpreted with caution. There were no meaningful differences in the overall patterns of systemic events across these subgroups.

The frequencies of common systemic events reported after any dose of BNT162b2 in the SARS-CoV-2 baseline status (positive or negative) subgroups were:

- Fatigue: baseline positive: 35.5%, baseline negative: 46.0%
- Fever: baseline positive: 10.0%, baseline negative: 10.6%
- Headache: baseline positive: 10.4%, baseline negative: 8.4%.

After any of three doses of BNT162b2 3-µg in the 2 to <5 years of age group, the frequency and pattern of systemic events in baseline positive children was similar to those who were

baseline negative and did not suggest any clinically meaningful difference based on prior infection status.

The reactogenicity data for participant subgroups based on their baseline SARS-CoV-2 positive or negative status are shown as tabular summary data for local reactions (Appendix 6D -Table 1 and Table 2) and systemic events (Appendix 6D -Table 3 and Table 4).

Adults 18 through 55 years (from C4591031 Substudy D)

Any local reactions reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI (78.6%) and BNT162b2 (79.4%) groups, and most events were mild or moderate in severity. No Grade 4 local reactions were reported.

Across the BNT162b2 OMI and BNT162b2 vaccine groups, the frequencies of the most commonly reported local reaction of pain at the injection site were ≤78.0% for baseline positive and ≤80.8% baseline negative participants, respectively. The baseline positive subgroup included a limited number of participants, and their results should be interpreted with caution. Overall, numerical differences in any of the local reactions by SARS-CoV-2 baseline status were not considered clinically meaningful.

Any systemic events reported within 7 days after first study (Dose 4) vaccination for Cohort 2 participants were similar in the BNT162b2 OMI (77.6%) and BNT162b2 (72.9%) groups, and most events were mild or moderate in severity. No Grade 4 systemic events were reported.

Across the BNT162b2 OMI and BNT162b2 vaccine groups, the frequencies of headache were ≤46.7% for baseline positive and ≤48.4% for baseline negative participants, respectively. For fatigue, the other most commonly reported systemic event, the frequencies in baseline positive participants were 70.0% (2-sided 95% CI: 55.4, 82.1) for BNT162b2 OMI compared to 44.4% (2-sided 95% CI: 29.6, 60.0) for BNT162b2. Frequencies of fatigue in baseline negative participants were 63.1% (2-sided 95% CI: 56.7, 69.2) and 63.2% (2-sided 95% CI: 57.1, 69.1) for the BNT162b2 OMI and BNT162b2 groups, respectively. The baseline positive subgroup included a limited number of participants, which contributed to wide confidence intervals around the point estimate, and their results should be interpreted with caution. Overall, numerical differences in any of the systemic events by SARS-CoV-2 baseline status were not considered clinically meaningful.

The reactogenicity data for participant subgroups based on their baseline SARS-CoV-2 positive or negative status are shown as tabular summary data for local reactions (Appendix 6D -Table 9 and Table 10) and systemic events (Appendix 6D -Table 11 and Table 12).

16.3.3.3. Local Adverse Reactions

Search criteria - PTs Erythema; Injection site erythema; Injection site pain; Injection site swelling; Swelling.

Of the 8654 cases, 57 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 (rheumatoid arthritis flare-up (2 cases), superficial vein thrombosis, and total knee replacement)
- In 15 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 38 cases (cases reporting exposure in utero or exposure during lactation are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*).

Therefore, 8597 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: 8597 (1.7% of 507,683 cases, the total PM dataset), compared to 21,240 cases (3.2%) retrieved in the PSUR #2.
- MC cases (3250), NMC cases (5347).
- Country of incidence (>2%): UK (1629), Germany (1121), Malaysia (781), Japan (368), US (361), France (360), Italy (305), Poland (294), Australia (275), Netherlands (253), Sweden (247), Ireland (219), Philippines (213), Belgium (189); the remaining 1982 cases were distributed among 54 countries.
- Subjects' gender: female (6266), male (2050) and unknown (281).
- Subjects' age in years (n = 7836), range: 2 - 98, mean: 43.7, median: 43.0.
- Medical history (n = 2461):[129] the most frequently (>50) reported medical conditions included Hypertension (266), Asthma (215), Drug hypersensitivity (189), Hypersensitivity (158), Seasonal allergy (154), Food allergy (131), Hypothyroidism (104), Immunodeficiency (77), Depression (72), Fibromyalgia (64), Diabetes mellitus (60), Migraine (54), Anxiety (52), and Gastrooesophageal reflux disease (51).
- COVID-19 Medical history (n = 453): COVID-19 (259), Suspected COVID-19 (184), Post-acute COVID-19 syndrome (7), COVID-19 immunisation (2), Coronavirus infection (1), SARS-CoV-2 test positive (1), COVID-19 pneumonia (1).
- Co-suspect vaccines/medications (n = 121): those reported in ≥ 2 cases included adalimumab (15), influenza vaccine (9), COVID-19 vaccine MRNA [MRNA 1273] (8),

[129] Some cases reported more than 1 medical history event.

COVID-19 vaccine NRVV AD [CHADOX1 NCOV-19] (5), hepatitis a vaccine (4), mepolizumab (4), COVID-19 vaccine (3), herbal pollen nos (3), influenza vaccine INACT SAG 4v (3), influenza vaccine INACT SPLIT 4v (3), tocilizumab (3), varicella zoster vaccine RGE (CHO) (3), apixaban (2), COVID-19 vaccine INACT (VERO) CZ02 (2), diphtheria vaccine toxoid, pertussis vaccine acellular, tetanus vaccine toxoid (2), dupilumab (2), hyaluronic acid, lidocaine (2), ibuprofen (2), natalizumab (2), ocrelizumab (2), tick-borne encephalitis vaccine (2).

- Number of relevant events: 9243.
- Relevant event seriousness:[42] serious (1868), non-serious (7380).
- Most frequently reported relevant PTs (≥2%): Erythema (4137), Swelling (4036), Injection site pain (690), and Injection site swelling (212).
- Most frequently co-reported PTs (> 5%): Headache (1404), Pruritus (1402), Pyrexia (1302), Immunisation (1187), Pain (1160), Fatigue (1108), Pain in extremity (1017), Off label use (1007), Lymphadenopathy (970), Interchange of vaccine products (916), Rash (848), Myalgia (782), Axillary pain (778), Vaccination site pain (778), Arthralgia (723), Injection site pain (690), Peripheral swelling (676), Chills (644), Nausea (559), Dizziness (549), Malaise (530), and Dyspnoea (514).
- Time to event onset (n = 5683)[130] range: range: <24 hours to 366 days, median: 1 day.
  - <24 hours: 2059 events (1 of which had a fatal outcome)[131];
  - 1 day: 1673 events;
  - 2-7 days: 1334 events;
  - 8-14 days: 264 events;
  - 15-30 days: 172 events;
  - 31-181 days: 181 events.
- Duration of relevant events (n = 1328 out of 9440 occurrences with outcome of resolved/resolved with sequelae), range = <24 hours to 233 days, median 3 days.
  - <24 hours: 310 events;
  - 1 day: 150 events;
  - 2 - 7 days: 499 events;
  - 8-14 days: 130 events;
  - 15-30 days: 67 events;
  - 31-180 days: 167 events;
  - > 180 days: 5 events.

[130] This number does not include 3598 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[131] In this case, the subject died from a fatal anaphylactic reaction.

- Relevant event outcome:[78] fatal (6), resolved/resolving (4065), resolved with sequelae (99), not resolved (2582), unknown (2524).

  - There were 6 cases reporting fatal events of interest (Erythema [4 cases] and Swelling [2 case]) in elderly (4 cases) and adult (2 cases) patients. Time to onset of fatal events were < 24 hours (1 event), 1 day (1 event), 3 days (1 event), 4 days (1 event), and unknown days (2 events). Review of these cases identified additional fatal adverse events reported in these cases and the local adverse reactions were not the primary cause of death in these cases.

Analysis by age group

PM: Paediatric (512), Adults (6972), Elderly (373) and Unknown (740).

Event of Interest	Paediatric (n/%)	Adult (n/%)	Elderly (n/%)	Unknown (n/%)
Erythema	323 (59.7)	2885 (41.2)	678 (63.8)	251 (39.7)
Injection site erythema	9 (1.7)	137 (2.0)	14 (1.3)	8 (1.3)
Injection site pain	16 (3.0)	617 (8.8)	47 (4.4)	10 (1.6)
Injection site swelling	10 (1.8)	183 (2.6)	15 (1.4)	4 (0.6)
Swelling	183 (33.8)	3185 (45.5)	309 (29.1)	359 (56.8)
Total[a]	**541**	**7007**	**1063**	**632**

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

- PM

  - Number of subjects with comorbidities: 38,787 (7.6% of 507,683 cases, the total PM dataset). Subjects with comorbidities were reported in (902/10.5 %) of the Local Adverse Reactions dataset. Given the nature of the adverse events of interest reported (Erythema, Injection site erythema, Injection site pain, Injection site swelling, Swelling) and the percentage of patients with comorbidities in the dataset, there were no differences between the group with comorbidities and the one without comorbidities.

Analysis by dose

- PM
  - Number of post-authorisation vaccine doses[132] administered at the time of the event onset: Dose 1 in 2140 cases, Dose 2 in 1874 cases, Dose 3 in 2627 cases, Dose 4 in 77 case, Dose 5 in 1 case, and the dose number was not specified in 2039 cases.

PT	Dose 1[a] (n/%)	Dose 2[a] (n/%)	Dose 3[a] (n/%)	Dose 4[a] (n/%)	Dose 5[a] (n/-%)	Dose Unspecified[a] (n/%)
Erythema	1200 (53.2)	998 (50.0)	1068 (38.5)	47 (58.8)	-	917 (39.7)
Injection site erythema	23 (1.0)	45 (2.3)	28 (1.0)	2 (2.5)	-	74 (3.2)
Injection site pain	91 (4.0)	61 (3.1)	47 (1.7)	3 (3.8)	-	492 (21.3)
Injection site swelling	12 (0.5)	14 (0.7)	11 (0.4)	1 (1.3)	-	117 (5.1)
Swelling	930 (41.2)	877 (44.0)	1619 (58.4)	27 (33.8)	1 (100)	648 (28.1)
Total	**2256**	**1995**	**2773**	**80**	**1**	**2308**

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 8597 relevant cases representing 1.7 % of the cases in the reporting period. The majority of events (79.8 %) were non-serious events with 44.9% of the events resolved, resolved with sequelae or resolving at the time of reporting. There were 9 fatal cases describing fatal local adverse reactions in 6 cases; two were in adult and 4 were elderly subjects. Three of the 9 fatal cases did not report fatal local adverse reaction events. Review of these cases indicated that there were additional fatal adverse events reported and the event of interests (Erythema, Swelling) were not the primary cause of death in these subjects. When reported, the majority onset of events occurred within to <24 hours, with durations lasting <24 hours to 7 days.

The PM data appears to differ from the clinical trial data where injection site pain is generally the most frequently reported local reactogenicity event in adults and children. However, this is considered to be an effect of coding conventions given that commonly co-reported PTs in the cases are: Pain, Pain in extremity and Vaccination site pain. Evaluation of local adverse reaction cases did not reveal any significant new safety information. Local adverse reactions are appropriately described in the RSI. Surveillance of local adverse reactions will continue.

16.3.3.4. Systemic Adverse Reactions

Search criteria - PTs Arthralgia; Chills; Fatigue; Headache; Myalgia; Pyrexia.

[132] Number of vaccine doses is reported by case number.

Of the 167,869 cases, 98 cases were determined to be non-contributory and were not included in the discussion due to involving neonate, or infants exposed to the vaccine through breastfeeding.

Clinical Trial Data

- Number of cases: 11 (BNT162b2 [10], and blinded therapy [1]) (1.6% of 668 cases, the total CT dataset) compared to 4 cases (0.6%) retrieved in the PSUR #2.
- Country of incidence: US (7), Germany (2), Finland, Spain (1 each).
- Subjects' gender: male (11).
- Subjects' age (n = 11), range: 23 months to 79 years; median 46 years.
- Medical history (n = 10, >1 occurrence): Hypertension (3), Dermatitis atopic, Gastrooesophageal reflux disease, Insomnia (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspects: None.
- Number of relevant events: 11.
- Relevant PTs: Pyrexia (6), Arthralgia (3), Headache, and Myalgia (1 each), none of which were assessed as related to BNT162b2 by the investigator and Sponsor.
- Time to event onset (n = 11): range: 21 to 282 days, median: 114 days (none of the events had a fatal outcome).
  - 21-30 days: 2 events;
  - 31-90 days: 3 events;
  - 91-180 days: 4 events;
  - 282 days: 1 event.
- Duration of relevant events (n = 9, all of which were reported with an outcome of resolved), range: 1 day 6 hours to 17 days, median 4 days.
  - 1-7 days: 7 events;
  - 8-17 days: 2 events.
- Relevant event outcome: resolved/resolving (11).

Post-Authorisation Data

- Number of cases: 167,760 (33% of 507,683 cases in the total PM dataset), compared to 279,184 (42.5% retrieved in the PSUR #2).
- MC cases (47,132), NMC cases (120,628).

- Country of incidence (top 10 countries): Germany (45,946), Netherlands (20,067), UK (10,862), Australia (7333), Iraq (6827), France (6453), Belgium (5932), Sweden (5441), Austria (4818), Japan (4718); the remaining cases were distributed among 89 countries.
- Subjects' gender: female (116,859), male (47,526) and unknown (3375).
- Subjects' age in years (n = 156,917), range: 3 days – 104 years, mean: 41.2; median: 40.0.
- Medical history (n = 39604): the most frequently (>1000 cases) reported medical conditions included Hypertension (4039), Disease risk factor (3139), Asthma (3026), Seasonal allergy (2591), Drug hypersensitivity (2144), Hypersensitivity (1801), Hypothyroidism (1404), Food allergy (1363), Diabetes mellitus (1005).
- COVID-19 Medical history (n = 9126): COVID-19 (6235), Suspected COVID-19 (2812), Post-acute COVID-19 syndrome (157), COVID-19 pneumonia (46), Coronavirus infection (44), SARS-CoV-2 test positive (33), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (18 each), SARS-CoV-2 antibody test positive (2), Breakthrough COVID-19, Coronavirus pneumonia, Coronavirus test positive, and COVID-19 treatment (1 each).
- Co-suspects (n = 1652): the most frequently (≥10 occurrences) reported co-suspect medications included COVID-10 vaccine MRNA (MRNA 1273) (268), influenza vaccine (181), adalimumab (167), COVID-10 vaccine NRVV AD (CHADOX1 NCOV19) (108), COVID-10 vaccine (97), influenza vaccine INACT SAG 4V (53), influenza vaccine INACT SAG 4V (46), ocrelizumab (40), upadacitinib (26), pneumococcal vaccine polysacch 23V (23), influenza vaccine INACT SPLIT 3V (22), levothyroxine, paracetamol (17 each), JNJ 78436735 (16), ethinylestradiol, levonorgestrel (11), acetylsalicylic acid, desogestrel, hepatitis A vaccine (10 each).
- Number of relevant events: 310,383.
- Relevant event seriousness[42]: serious (36801), non-serious (273,863).
- Relevant PTs: Headache (77,970), Fatigue (67,855), Pyrexia (57,671), Myalgia (43,916), Chills (33,541), and Arthralgia (29,430).
- Time to event onset (n = 253,501[133]) range: <24 hours to 3654 days, median: 1 day.
  - <24 hours: 106,574 events (42 of which had a fatal outcome);
  - 1 day: 97,138 events (41 of which had a fatal outcome);
  - 2-7 days: 30,202 events (42 of which had a fatal outcome);
  - 8-14 days: 6818 events (21 of which had a fatal outcome);
  - 15-30 days: 5752 events (18 of which had a fatal outcome);
  - 31-180 days: 6175 events (40 of which had a fatal outcome);
  - 181-240 days: 472 events (none of which had a fatal outcome);
  - 241-365 days: 303 events (none of which had a fatal outcome);
  - 366-500 days: 56 events (none of which had a fatal outcome);
  - 501-3654 days: 11 events (none of which had a fatal outcome).

[133] This number does not include events which occurred prior to vaccine administration.

- Duration of relevant events (n = 76,627[134], out of which 76,067 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 1 year, 2 months 8 days, median 2 days.
  - <24 hours: 6027 events;
  - 1-29 days: 67,465 events;
  - 30-365 days: 3126 events;
  - >365 days = 9 events.
- Relevant event outcome[78]: fatal (300), resolved/resolving (175,756), resolved with sequelae (3756), not resolved (86,147), unknown (45,676).
  - In 233 cases, the following relevant events (300) were reported as fatal: PTs Pyrexia (119), Fatigue (63), Headache (55), Chills (29), Myalgia (20), and Arthralgia (14). More than half (124 of 233 cases, 53.2%) of the cases with a fatal outcome involved elderly subjects.

Analysis by age group

CT: Paediatric (5, PTs Pyrexia [4], Myalgia [1]), Adults (1, PT Headache), Elderly (5, PTs Arthralgia [3], Pyrexia [2]).

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

PM

- An analysis of relevant PM events by age group, event seriousness and event outcome are provided in Table 54. Per the RSI, (CDS version 13.0, dated 10 May 2022), the most frequent systemic adverse reactions in subjects 16 years of age and older (in order from highest to lowest frequencies) after 2 doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10% each); and after booster dose, were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%). In adolescent subjects 12 through 15 years of age after 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%). In children 5 through <12 years of age after 2 doses were injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%); and after booster dose

[134] 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.

were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

– In the current reporting interval, the most frequent systemic adverse reactions in subjects 16 years of age and older (in order from highest to lowest frequencies) were PTs Headache (69,392), Fatigue (61,567), Pyrexia (48,928), Myalgia (40,707), Chills (30,837) and Arthralgia (27,333); the most frequent systemic adverse reactions in adolescents 12 through 15 years of age were PTs Headache (4485), Pyrexia (4727), Fatigue (2381), Myalgia (1164), Chills (1121), Arthralgia (614). Across the age groups in the table below, the greatest number of events were reported in the adult population, followed by the elderly. In general, relevant events were more likely to be assessed as non-serious and/or associated with a resolving outcome with increasing age. Generally, there were less relevant events associated with a worse outcome (not resolved/fatal).

Table 54. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 14,492 n (%)	**Adults N = 256,344 n (%)**	**Elderly N = 22,420 n (%)**	**Unknown N = 17,114 n (%)**
Arthralgia				
Total Events	614 (4.2%)	24196 (9.4%)	3137 (14.0%)	1482 (8.7%)
Serious Events	118 (0.8 %)	3605 (1.4%)	665 (3.0%)	314 (1.8%)
Event Outcome[a]: Fatal	0 (0.0%)	5 (<0.01%)	9 (<0.1%)	0 (0.0%)
Not Resolved	200 (1.4%)	9051 (3.5%)	1333 (5.9%)	502 (2.9%)
Resolved with sequelae	1 (<0.1%)	335 (0.1%)	72 (0.3%)	9 (0.1%)
Resolved/Resolving	294 (2.0%)	11886 (4.6%)	1197 (5.3%)	501 (2.9%)
Unknown	120 (0.8%)	3052 (1.2%)	547 (2.4%)	478 (2.8%)
Chills				
Total Events	1121 (7.7%)	28825 (11.2%)	2012 (9.0%)	1582 (9.2%)
Serious Events	144 (1.0%)	2261 (0.9%)	278 (1.2%)	211 (1.2%)
Event Outcome: Fatal	1 (<0.1%)	13 (<0.1%)	15 (0.1%)	0 (0.0%)
Not Resolved	232 (1.6%)	5390 (2.1%)	405 (1.8%)	220 (1.3%)
Resolved with sequelae	2 (<0.1%)	190 (0.1%)	23 (0.1%)	5 (<0.1%)
Resolved/Resolving	707 (4.9%)	20191 (7.9%)	1237 (5.5%)	923 (5.4%)
Unknown	180 (1.2%)	3081 (1.2%)	334 (1.5%)	436 (2.5%)
Fatigue				
Total Events	2381 (16.4%)	56702 (22.1%)	4865 (21.7%)	3904 (22.8%)
Serious Events	427 (2.9%)	6649 (2.6%)	949 (4.2%)	648 (3.8%)
Event Outcome: Fatal	0 (0.0%)	17 (0.01%)	43 (0.2%)	3 (0.02%)
Not Resolved	696 (4.8%)	19422 (7.6%)	1648 (7.4%)	853 (5.0%)
Resolved with sequelae	17 (0.1%)	801 (0.3%)	93 (0.4%)	17 (0.1%)
Resolved/Resolving	1179 (8.1%)	28495 (11.1%)	2065 (9.2%)	1812 (10.6%)
Unknown	496 (3.4%)	8308 (3.2%)	1055 (4.7%)	1240 (7.2%)
Headache				
Total Events	4485 (30.9%)	64679 (25.2%)	4713 (21.0 %)	4090 (23.9%)

Table 54. Analysis of Systemic Adverse Reactions by Age Group, Event Seriousness and Event Outcome

	Paediatric N = 14,492 n (%)	Adults N = 256,344 n (%)	Elderly N = 22,420 n (%)	Unknown N = 17,114 n (%)
Serious Events	735 (5.1%)	7237 (2.8%)	824 (3.7%)	654 (3.8%)
Event Outcome: Fatal	6 (<0.1%)	29 (<0.1%)	18 (0.1%)	2 (<0.1%)
Not Resolved	1110 (7.7%)	19818 (7.7%)	1361 (6.1%)	973 (5.7%)
Resolved with sequelae	24 (0.2%)	931 (0.4%)	98 (0.4%)	26 (0.2%)
Resolved/Resolving	2523 (17.4%)	35703 (13.9%)	2412 (10.8%)	1916 (11.2%)
Unknown	829 (5.7%)	8421 (3.3%)	834 (3.7%)	1186 (6.9%)
Myalgia				
Total Events	1164 (8.0%)	37276 (14.5%)	3431 (15.3%)	2043 (11.9%)
Serious Events	185 (1.3%)	3465 (1.4%)	535 (2.4%)	266 (1.6%)
Event Outcome: Fatal	0 (0.0%)	12 (<0.01%)	7 (<0.1%)	1 (<0.1%)
Not Resolved	322 (2.2%)	11931 (4.7%)	1371 (6.1%)	513 (3.0%)
Resolved with sequelae	5 (0.03%)	587 (0.2%)	84 (0.4%)	16 (0.1%)
Resolved/Resolving	612 (4.2%)	20522 (8.0%)	1486 (6.6%)	989 (5.8%)
Unknown	226 (1.6%)	4306 (1.7%)	492 (2.2%)	528 (3.1%)
Pyrexia				
Total Events	4727 (32.6%)	44666 (17.4%)	4262 (19.0%)	4013 (23.4%)
Serious Events	838 (5.8%)	4608 (1.8%)	756 (3.4%)	429 (2.5%)
Event Outcome: Fatal	10 (0.1%)	45 (<0.1%)	61 (0.3%)	3 (<0.1%)
Not Resolved	704 (4.9%)	7166 (2.8%)	561 (2.5%)	361 (2.1%)
Resolved with sequelae	13 (0.1%)	348 (0.1%)	50 (0.2%)	9 (0.1%)
Resolved/Resolving	3202 (22.1%)	30692 (12.0%)	2623 (11.7%)	2439 (14.3%)
Unknown	802 (5.5%)	6532 (2.5%)	974 (4.3%)	1215 (7.1%)

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: 13,030 (2.6% of 508,351 cases in the total dataset and 7.8% of 167,771 [11 CT and 167,760 PM] cases reporting systemic adverse reactions).

CT:

- None of the CT cases reported selected comorbidities.

PM:

- An analysis of relevant PM events by presence of selected comorbidities, event seriousness and event outcome is provided in Table 55. The total proportion of relevant events were generally evenly distributed among subjects that reported selected comorbidities and subjects that did not report selected comorbidities. In subjects with selected comorbidities, the relevant event was more likely to be assessed as non-serious and/or with a resolved or resolving event outcome. Of note, subjects

that reported comorbidities were more likely to be of advanced age, polypharmacy users, report more AEs on average (e.g., concurrent conditions) and/or prone to hospitalisation; therefore, assessment of the contributory role of BNT162b2 on the seriousness and outcome of these relevant events is confounded.

Table 55. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome

	Without Comorbidities N = 288085 n (%)	**With Comorbidities N = 22298 n (%)**
Arthralgia		
Total Events	26701 (9.3%)	2729 (12.2%)
Serious Events	23750 (8.2%)	1019 (4.6%)
Event Outcome[a]: Fatal	13 (<0.1%)	1 (<0.1%)
Not Resolved	9994 (3.5%)	1092 (4.9%)
Resolved with sequelae	368 (0.1%)	49 (0.2%)
Resolved/Resolving	12832 (4.5%)	1059 (4.7%)
Unknown	3638 (1.3%)	559 (2.5%)
Chills		
Total Events	31535 (10.9%)	2006 (9.0%)
Serious Events	2384 (0.8%)	510 (2.3%)
Event Outcome: Fatal	19 (<0.1%)	10 (<0.1%)
Not Resolved	5844 (2.0%)	404 (1.8%)
Resolved with sequelae	190 (0.1%)	30 (0.1%)
Resolved/Resolving	21867 (7.6%)	1209 (5.4%)
Unknown	3671 (1.3%)	360 (1.6%)
Fatigue		
Total Events	62443 (21.7%)	5412 (24.3%)
Serious Events	6977 (2.4%)	1696 (7.6%)
Event Outcome: Fatal	37 (<0.1%)	26 (0.1%)
Not Resolved	20820 (7.2%)	1800 (8.1%)
Resolved with sequelae	815 (0.3%)	113 (0.5%)
Resolved/Resolving	31487 (10.9%)	2109 (9.5%)
Unknown	9670 (3.4 %)	1430 (6.4%)
Headache		
Total Events	72452 (25.1%)	5518 (24.7%)
Serious Events	7797 (2.7%)	1653 (7.4%)
Event Outcome: Fatal	45 (<0.1%)	10 (<0.1%)
Not Resolved	21581 (7.5%)	1682 (7.5%)
Resolved with sequelae	984 (0.3%)	95 (0.4%)
Resolved/Resolving	39917 (13.9%)	2673 (12.0%)
Unknown	10186 (3.5%)	1086 (4.9%)
Myalgia		
Total Events	41272 (14.3%)	2644 (11.9%)
Serious Events	3630 (1.3%)	821 (3.7%)
Event Outcome: Fatal	16 (<0.1%)	4 (<0.1%)
Not Resolved	13190 (4.6%)	947 (4.2%)
Resolved with sequelae	624 (0.2%)	68 (0.3%)

Table 55. Analysis of Systemic Adverse Reactions by Presence of Comorbidities, Event Seriousness and Event Outcome

	Without Comorbidities N = 288085 n (%)	With Comorbidities N = 22298 n (%)
Resolved/Resolving	22437 (7.8%)	1189 (5.3%)
Unknown	5109 (1.8%)	444 (2.0%)
Pyrexia		
Total Events	53682 (18.6%)	3989 (17.9%)
Serious Events	5362 (1.9%)	1269 (5.7%)
Event Outcome: Fatal	77 (<0.1%)	42 (0.2%)
Not Resolved	8104 (2.8%)	689 (3.1%)
Resolved with sequelae	367 (0.1%)	53 (0.2%)
Resolved/Resolving	36678 (12.7%)	2299 (10.3%)
Unknown	8594 (3.0%)	929 (4.2%)

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 47,268 cases, 2 doses in 49,553 cases; 3 doses in 44,738 cases, 4 doses in 893 cases, and in 25,515 cases the dose was either not specified or reported as others.

CT:

- Vaccination dose number: 2 doses (3), 3 doses (7) and 4 doses (1).
- A meaningful comparison by dose is not possible due to the low number of CT cases.

PM:

- An analysis of relevant PM events by dose, event seriousness and event outcome are provided in Table 56. In general, the total proportion of relevant events, event seriousness, and event outcome were highest in those subjects who had received three doses of the vaccine; following this, most events were reported in those who had received two doses of the vaccine.

Table 56. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 78166 n (%)	2 Doses N = 92344 n (%)	3 Doses N = 94444 n (%)	4 Doses N = 1607 n (%)	Dose Not Specified/ Other N = 44080 n (%)
Arthralgia					
Total Events	7235 (9.3%)	8451 (9.2%)	9471 (10.0%)	164 (10.2%)	4147 (9.4%)
Serious Events	925 (1.2%)	1497 (1.6%)	1920 (2.0%)	61 (3.8%)	312 (0.7%)
Event Outcome[a]: Fatal	2 (0.003%)	2 (0.002%)	2 (0.002%)	0 (0.0%)	8 (0.02%)
Not Resolved	2866 (3.7%)	3143 (3.4%)	3590 (3.8%)	66 (4.1%)	1442 (3.3%)
Resolved with sequelae	138 (0.2%)	167 (0.2%)	75 (0.1%)	1 (0.1%)	40 (0.1%)
Resolved/Resolving	3128 (4.0%)	3795 (4.1%)	4810 (5.1%)	63 (3.9%)	2099 (4.8%)
Unknown	1143 (1.5%)	1405 (1.5%)	1054 (1.1%)	38 (2.4%)	571 (1.3%)
Chills					
Total Events	5860 (7.5%)	10310 (11.2%)	12888 (13.6%)	228 (14.2%)	4270 (9.7%)
Serious Events	403 (0.5%)	731 (0.8%)	1506 (1.6%)	66 (4.1%)	191 (0.4%)
Event Outcome: Fatal	3 (0.004%)	6 (0.01%)	7 (0.01%)	1 (0.1%)	12 (0.03%)
Not Resolved	1312 (1.7%)	1617 (1.8%)	2591 (2.7%)	43 (2.7%)	689 (1.6%)
Resolved with sequelae	68 (0.1%)	81 (0.1%)	45 (0.05%)	1 (0.1%)	26 (0.1%)
Resolved/Resolving	3650 (4.7%)	7163 (7.8%)	9223 (9.8%)	124 (7.7%)	2923 (6.6%)
Unknown	833 (1.1%)	1472 (1.6%)	1048 (1.1%)	59 (3.7%)	624 (1.4%)
Fatigue					
Total Events	19275 (24.7%)	20318 (22.0%)	20040 (21.2%)	365 (22.7%)	7923 (18.0%)
Serious Events	1821 (2.3%)	2636 (2.9%)	3578 (3.8%)	100 (6.2%)	557 (1.3%)
Event Outcome: Fatal	14 (0.02%)	15 (0.02%)	20 (0.02%)	4 (0.2%)	10 (0.02%)
Not Resolved	6141 (7.9%)	6625 (7.2%)	7214 (7.6%)	95 (5.9%)	2567 (5.8%)
Resolved with sequelae	333 (0.4%)	354 (0.4%)	140 (0.1%)	6 (0.4%)	100 (0.2%)
Resolved/Resolving	9654 (12.4%)	9752 (10.6%)	10117 (10.7%)	141 (8.8%)	3956 (9.0%)
Unknown	3224 (4.1%)	3744 (4.1%)	2694 (2.9%)	124 (7.7%)	1325 (3.0%)
Headache					
Total Events	21087 (27.0%)	22687 (24.6%)	22345 (23.7%)	336 (20.9%)	11546 (26.2%)
Serious Events	2017 (2.6%)	2789 (3.0%)	3801 (4.0%)	100 (6.2%)	754 (1.7%)
Event Outcome: Fatal	5 (0.01%)	16 (0.02%)	14 (0.01%)	0 (0.0%)	20 (0.05%)
Not Resolved	7047 (9.0%)	6399 (6.9%)	6940 (7.3%)	86 (5.4%)	2801 (6.4%)
Resolved with sequelae	402 (0.5%)	389 (0.4%)	173 (0.2%)	2 (0.1%)	119 (0.3%)
Resolved/Resolving	10387 (13.3%)	12253 (13.3%)	12977 (13.7%)	167 (10.4%)	6815 (15.5%)
Unknown	3312 (4.2%)	3756 (4.1%)	2322 (2.5%)	82 (5.1%)	1808 (4.1%)

Table 56. Analysis of Systemic Adverse Reactions by Dose, Event Seriousness and Event Outcome

	1 Dose N = 78166 n (%)	2 Doses N = 92344 n (%)	3 Doses N = 94444 n (%)	4 Doses N = 1607 n (%)	Dose Not Specified/ Other N = 44080 n (%)
Myalgia					
Total Events	10242 (13.1%)	13060 (14.1%)	14189 (15.0%)	179 (11.1%)	6262 (14.2%)
Serious Events	875 (1.1%)	1442 (1.6%)	1820 (1.9%)	48 (3.0%)	274 (0.6%)
Event Outcome: Fatal	3 (0.004%)	4 (0.004%)	8 (0.01%)	1 (0.1%)	4 (0.01%)
Not Resolved	3622 (4.6%)	3972 (4.3%)	4818 (5.1%)	56 (3.5%)	1677 (3.8%)
Resolved with sequelae	228 (0.3%)	296 (0.3%)	97 (0.1%)	1 (0.1%)	73 (0.2%)
Resolved/Resolving	4740 (6.1%)	6786 (7.3%)	8202 (8.7%)	86 (5.4%)	3811 (8.6%)
Unknown	1676 (2.1%)	2047 (2.2%)	1095 (1.2%)	35 (2.2%)	706 (1.6%)
Pyrexia					
Total Events	14467 (18.5%)	17518 (19.0%)	15511 (16.4%)	335 (20.8%)	9932 (22.5%)
Serious Events	1129 (1.4%)	2027 (2.2%)	2800 (3.0%)	114 (7.1%)	575 (1.3%)
Event Outcome: Fatal	13 (0.02%)	29 (0.03%)	30 (0.03%)	6 (0.4%)	42 (0.1%)
Not Resolved	2382 (3.0%)	2363 (2.6%)	2861 (3.0%)	46 (2.9%)	1159 (2.6%)
Resolved with sequelae	104 (0.1%)	149 (0.2%)	99 (0.1%)	6 (0.4%)	62 (0.1%)
Resolved/Resolving	9807 (12.5%)	11559 (12.5%)	10224 (10.8%)	185 (11.5%)	7250 (16.4%)
Unknown	2200 (2.8%)	3464 (3.8%)	2364 (2.5%)	94 (5.8%)	1427 (3.2%)

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.

Conclusion

Systemic adverse reactions were reported in 167,771 (11 CT and 167,760 PM) cases representing 33.0 % of the cases in the total dataset for the reporting period. The majority of events (88.2%) were non-serious events with 57.8% of the events resolved, resolved with sequelae or resolving at the time of reporting. Evaluation of systemic adverse reaction cases did not reveal any significant new safety information based on analysis by age group, by presence of comorbidities or by dose. Systemic adverse reactions are appropriately described in the RSI. Surveillance of systemic adverse reactions will continue.

16.3.3.5. Severe Reactogenicity

Search criteria - PT Extensive swelling of vaccinated limb.

Upon review, 4 cases were determined to be non-contributory and were not included in the discussion since they involved exposure to the vaccine during the mother's pregnancy or through breastfeeding.[99]

Clinical Trial Data

During the current reporting interval, there were no serious CT cases indicative of extensive swelling of vaccinated limb; no cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 1613 (0.32% of 507,683 cases, the total PM dataset), compared to 1558 cases (0.24%) retrieved in the PSUR #2.
- MC cases (196), NMC cases (1417).
- Country of incidence: Netherlands (921), Belgium (590), Iraq (26), Australia (24), UK (12), France, Germany (8 each), Philippines (5); the remaining 19 cases were distributed among 10 countries.
- Subjects' gender: female (1310), male (300) and unknown (3).
- Subjects' age in years (n = 1536), range: 7 – 94, mean: 38.3, median: 36.0.
- Medical history (n = 497): the relevant reported medical conditions included Drug hypersensitivity (24), Hypersensitivity (8), Allergic reaction to excipient, Allergy to vaccine, Reaction to preservatives (1 each).
- COVID-19 Medical history (n = 219): medical conditions reported included COVID-19 (162), Suspected COVID-19 (54), Post-acute COVID-19 syndrome (2), and SARS-CoV-2 test positive (1).
- Co-suspects (n= 17 cases): Influenza vaccine (6), Pneumococcal vaccine polysacch 23V (2).
- Number of relevant events: 1613
- Relevant event seriousness: serious (202), non-serious (1,411).
- Time to event onset (n = 1450)[135], range: range: <24 hours to 175 days, median: 1 day.
  - <24 hours: 589 events;
  - 1 day: 649 events;
  - 2-7 days: 185 events;
  - 8-14 days: 9 events;
  - 15-30 days: 7 events;
  - 31-180 days: 11 events.
- Duration of relevant events (n = 375 out of 1,615 occurrences with outcome of resolved/resolved with sequelae), range: <24 hours to 157 days, median 4 days.
  - <24 hours: 6 events;

[135] This number does not include 165 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.

- 1 day: 43 events;
- 2 - 7 days: 278 events;
- 8-14 days: 30 events;
- 15-30 days: 7 events;
- 31-180 days: 11 events.

- Relevant event outcome:[78] fatal (1), resolved/resolving (910), resolved with sequelae (8), not resolved (583), unknown (112).

The reported relevant PT included Extensive swelling of vaccinated limb (1613). During the reporting period, 1 case was received from a Health Authority, reporting the relevant PT Extensive swelling of vaccinated limb with a fatal outcome. This case described a 14-year-old male patient who received BNT162b2 intramuscularly for COVID-19 immunisation and experienced swelling of limb. The patient also experienced difficulty breathing (PT Dyspnoea), cyanosis (PT Cyanosis) and oedematous lower extremities (PT Oedema), all of which were reported as non-serious events. The reported cause of death was peripheral swelling. Limited information was provided in this case precluding a meaningful medical assessment, including a lack of event onset dates, event details, test results, medical history, and concomitant medications.

A majority of the cases did not describe the type or extent of swelling and reported (verbatim) terms such as, "extensive swelling of the arm, reaction at or around the injection site, swelling limb, or extended swelling of the arm: extensive swelling of vaccinated limb". Many cases also reported additional events related to pain, warmth, or erythema at the injection site, with no additional relevant details. Most cases described localized redness or swelling limited to the injection site and/or reports of lymph node swelling with no evidence in the case detail regarding any additional extensive swelling. For those cases reporting details of swelling, most appeared limited to the area surrounding the injection site with little evidence of additional extensive swelling of the rest of the limb. In a majority of the cases reporting swelling associated with the injection site, it was not reported if treatment was required, and no case reported long lasting or permanent sequelae following the event.

Analysis by age group

PM: Paediatric (25), Adult (1506), Elderly (65), Unknown (17).

A higher reporting proportion of events coded to the PT Extensive swelling of vaccinated limb was observed in elderly versus adult population (26.5% in elderly vs 20.3% in adults). Due to the relative low volume of cases in the paediatric population, a meaningful comparison of the same with the other age groups was not possible.

Analysis by presence of comorbidities

Number of subjects reporting comorbidities: 51 (3.2% of the cases reporting the event severe reactogenicity). A higher reporting proportion of severe reactogenicity was reported in patients without significant comorbidities (96.9%) when compared to patients with significant comorbidities.

The reporting proportion of the event severe reactogenicity with the outcome of resolved/resolving (58.8%) is slightly higher in individuals with comorbid conditions when compared to the reporting proportion observed in the individuals without comorbidities (56.3 % of events with resolved/resolving).

Conclusion

There was a total of 1613 cases in the safety database reporting the PT Extensive swelling of vaccinated limb with the use of BNT162b2 which were mostly reported from the Netherlands (921) and Belgium (590). A majority of the cases involved females (1310, 81.2%) and were reported in subjects aged 31-50 years (793, 49.2%). Two-hundred and two (202; 12.5%) of the events were assessed as serious due to meeting medically significant criteria (there were 6 hospitalisations due to reported events). There was 1 case reporting a fatal outcome. One thousand two hundred and thirty-seven (1237) cases reported time to onset of the event as the same day or the day following vaccination. The majority of cases reporting swelling associated with the injection site, did not report that treatment was required, and no case reported long lasting or permanent sequelae following the event.

Injection site swelling and lymphadenopathy are listed adverse drug reactions in the RSI for BNT162b2, and based on the data reviewed, there is insufficient evidence from reported cases to date that would warrant a change to the existing product information.

16.3.3.6. Age-Related Adverse Reactions

All adverse events reported during the reporting period were reviewed in the context of age categories. 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: 668 (cross-referenced to Section 6.3.1.1.1 *General Overview of the Safety Database - Clinical Trials Data*)
- Time to event onset (n = 793), range: <24 hours to 558 days, median: 116 days.
  - <24 hours: 5 events (none of which had a fatal outcome;
  - 1 day: 8 events;
  - 2-7 days: 28 events;
  - 8-14 days: 11 events;
  - 15-30 days: 47 events;
  - 31-180 days: 548 events;
  - >181 days: 146 events.
- Relevant event outcome: fatal (50), resolved/resolving (663), resolved with sequelae (49), not resolved (115), unknown (3).

Post-Authorisation Data

- Number of cases: 507,683 (cross-referenced to Section 6.3.1.1.2 *General Overview of the Safety Database – Post-Authorisation Data*)
- Time to event onset (n = 1,196,069), range: <24 hours to 7337 days, median: 1 day.
  - <24 hours: 477,739 events (1067 of which had a fatal outcome);
  - 1 day: 284,078 events;
  - 2-7 days: 182,163 events;
  - 8-14 days: 57,900 events;
  - 15-30 days: 54,875 events;
  - 31-180 days: 127,948 events;
  - >181 days: 11,366 events.
- Relevant event outcome:[78] fatal (8526), resolved/resolving (595,395), resolved with sequelae (26,518), not resolved (434,513), unknown (536,733).

Analysis by age group

- CT: Paediatric (103), Adults (336), Elderly (211) and Unknown (1).

The 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group is presented are Table 57, Table 58 and Table 59. Of note, 139 cases reported 151 events pertaining the Infections and infestations SOC, which was included among the SOCs of the most frequently reported AEs in all 3 age groups.

There were 59 cases reporting 65 events in the Cardiac disorders SOC for the adult and elderly age group. Forty-five (45) cases reported relevant medical history (e.g., coronary artery disease, atrial fibrillation, congestive cardiac failure, cardiovascular disorder), which may have contributed to the relevant events. The most frequently reported events (≥3 occurrences) in the Cardiac disorders SOC for the adult and elderly age group were Atrial fibrillation (16), Myocardial infarction (9), Cardiac failure congestive, Coronary artery disease (5 each), Acute coronary syndrome, Acute myocardial infarction (4 each), Angina pectoris and Angina unstable (3).

There were 96 cases reporting 98 events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group. Twenty-eight (28) cases reported pre-existing medical history of cancer (e.g., basal cell carcinoma, neoplasm malignant, pituitary tumour benign, prostate cancer). The most frequently reported events (≥3 occurrences) in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC for the adult and elderly age group were Prostate cancer (13), Adenocarcinoma of colon, Breast cancer, Pancreatic carcinoma (5 each), Brain neoplasm (4), Invasive ductal breast carcinoma, and Oesophageal carcinoma (3 each). When reported, latency ranged from 1 day to 437 days with a median of 104 days. Of the 78 events reporting latency, the majority of the relevant event latency (65 events) was reported between 1 day to 6 months.

There were 7 cases reporting 9 events in the Psychiatric disorders SOC for the paediatric age group. The 9 events reported were Depression, Suicidal ideation, Suicide attempt (2 each), Depression suicidal, Major depression and Mental status changes (1 each). The events were assessed as unrelated to BNT162b2/Blinded therapy by the investigator and the Sponsor.

Table 57. 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	76	50	25	0
Injury, poisoning and procedural complications	58	9	16	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44	1	54	0
Cardiac disorders	33	1	32	0
Gastrointestinal disorders	31	11	19	0

Table 58. Clinical Trial Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

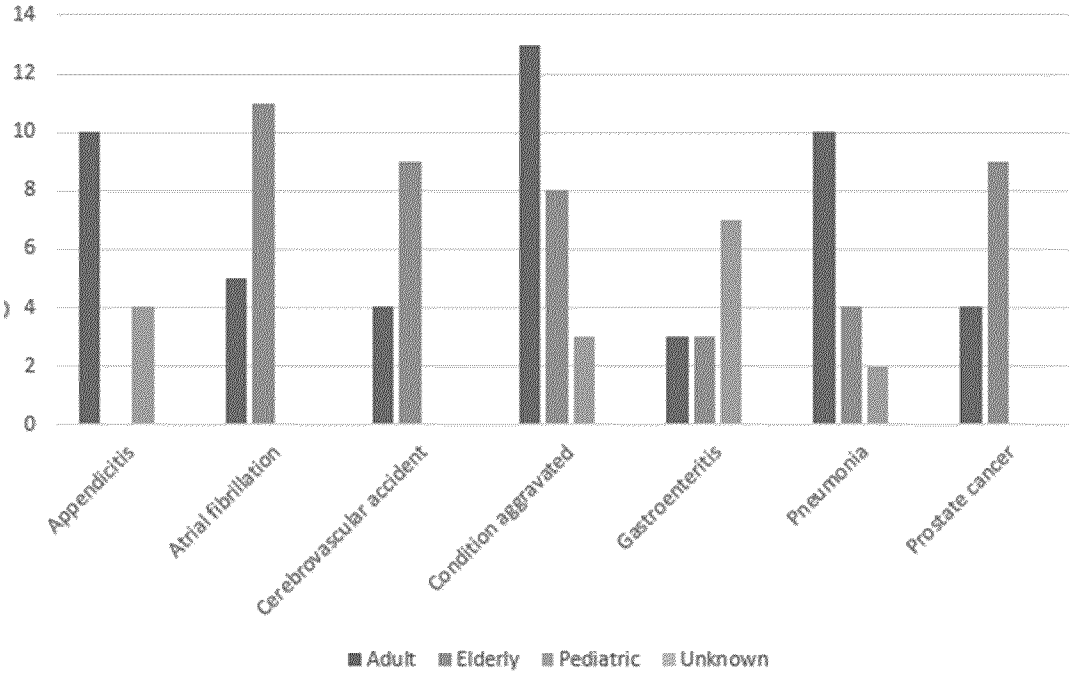
SOC	Paediatric	Adult	Elderly	Unknown
Infections and infestations	50	76	25	0
Gastrointestinal disorders	11	31	19	0
Injury, poisoning and procedural complications	9	58	16	0
Nervous system disorders	9	28	26	0
Psychiatric disorders	9	18	1	0

Table 59. 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)	54	44	1	0
Cardiac disorders	32	33	1	0
Nervous system disorders	26	28	9	0
Infections and infestations	25	76	50	0
Musculoskeletal and connective tissue disorders	22	16	2	0

The distribution of the most frequently reported serious PTs (≥ 2%) by age group in the 651 CT cases where the participants were directly exposed to BNT162b2, is shown in Figure 13 below.

Figure 13. Events Reported in ≥2% of All Clinical Trial Cases by Age Group



- PM: Paediatric (31,832), Adults (361,138), Elderly (56,588) and Unknown (56,647).

The top 5 MedDRA SOCs with the most frequently reported events for the current reporting period for each age group are presented in Table 60, Table 61, and Table 62. The top 5 SOCs were generally comparable for all age groups except Reproductive system and breast disorders in the adult age group, Skin and subcutaneous tissue disorders in the paediatric age group and Infections and infestations in the elderly age group.

In the Reproductive system and breast disorders SOC for adult age group, event seriousness was assessed as serious (8609) and non-serious (61,891). Event outcome was reported as resolved/resolving (19,328), not resolved (33,732), resolved with sequelae (1,390), unknown (16,268), and fatal (6). The most commonly reported PTs (>1000 occurrences) in Reproductive system and breast disorders for the adult age group were Heavy menstrual bleeding (11,691), Menstrual disorder (11,655), Menstruation irregular (6481), Dysmenorrhoea (5824), Intermenstrual bleeding (5650), Amenorrhoea (5267), Polymenorrhoea (4522), Menstruation delayed (4500), Oligomenorrhoea (1818), Breast pain (1816), Vaginal haemorrhage (1588), and Postmenopausal haemorrhage (1028). It is not unexpected for these events of reproductive system and breast disorders to be reported more frequently in adult subjects compared to elderly and paediatric subjects (males or females of non-puberty age).

In the Skin and subcutaneous tissue disorders SOC for paediatric age group, event seriousness was assessed as serious (966) and non-serious (4194). Event outcome was reported as resolved/resolving (2903), not resolved (1161), resolved with sequelae (20), unknown (1085), and fatal (3). The fatal cases are reviewed in Section 16.3.4.1 *Death*. The

most commonly reported PTs (≥110 occurrences) in Skin and subcutaneous tissue disorders for the paediatric age group were Rash (1538), Pruritus (718), Urticaria (681), Erythema (326), Hyperhidrosis (270), Rash pruritic (198), Cold sweat (131), and Sensitive skin (110). Most of these events are listed or consistent with listed events as per the current RSI.

In the Infections and infestations SOC for elderly age group, event seriousness was assessed as serious (11,447) and non-serious (2756). Event outcome was reported as resolved/resolving (3096), not resolved (2014), resolved with sequelae (157), unknown (8305), and fatal (649). The fatal cases are reviewed in Section 16.3.4.1 *Death*. The most commonly reported PTs (>250 occurrences) in Infections and infestations for the elderly age group were coded to the PTs COVID-19 (8394), Herpes zoster (1771), Suspected COVID-19 (462), COVID-19 pneumonia (408), Influenza (407), Pneumonia (346), and Nasopharyngitis (251). It is not unexpected for these events to be reported more frequently in elderly subjects compared to adult and paediatric subjects.

Table 60. 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	Elderly	Paediatric	Unknown
General disorders and administration site conditions	367,077	42,066	23,304	27,093
Nervous system disorders	160,280	20,808	12,369	10,612
Musculoskeletal and connective tissue disorders	120,125	15,881	4,256	8,578
Reproductive system and breast disorders	70,479	508	2,048	4,882
Gastrointestinal disorders	62,657	8,009	6,830	4,159

Table 61. Post-Authorisation Data: Number of AEs in the Top 5 Frequently Reported System Organ Classes for Paediatric Group Compared with Other Age Groups

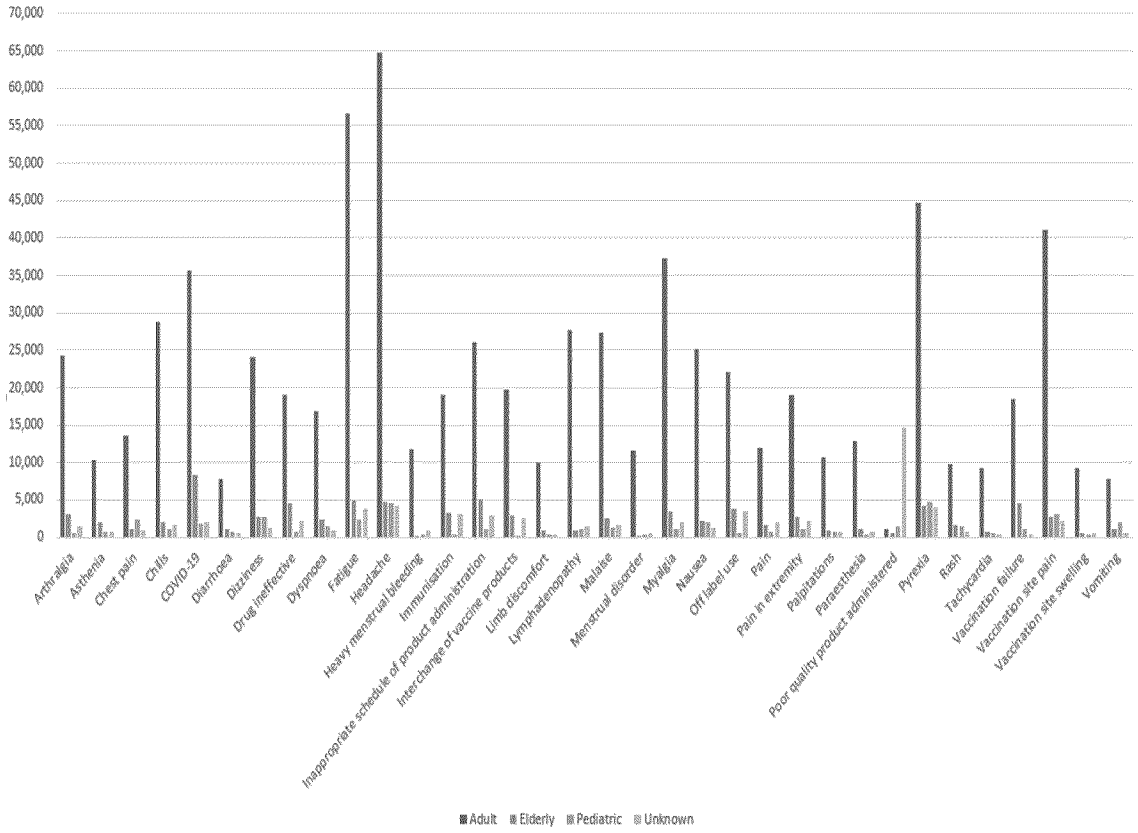
SOC	Paediatric	Adult	Elderly	Unknown
General disorders and administration site conditions	23,304	367,077	42,066	27,093
Nervous system disorders	12,369	160,280	20,808	10,612
Injury, poisoning and procedural complications	9,921	61,730	12,498	44,688
Gastrointestinal disorders	6,830	62,657	8,009	4,159
Skin and subcutaneous tissue disorders	5,158	44,803	8,423	3,972

Table 62. 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	42,066	367,077	23,304	27,093
Nervous system disorders	20,808	160,280	12,369	10,612
Musculoskeletal and connective tissue disorders	15,881	120,125	4,256	8,578
Infections and infestations	14,201	60,151	3,655	4,094
Injury, poisoning and procedural complications	12,498	61,730	9,921	44,688

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



Conclusion

The most frequently reported SOCs and overall PTs with the COVID-19 vaccine across the age groups were listed or consistent with listed events as per the current RSI. The analysis of age-related AEs did not identify any new significant safety information.

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, e.g., when time to event onset for the relevant PTs is same day or 1 day after vaccination[136]).

Of the 82,924 cases including PTs indicative of vaccination stress/anxiety related ADRs, 43,122 cases were determined to be non-contributory and were not included in the discussion:

- since exposure to the vaccine occurred during the mother' pregnancy or through breastfeeding (4 cases)
- since the relevant PTs were reported with time to event onset ≥ 2 days, unknown or with unmeaningful values (43,118 cases).

Clinical Trial Data

- Number of cases: 2, both involving BNT162b2 (0.3 % of 668 cases in the total CT dataset) compared to no cases[137] retrieved in the PSUR #2.
- Country of incidence: Israel, Poland (1 each).
- Subjects' gender: male (2).
- Subjects' age in years (n = 2), 10 years and 73 years.
- Medical history: Hypertension, Hypercholesterolaemia, Myocardial ischaemia and Glucose-6-phosphate dehydrogenase deficiency (1 each).
- COVID-19 Medical history: none.
- Co-suspects: none.
- Reported relevant PTs: Dyspnoea and Syncope (1 each).
- Time to event onset: 1 days for both the relevant events.
- Duration of relevant events: 1 day for the event Syncope, 5 days for the event Dyspnoea.
- Relevant event outcome: resolved (2).

Post-Authorisation Data

- Number of relevant cases: 39,800 (7.8% of 507,683 cases, the total PM dataset), compared to 56,230 cases[138] (8.6%) retrieved in the PSUR #2.

---

[136] To have consistency with the concept of vaccination stress/anxiety related ADRs, the search criteria has been restricted to relevant PTs with time to event onset equal to same day or 1 day after vaccination.

[137] In PSUR #2, 15 cases originating from clinical trials reported the relevant PTs, but none of these cases included events indicative of vaccination stress/anxiety related ADRs with time to event onset ≤ 1 day.

[138] In PSUR #2, 104,405 cases originating from PM sources reported the relevant PTs, and 56,230 cases included 69,338 events indicative of vaccination stress/anxiety related ADRs with time to event onset ≤ 1 day.

- MC cases (13,225), NMC cases (26,575).
- Country of incidence (≥2%): Germany (13,472), Philippines (2881), Australia (2621), UK (2310), France (2286), Italy (1507), Netherlands (1483), Denmark (1229), Sweden (1047), Austria (1038), Romania (940), Poland (873); the remaining 8113 cases were distributed among 58 countries.
- Subjects' gender: female (28,653), male (10,626) and unknown (521).
- Subjects' age (n = 38,473), range: 10 weeks[139] – 100 years, mean: 39.8 years, median: 39.0 years.
- Medical history (n = 21,834): the most frequently (≥2%) reported relevant medical conditions included Asthma (1033), Hypertension (999), Seasonal allergy (917), Drug hypersensitivity (793), Hypersensitivity (633), Food allergy (548).
- COVID-19 Medical history (n = 1616): COVID-19 (1131), Suspected COVID-19 (393), Post-acute COVID-19 syndrome (47), SARS-CoV-2 test positive (11), COVID-19 pneumonia (10), Coronavirus infection (9), Asymptomatic COVID-19 (7), Exposure to SARS-CoV-2(5), SARS-CoV-2 antibody test positive (2), COVID-19 treatment (1).
- Co-suspects (n = 151 cases): the most frequently (≥ 8 occurrences) reported co-suspect vaccines/medications included influenza vaccine (41) and mestranol/norethisterone (8).
- Number of relevant events: 50,360.
- Relevant event seriousness:[42] serious (12,116), non-serious (38,264).
- Most frequently reported relevant PTs (≥2%): Dizziness (16,611), Dyspnoea (7875), Paraesthesia (6846), Tachycardia (4757), Palpitations (4754), Blood pressure increased (2539), Hyperhidrosis (2339), Syncope (2294) and Loss of consciousness (1037).
- Time to event onset:
  - <24 hours: 31,865 events (48 of which had a fatal outcome);
  - 1 day: 18,534 events (33 of which had a fatal outcome).
- Duration of event (n = 12,385 of 18,547 relevant events with outcome of resolved/resolved with sequelae), range: < 24 hours to 447 days, median: 1 day.
  - <24 hours: 4908 events;
  - 1 day: 2265 events;
  - 2-7 days: 3328 events;
  - 8-14 days: 548 events;
  - 15-30 days: 443 events;
  - 31-181 days: 722 events;
  - 182-240 days: 103 events;

[139] This infant subject received the vaccination for adult (cross-referenced to Section 9.2 *Medication errors*).

- 241-447 days: 68 events.

- Relevant event outcome:[78] fatal (81), resolved/resolving (26,704), resolved with sequelae (1170), not resolved (16,695), unknown (5789).

  - In 73 cases (reporting 81 relevant evets with fatal outcome), the reported causes of death (≥18 occurrences) were coded to the PTs Dyspnoea (39) and Loss of consciousness (18). Most (49 of 81 cases) of the fatal cases involved elderly subjects. When the medical history was provided (41 cases), the most frequently (≥ 5 occurrences) relevant medical conditions included hypertension (19), diabetes mellitus (11), cardiac failure and chronic obstructive pulmonary disease (5 each).

Analysis by age group

- CT Data: Paediatric (1) and Adults (1).

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

- PM Data: Paediatric (3681), Adults (31,950), Elderly (2921) and Unknown (1248).

  - No significant difference was observed in the reporting proportion of frequently (≥2%) reported relevant events between the adult and elderly populations. A higher reporting proportion of relevant PT Syncope was observed in the paediatric population when compared to the adult or elderly population (15.2% in paediatric vs 4.6% in adult vs 6.1% in elderly subjects). This is consistent with expectations based on age-related event reports from other vaccines.[140]

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 3277 (0.8 % of the cases reporting stress/anxiety ADRs).

  - Upon review, no significant difference in the occurrence of the most frequently reported AEs related to vaccination stress/anxiety and in relevant AEs with fatal outcome in the subjects with comorbidities compared to the population without underlying diseases was identified, apart from the event syncope that was reported with higher proportion (6.3%) in subjects with comorbidities with respect to subjects without comorbidities (0.6%). The subjects' underlying conditions are likely to be contributory to the occurrence of syncope in these cases.

Conclusion

---

[140] 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.

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".
- If the case contains one of the following terms: High Level Group Term: Fatal outcomes; Preferred Terms: Assisted suicide, Completed suicide.

Clinical Trial Data

- Number of cases: 34[141] (blinded therapy [4] and BNT162b2 [30]) (5.1 % of 668 cases, the total CT dataset) compared to 44 cases (6.1%) retrieved in the PSUR #2.
- Country of incidence: the US (29), Brazil (2), Argentina, South Africa and Turkey (1 each).
- Subjects' gender: female (10) and male (24).
- Subjects' age in years (n = 34), range: 19.0 – 87.0 years, mean: 59.8 years, median: 63.5 years.
- Medical history (n = 28): the most frequently (>3 occurrences) reported medical conditions included Hypertension (16), Depression (12), Anxiety (7), Type 2 diabetes mellitus (6), Seasonal allergy (5), and Osteoarthritis (4).
- COVID-19 Medical history: None.
- Causes of death most frequently reported (>2 occurrences): Death (6), Disease progression (5), and Completed suicide (4).
- Autopsy results: None
- Events with a fatal outcome (n = 48): The most frequently reported PTs (>2 occurrences): Death (6) and Completed suicide (4). None of the fatal events are considered related to blinded therapy/BNT162b2.

[141] During the current reporting interval, there were 3 additional cases reporting subjects' death that were excluded from further analysis in this subsection as: death was mentioned as an incidental information only with none of the reported events presenting a fatal outcome (2) and a case which involved transplacental exposure is reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.

- Co-suspects (n= 1 case): Alprazolam, bupropion, cyclobenzaprine, trazadone, venlafaxine (1 each).
- Time to fatal event onset (n = 40),[142] range: 6 – 348 days, median: 119 days.
  - 2-7 days: 1 event;
  - 31-181 days: 30 events;
  - 182-240 days: 5 events;
  - 241-365 days: 4 events

Post-Authorisation Data

- Number of cases: 3163[143] (0.6% of 507,683 cases, the total PM dataset) compared to 5215 (0.8%) analysed in the PSUR #2.
- MC cases (2061), NMC cases (1102).
- Country of incidence (≥107 occurrences): Germany (655), France (304), Japan (252), Philippines (205), Austria (194), the UK (164), Malaysia (151), the US (138), Australia (122), and Italy (107).
- Subjects' gender: female (1304), male (1722), unknown (137).
- Subjects' age in years (n = 2901), range: 5.0 – 107.0 years, mean: 68.0 years, median: 73.0 years.
- Medical history (n = 1631)[144]: The most frequently reported (>70 occurrences) medical conditions included cardiac and vascular disorders [e.g., Hypertension (588), Atrial fibrillation (171), Cardiac failure (113), Dyslipidaemia (80), and Myocardial ischaemia (72)]. Other most frequently reported (>70 occurrences) medical conditions included Diabetes mellitus (169), Type 2 diabetes mellitus (117), Obesity (102), Chronic obstructive pulmonary disease (95), Dementia (83), and Chronic kidney disease (72).
- COVID-19 Medical history (n = 98): COVID-19 (86), Suspected COVID-19 (9), COVID-19 pneumonia (8), Coronavirus infection, Post-acute COVID-19 syndrome, and SARS-CoV-2 antibody test positive (1 each).
- Causes of death most frequently reported (>100 occurrences): Death (739), COVID-19 (301), Cardiac arrest (215), Dyspnoea (185), Myocardial infarction (154), Vaccination

[142] This number does not include 6 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[143] During the current reporting interval, there were 159 additional cases reporting subjects' death that were excluded from further analysis in this subsection as: death was mentioned as incidental information only with none of the reported events having a fatal outcome (77) and cases which reported foetal death/spontaneous abortion/involved transplacental exposure are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women* (82).

[144] This list excluded the medical history terms indicative of COVID-19. Of note, more than 1 medical history was reported in some cases.

failure (144), Drug ineffective (131), COVID-19 pneumonia (129), Sudden death (110), Pulmonary embolism (105), Cardio-respiratory arrest (102), and Cardiac failure (101).

- Autopsy results were provided in 165 cases and the most commonly reported (≥7 occurrences) were: Pulmonary embolism (22), Myocarditis (18), Pulmonary oedema (12), Arteriosclerosis coronary artery, Myocardial infarction, Myocardial ischaemia (10 each), Acute myocardial infarction, Arteriosclerosis (9 each), Arrhythmia, Death (8 each), Cardiac failure (7).
- Co-suspect vaccines/medications (n = 144): the most frequently reported (>3 occurrences) were COVID-19 vaccine (25), influenza vaccine (16), COVID-19 vaccine MRNA (MRNA 1273) (15), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (14), influenza vaccine INACT SPLIT 4V (8), influenza vaccine INACT SAG 4V (6), casirivimab/imdevimab (5), apixaban, furosemide, and lenalidomide (4 each).
- Cases with confounders and risk factors: 1726 fatal cases included one or more contributing factors, which precluded a meaningful causality assessment: co-suspect (144 cases), concomitant drugs (638 cases) and/or underlying medical history/risk factors (1652 cases).
- Events with a fatal outcome (n = 8335): The most frequently reported (>100 occurrences) fatal events were coded to the PTs: Death (652), COVID-19 (340), Immunisation (240), Cardiac arrest (222), Vaccination failure (218), Dyspnoea (217), Drug ineffective (209), Off label use (193), Myocardial infarction (155), Interchange of vaccine products (144), Sudden death (140), COVID-19 pneumonia (137), Pyrexia (119), Pulmonary embolism (116), and Cardiac failure (102).
- Time to fatal event onset (n = 5580),[145] range: <24 hours to 365 days, median: 8 days.
  - Same day: 1030 events;
  - 1 day: 592 events;
  - 2-7 days: 1058 events;
  - 8-14 days: 608 events;
  - 15-30 days: 621 events;
  - 31-181 days: 1463 events;
  - 182-240 days: 117 events
  - 241-365 days: 91 events

Analysis by age group

- CT: Adults (18-64) (17) and Elderly (65 years and older) (17).
  - A meaningful comparison between age groups is not possible due to the low number of cases with a fatal outcome.

[145] This number does not include 4 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- PM: Paediatric (17 years and under) (82), Adults (18-64 years) (932), Elderly (65 years and older) (1946), and Unknown (203).

  - There is a significant difference observed in the reporting proportion for the majority of the frequently reported fatal events (>100 occurrences) in the elderly population when compared to the adult population due to a higher proportion of fatal cases reported in subjects over 64 years of age (61.5% vs 29.5%, respectively). There is no meaningful comparison between elderly vs paediatric population possible due to the low number of paediatric fatal cases reported (2.6% vs 61.5%, respectively).

Most of the cases reporting a fatal outcome (42.1%) were in subjects over 75 years of age. The elderly population is generally considered a priority group targeted for vaccination by many regions and countries, including Europe and the US (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2.[146,147,148]

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 1094 (0.2 % of 508,351, the total dataset) when compared to 2090 (0.3% of 658,249 cases) in the PSUR #2.

- Upon review, there were no significant differences observed in the patterns of the most frequently reported fatal events (>100 occurrences) between the group with comorbidities and the one without comorbidities.

Analysis by dose

- Number of vaccine doses administered at the time of the subjects' death:

  - First dose (378 cases)
  - Second dose (934 cases). Of the 934 cases, 163 cases (17.5 %) reported a latency of same day to 3 days after vaccination. There were 2477 fatal events. The most frequently reported (>100 occurrences) fatal events were coded to the PTs COVID-19 (178), Death (154), Drug ineffective (113), Vaccination failure (111).
  - Third dose (1084 cases). Majority of these cases (>50 occurrences) originated from Germany (240), Japan (151), France (139), the UK (78), and Austria (56). There were 3267 fatal events. The most frequently reported (>100 occurrences) fatal events were

[146] Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA. ECDC, February 2021.

[147] https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/COVID-19/evidence-table-phase-1b-1c.html.

[148] 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).

coded to the PTs Death (206) Immunisation[43] (188), Off label use (117), COVID-19 (112), Interchange of vaccine products (107), and Vaccination failure (101).

- Fourth dose (71 cases). Majority of these cases (>10 occurrences) originated from Germany (23), France, and the UK (11 each). There were 254 fatal events. The most frequently reported (>20 occurrences) fatal events were coded to the PTs Off label use (42) Immunisation[43] (39), and Death (22).
- Fifth dose (1 case). This is a spontaneous case reported by a consumer. In this case, a 66-year-old male subject received BNT162b2, as dose 5 (booster), for COVID-19 immunisation (Off label use). Relevant medical history included interchange of vaccine products (first 2 doses with Coronavac; third and fourth doses with BNT162b2) and hospitalisation for the drop in oxygen saturation. The subject's condition worsened after receiving the fifth dose and he experienced immunisation reaction such as low oxygen saturation, lung oedema, abnormal lung function and shortness of breath, and he died 3 days later. Oxygen deficiency and failure of the lungs to function were cited as the cause of death. It was unknown if an autopsy was performed.
- In the remaining cases (695), dose number was not specified at the time of the subject's death.

Literature

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

Conclusion

No new risks were identified following review of fatal cases.

16.3.4.1.1. Death Review by Age Group

This is a high-level overview of the 3197 cases in the interval reporting period (see Section 16.3.4.1 for further details). According to the corePSUR19[75] summary tabulation of fatal reports by Age groups and SOCs is provided in Appendix 6C.1[149].

Interval Reporting Period

- CT (34 cases): Adults (18-64) (17) and Elderly (65 years and older) (17)

[149] Please note that the numbers of AEs reported in the appendix may not match with the numbers of AEs reported in Table 63 and Table 64, since in the appendix all the events included in the fatal cases are reported, while in the above mentioned tables, only AEs with fatal outcome are reported.

The top 6 MedDRA SOCs with the most frequently reported (>3 occurrences) events with the total number of fatal events in the interval period by age group is presented in the table below.

Table 63. 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
General disorders and administration site conditions	10	0	3	0	3	4
Injury, poisoning and procedural complications	8	0	5	1	1	1
Infections and infestations	5	0	1	0	1	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0	0	0	0	5
Cardiac disorders	4	0	1	0	0	3
Psychiatric disorders	4	1	3	0	0	0

Of note, multiple AEs may be reported in a single case.

- PM (3163 cases): Paediatric (17 years and under) (82), Adults (18-64 years) (932), Elderly (65 years and older) (1946), and Unknown (203).

The top 5 MedDRA SOCs with the most frequently reported (>500 occurrences) events with a fatal outcome cumulative by age group in the post-authorisation data are presented in the table below.

Table 64. 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 and administration site conditions	2059	52	33	242	172	278	1161	121
Cardiac disorders	1197	42	30	168	133	192	588	44
Nervous system disorders	950	30	36	120	96	151	483	34
Infections and infestations	824	16	11	42	42	106	580	27
Respiratory, thoracic and mediastinal disorders	779	29	16	97	75	129	413	20

Of note, multiple AEs may be reported in a single case.

Cumulative Reporting Period

This is a high-level overview of the 13,659 relevant cumulative cases with a fatal outcome. According to the corePSUR19 guidance,[75] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 6C.2[150].

Clinical Trial Data

- Number of cases: 150[151] (6.2% of 2426 cases, the total CT dataset; 143 cases involved blinded therapy [67]/BNT162b2 [76]). In the remaining 7 cases subjects received placebo.
- Causes of death most frequently reported (>7 occurrences): Disease progression (29), Cardiac arrest (15), Death (14), Completed suicide (10), Cardio-respiratory arrest, Myocardial infarction (8 each).
- Autopsy results were provided in 10 cases and the most commonly (≥2 occurrences) reported were: Arteriosclerosis, Hypertensive heart disease, Pulmonary embolism (2 each).
- Events with a fatal outcome (n = 198): The most frequently reported PTs (≥5 occurrences) were: Death (14), Completed suicide (10), Cardio-respiratory arrest (9), Cardiac arrest, Myocardial infarction (8 each), Pulmonary embolism (6), Acute respiratory failure, COVID-19, COVID-19 pneumonia, and Septic shock (5 each). None of these events are considered related to blinded therapy/BNT162b2.

Post-Authorisation Data

- Number of cases: 13,509[152] (0.9 % of 1,484,945 cases, the total cumulative PM dataset).
- MC cases (9582), NMC cases (3927).
- Causes of death most frequently reported (>500 occurrences): Death (3145), COVID-19 (1296), Cardiac arrest (892), Dyspnoea (725), Sudden death (618), Myocardial infarction (610), Vaccination failure (574), Cardio-respiratory arrest (557), Pyrexia (541), Drug ineffective (517), and Pulmonary embolism (514).

---

[150] Please note that the numbers of AEs reported in the appendix may not match with the numbers of AEs reported in Table 65 and Table 66, since in the appendix all the events included in the fatal cases are reported, while in the above mentioned tables, only AEs with fatal outcome are reported.

[151] There were 16 additional cases reporting subject deaths that were excluded from further analysis in this subsection because: death was mentioned as incidental information only with none of the reported events presenting a fatal outcome (12) and cases which involved transplacental exposure/baby cases (4) are reviewed in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.

[152] During the current reporting interval, there were 492 additional cases reporting subject deaths that were excluded from further analysis in this subsection because: death was mentioned as incidental information only with none of the reported events presenting a fatal outcome (227) 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* (265).

- Autopsy results were provided in 725 cases and the most commonly reported (>30 occurrences) were: Pulmonary embolism (82), Pulmonary oedema (61), Arteriosclerosis (54), Myocardial infarction (50), Arteriosclerosis coronary artery (48), Acute myocardial infarction (46), Myocarditis (39), Cardiac hypertrophy (33), and Cardiomegaly (31).
- Events with a fatal outcome (n = 32,992): The most frequently reported (>500 occurrences) events were coded to the PTs: Death (3016), COVID-19 (1389), Cardiac arrest (911), Dyspnoea (813), Vaccination failure (737), Drug ineffective (716), Sudden death (704), Pyrexia (622), Myocardial infarction (619), Cardio-respiratory arrest (575), and Pulmonary embolism (536).

Analysis by age group:

- CT: Adults (79), and Elderly (71).

  The top 6 MedDRA SOCs with the most frequently reported (≥15 occurrences) events with a fatal outcome cumulative by age group is presented in the table below.

Table 65. 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	18-24 years	25-49 years	50-59 years	60-69 years	70+ years
Infections and infestations	35	0	5	9	11	10
Cardiac disorders	34	0	3	8	10	13
General disorders and administration site conditions	25	0	5	5	8	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24	0	0	2	7	15
Injury, poisoning and procedural complications	18	1	9	2	4	2
Respiratory, thoracic and mediastinal disorders	17	0	2	3	9	3

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) (161), Adults (18-64 years) (2708), Elderly (65 years and older) (9568) and Unknown (1072).

The top 5 MedDRA SOCs with the most frequently reported (>3000 occurrences) events with a fatal outcome cumulative by age group in the PM data are presented in the table below.

Table 66. 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 and administration site conditions	8735	115	65	612	534	956	5720	733
Cardiac disorders	5014	78	59	539	433	700	3075	130
Nervous system disorders	3818	56	63	336	311	516	2433	103
Respiratory, thoracic and mediastinal disorders	3535	62	32	282	251	444	2395	69
Infections and infestations	3473	28	21	108	118	355	2596	247

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 the elderly population when compared to the adult population (70.8% vs 20.0%, respectively). A meaningful comparison between the elderly vs paediatric population is not possible due to the low number of paediatric fatal cases reported (1.2% vs 70.8%, respectively).

- Most of the cases reporting a fatal outcome (53.7%) were in subjects over 75 years of age. The elderly population were generally considered a priority group targeted for vaccination by many regions and countries, including Europe and the US (with various lower age cut-offs across countries), because of their higher risk of severe disease and mortality if infected with SARS-CoV-2. [146,147,148]

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 1605 cases, 9 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- Overdose was not implied (i.e., inquiry, past expiry, underdose[153]) in 7 cases
- the reported PTs of overdose referred to vitamin K/digoxin or occurred 17 days following vaccination in 2 cases.

Clinical Trial Data

There were no[154] serious clinical trial cases of overdose of the vaccine reported during the current interval period, similar to no cases in the PSUR #2.

Post-Authorisation Data

- Number of cases: 1595[155] (0.3% of 507,683 cases, the total PM dataset), compared to 1985 cases (0.3%) retrieved in the PSUR #2.
- MC cases (1237), NMC cases (358).
- Country of incidence (≥2%): US (769), Germany (168), Taiwan (100), Canada (92), France, Italy (82 each), Poland (48), UK (44), Portugal (32); the remaining 178 cases were distributed among 25 countries.
- Subjects' gender: female (572), male (444), and unknown (579).
- Subjects' age in years (n = 1029), range: 1 – 101 years, mean: 27.6 years, median: 17 years.
- Medical history (n = 185): the most frequently (≥4 occurrences) reported medical conditions included: Hypertension (26), Asthma, COVID-19 (20 each), Diabetes mellitus, Hypersensitivity (10 each), Obesity (9), Food allergy (8), Anxiety, Attention deficit hyperactivity disorder, Drug hypersensitivity (7 each), Depression, Interchange of vaccine products (6 each), Autoimmune thyroiditis, Type 2 diabetes mellitus (4 each).
- Co-suspect vaccines/medications: COVID-19 vaccine MRNA (MRNA 1273) (4), Influenza vaccine (2), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19), Diphtheria vaccine toxoid/pertussis vaccine acellular/tetanus vaccine toxoid,

[153] A 13 year old subject received the "orange cap" booster (for ages 5 to <12) rather than the ≥ 12 years dose.

[154] Two cases involved paracetamol and cocaine.

[155] Among these cases, 239 involved the Tris/Sucrose formulation (cross-referenced to Section 6.3.1.1.2.2 *Tris/Sucrose Presentation*).

enzalutamide, HPV vaccine VLP RL1 4V (yeast), Hydrocortisone, JNJ 78436735, Mirogabalin besilate, Pneumococcal vaccine conj 20V (CRM197) (1 each).

- Number of relevant events: 1595.
- Relevant event seriousness: serious (83), non-serious (1512).
- Relevant PTs: Overdose (1510), Accidental overdose (81), and Intentional overdose (4).
- Relevant event outcome: resolved/resolving (68), not resolved (12), fatal (3), resolved with sequelae (2), unknown (1510).
- Most frequently co-reported PTs (≥2%): Product preparation error (663), Product preparation issue (237), Product administered to patient of inappropriate age (121), Poor quality product administered (107), Expired product administered (96), Pyrexia (88), Headache (79), Pain in extremity (62), Vaccination site pain (59), Product temperature excursion issue (55), Chest pain (45), Fatigue (37), Product administration error (36), Asthenia, Off label use (35 each), Dizziness (34), Chest discomfort, Immunisation, Incorrect dose administered (33 each).

Analysis by age group

- Paediatric (630), Adults (420), Elderly (89) and Unknown (456).
  - Upon review, no significant differences in the reporting proportion of the most frequently co-reported AEs were noted between the different age groups.

Analysis by presence of comorbidities

- Number of subjects with comorbidities: 63 (4.0% of the total cases reporting overdose).
- Upon review, no significant differences in the occurrence of the most frequently co-reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

Literature

Review of the literature did not identify any significant new information regarding overdoses of BNT162b2.

Conclusion

The most frequently reported reasons (≥ 2%) for overdose were:

- administration of incorrect dose of diluted vaccine, different from the recommended 0.3 ml for the subjects aged ≥ 12 years and 0.2 ml for the paediatric subjects aged 5 through 11 years (411; 25.8% of the total cases reporting overdose);
- administration of undiluted vaccine (582; 36.5% of the total cases reporting overdose);

- dilution with a volume of sodium chloride different from the recommended 1.8 ml for the subjects aged ≥ 12 years and 1.3 ml for the paediatric subjects aged 5 through 11 years (170; 10.7% of the total cases reporting overdose);

- administration of more than 1 dose of vaccine (39; 2.4% of the total cases reporting overdose);

- incorrect vaccine formulation administered to paediatric subjects aged 5 through 11 years instead of the recommended 10 mcg dosage (71; 4.4% of the total cases reporting overdose).

In most cases, the incorrect preparation and/or administration of vaccine occurred by mistake. In 218 cases, the reason for overdose was not reported or unclear, 2 of which reported the PT Intentional overdose. In the remaining 2 cases reporting intentional overdose, an administration of 30 mcg in children (aged 9 and 10 years old) was reported.
No new significant safety information was identified based on the review of these cases. The majority of the most frequently co-reported AEs other than overdose and medication error PTs were events consistent with the known reactogenicity of the vaccine and listed in Section 4.8 *Undesirable effects* of the CDS.

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; Pharmaceutical nomadism[156]; Substance abuse; Substance abuser; Substance dependence; Substance use; Substance use disorder; Toxicity to various agents; Withdrawal syndrome.

Misuse Search Criteria: Intentional product misuses; Intentional device use issue; Intentional dose omission; Intentional medical device removal by patient; Intentional product use issue; Intentional removal of drug delivery system by patient; Intentional underdose; Performance enhancing product use; Prescription drug used without a prescription; Treatment noncompliance.

Of the 55 cases, 44 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

[156] This PT has been added to the Abuse Derived MedDRA Condition upon MedDRA upversioning to v.25.0.

- Eleven (11) cases reported the PT Toxicity to various agents. These cases described adverse events experienced by the subjects but did not involve abuse, intentional, excessive or non-therapeutic use of BNT162b2;

- Six (6) cases involved the abuse of illicit substances, including cannabis (2), delorazepam, "pain killers", and "used to be a drug addict before he had the vaccine", and multiple drugs [morphine, cannabis, methadone, amphetamines] (1 each);

- Four (4) cases reported the PT Intentional dose omission; one (1) case reported Intentional dose omission and Product dose omission issue; and one (1) case reported Product dose omission issue and Intentional product use issue. Each case involved drugs other than BNT162b2 (methotrexate (1), adalimumab (1), lenalidomide (1), and in 3 cases it was unclear as to which drug dose was omitted);

- Four (4) cases reported the PT Needle track marks following administration of BNT162b2; however, there was no information regarding intravenous drug abuse/substance use in these cases;

- Four (4) cases reported the PT Withdrawal syndrome; and two (2) cases reported the PT Disturbance in social behaviour. Each case described adverse events after receiving BNT162b2 by the subjects but did not involve abuse, intentional, excessive or non-therapeutic use of BNT162b2;

- Three (3) cases reported the PTs (Drug level increased [2 cases] and Drug level above therapeutic [1 case]) regarding co-suspect drugs clozapine (2) and citalopram hydrochloride (1);

- Two (2) cases involved Intentional product use issue; and one (1) case reported Intentional product misuse. Each case involved drugs other than BNT162b2 (apixaban [2], and adalimumab [1]);

- Two (2) cases reported Treatment noncompliance involving drugs other than BNT162b2 (brodalumab [1], and an unspecified drug used to treat an allergic reaction);

- One (1) case reported Drug dependence after receiving a single dose but did not report intentional, excessive or non-therapeutic use of BNT162b2;

- One (1) case reported the PT Drug withdrawal, which was associated with opiate withdrawal;

- One (1) case reported the PT Drug tolerance described as "built up tolerance to Humira medication".

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 #2.

Post-Authorisation Data

- Number of cases: 11 (0.002% of 507,683 cases, the total PM dataset), compared to 45 cases (0.01%) retrieved in the PSUR #2.
- MC cases (8), NMC cases (3).
- Country of incidence: Canada (3), Australia (2), Finland, Germany, Ireland, Japan, New Zealand, US (1 each).
- Subjects' gender: female (8), male (2), and unknown (1).
- Subjects' age in years (n = 9), range: 4 - 73, mean: 40.4, median: 49.0.
- Medical history (n = 7): Cardiac disorder, Drug hypersensitivity, Hypertension, Intracranial aneurysm, Malnutrition, Migraine with aura, Rheumatoid arthritis (1 each).
- COVID-19 Medical history: None.
- Co-suspect vaccines/medications (n = 8): abatacept, COVID-19 vaccine MRNA (MRNA 1273), dabrafenib, gabapentin, natalizumab, nivolumab, perindopril, trametinib (1 each).
- Number of events: 92 (of which 11 were events of interest).
- Relevant event seriousness: serious (5), non-serious (6).
- Relevant PTs: Intentional product misuse, Intentional product use issue (4 each), Intentional underdose (3).
- Co-reported AEs (≥2): Fatigue, Nausea, Off label use (3 each), Chest pain, Headache, Malaise, Poor quality product administered, Product storage error (2).
- Time to event onset (n = 3), range: < 24 hours, median: 0 days.
  - <24 hours: 3 cases.
- Relevant event outcome: fatal (1), not resolved (3), unknown (7).
- In the case involving the fatal outcome, a female subject (age unknown) received three vaccines COVID-19 (BNT162b2), pneumonia vaccine (unspecified) and the flu vaccine at one time. The patient experienced a myocardial infarction and died. Onset date of myocardial infarction was not reported.

Analysis by age group

- PM: Paediatric (2), Adults (5), Elderly (2), and Unknown (2).
  - 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: dose 1 in 1 case, dose 2 in 1 case, dose 3 in 1 case, and number of doses was not specified in 8 cases.
  - There are no differences between the AEs that occurred after the first, the second and the booster dose.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and abuse, dependence or misuse.

Conclusion

Overall, there were 11 cases representing 0.002% of the overall post-marketing dataset, that reported events indicative of misuse. These cases involved either improper storage, improper dilution of vaccine, administration of vaccine to unapproved age groups or administration of vaccine at a dose lower than the recommended dose. In general, the most frequently co-reported events observed in these cases were consistent with those observed in the overall population. No safety signals have emerged that would be considered specific to this population.

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 #2.

Post-Authorisation Data

- Number of cases: 20 (0.004% of 507,683 cases, the total PM dataset), compared to 41 cases (0.01%) retrieved in the PSUR #2.
- MC cases (18), NMC cases (2).
- Country of incidence: US (7), Germany (6), Australia (5), Brazil, Italy (1 each).
- Subjects' gender: female (14), male (4) and unknown (2).
- Subjects' age in years (n = 7), range: 2 – 58 years, mean: 37.1 years, median: 43.0 years.
- Medical history (n = 3): reported medical conditions included Abnormal behaviour, Anxiety, Asthma, Autism spectrum disorder, Cerebral palsy, Chronic active Epstein-Barr virus infection, COVID-19, Cyclic vomiting syndrome, Depression, Drug hypersensitivity, Gastrooesophageal reflux disease, Gene mutation, Gluten sensitivity,

Hypothyroidism, Iodine deficiency, Irritable bowel syndrome, Neurodermatitis, Obesity, Pain, Rubber sensitivity, Vitamin D deficiency (1 each).

- COVID-19 Medical history: COVID-19 (1).
- Co-suspect vaccines/medications (n =0).
- Number of events: 33 (of which 20 were events of interest).
- Relevant event seriousness: serious (1), non-serious (19).
- Relevant PTs: Occupational exposure to product (20).
- Co-reported AEs: Abdominal pain, Amylase decreased, Decreased appetite, Exposure via skin contact, Fatigue, Headache, Nausea, Ocular hyperaemia, Off label use, Pain, Product use issue, Underdose, Weight decreased (1 each).
- Time to event onset (n = 5), range: 0 and 224 days.
  - <24 hours: 4 events (none of which had a fatal outcome);
  - 1 day: 0 events;
  - 2-7 days: 0 events;
  - 8-14 days: 0 events;
  - 15-30 days: 0 events;
  - 31-180 days: 0 events.
- Relevant event outcome: resolved/resolving (2), resolved with sequelae (1), unknown (17).

Analysis by age group

- PM: Paediatric (2), Adults (5), Elderly (0) and Unknown (13).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and occupational exposure.

Conclusion

Overall, there were 20 cases representing 0.004% % of the overall post-marketing dataset, that reported events indicative of occupational exposure. Review of the cases did not identify any significant new information regarding the use of BNT162b2 and occupational exposure. No safety signals have emerged that would be considered specific to this population.

16.3.4.5. Lack of Therapeutic Efficacy

Company conventions for MedDRA coding of cases indicative of lack of efficacy:

The coding conventions for COVID-19 vaccine cases indicative of lack of efficacy was revised on 27 Sep 2021, as shown below:

- PT "Vaccination failure" is coded when ALL of the following criteria are met:
    - The subject received the appropriate series of two doses based on the CDS.
    - At least 7 days have elapsed since administration of the second dose.
    - The subject experiences COVID-19 infection (confirmed by laboratory tests or reported by HCP).
- PT "Drug ineffective" is coded when any of the following applies:
    - The COVID-19 infection is not reported by HCP or not confirmed 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 two doses within the correct intervals 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 vaccine.
    - The subject experiences COVID-19 infection 14 days after receiving the first dose up to and through 6 days after receipt of the second dose.
- Note: A case is considered a potential LOE case after the immune system has had sufficient time (14 days) to respond to the vaccine, even if the vaccination course is not complete.

This is the summary of the coding conventions based on the timing of vaccination:

From 1st dose to day 13 post 1st dose	**From day 14 post 1st dose to day 6 post 2nd dose**	**From day 7 post 2nd dose**
Code only the events describing the COVID-19 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[157]

Search criteria - PTs Drug ineffective; Vaccination failure.

- Of the 51,107 cases, 79 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - 18 cases are not considered true LOE cases because the subjects developed SARS-CoV-2 infection days 1-13 from the first dose.
  - 6 cases were invalidated in the safety database after the PSUR DLP.
  - 18 cases were not LOE reports (subjects did not develop SARS-CoV-2 infection).
  - In 37 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 for this reporting period or for the reporting period of PSUR #2.

Post-Authorisation Data

- Number of cases: 51,028 (10.1% of 507,683 cases, the total PM dataset), compared to 21,457 cases (3.3%) in PSUR #2. The increase in the reporting proportion of LOE cases was multifactorial. A high number of cases were reported from Austria (31,629 cases in the current PSUR), as compared to the previous PSURs (9009 cases in PSUR #2 and 204 cases in PSUR #1) due to the active solicitation of LOE cases, including retrospective cases, by the Austrian Board of Health starting from August 2021. In addition, the epidemiology of the virus has changed since December 2021 in that the Omicron variant has become predominant in most regions. BNT162b2 efficacy against Omicron variants is less than against the previous dominant variants of concern.
- MC cases (39,368), NMC cases (11,660).
- Relevant lack of efficacy events[158]: 51,028 (Vaccination failure [24,762] and Drug ineffective [26,266]).
- Country of incidence (≥2%): Austria (31,629), US (4734), UK (2316), Germany (1856), France (1478), Netherlands (1291); the remaining 7724 cases were distributed among 71 countries.
- Subjects' gender: female (27,177), male (21,802) and unknown (2049).

---

[157] 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.

[158] LOE PTs recorded in the 51,028 cases were Vaccination failure (24,404) and Drug ineffective (26,624). Upon review after DLP, some cases were re-assessed: in 423 cases the PT Drug ineffective was reassessed to Vaccination failure; and in 65 cases the PT Vaccination failure was reassessed to Drug ineffective.

- Subjects' age in years (n = 48,297), range: 1.5 – 107.0 years, mean: 47.3 years, median: 47.0 years.
- Relevant event seriousness: all serious.[159]

Confirmed vaccination failure (24,077 cases)

Vaccination failure was reported in 24,077 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 test, antigen test) COVID-19 infection, on or after day 7 post second dose. In 5029 of these 24,077 cases, a booster dose was also administered (including 4735 cases with administration of the third dose and 294 cases with administration of the fourth dose).

- Age groups: Child (40), Adolescent (1053), Adult (18,337), Elderly (4475) and Unknown (172).
- Time to event onset was known for 23,013 cases; in the remaining 1064 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 ≤ 90 days: 3938 subjects
    - ≥ 91 days to ≤ 180 days: 13,650 subjects
    - ≥ 181 days to ≤ 270 days: 799 subjects
    - ≥ 271 days to ≤ 360 days: 270 subjects
    - ≥ 361 days to ≤ 450 days: 70 subjects
    - ≥ 451 days to ≤ 501 days: 9 subjects
  - Time to onset reported after the third dose.
    - day 1 to ≤ 90 days: 3196 subjects
    - ≥ 91 days to ≤ 180 days: 671 subjects
    - ≥ 181 days to ≤ 270 days: 264 subjects
    - ≥ 271 days to ≤ 293 days: 7 subjects
  - Time to onset reported after the fourth dose.
    - day 1 to ≤ 90 days: 129 subjects
    - ≥ 91 days to ≤ 180 days: 9 subjects
    - 213 days: 1 subject

[159] Includes 5 cases where LOE was captured as non-serious and upgraded to serious after the PSUR DLP.

- Reported COVID-19 infection related events (>5 occurrences)[160]: COVID-19 (23,679), COVID-19 pneumonia (285), SARS-CoV-2 test positive, Suspected COVID-19[161] (107 each), Vaccine breakthrough infection (21), Breakthrough COVID-19 (8), and Post-acute COVID-19 syndrome (6).

- Outcome of COVID-19 infection related events: resolved/resolving (2187), resolved with sequelae (29), not resolved (673), unknown (21,115), and fatal (221).

- Of the 24,077 subjects with confirmed vaccination failure, in 880 cases, the COVID-19 events were severe, resulting in:

  - Hospitalisation (non-fatal/non-life threatening): 623
  - Disability: 13
  - Life threatening: 40
  - Death: 204.

Suspected vaccination failure (1402 cases)

Lack of efficacy (PTs Drug ineffective or Vaccination failure) was reported in 1402 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 test, antigen test) was not reported or clinical disease was unconfirmed (i.e., asymptomatic COVID-19). In 307 of these 1402 cases, a booster dose was also administered (including 300 cases with administration of the third dose and 7 cases with administration of the fourth dose).

- Age groups: Child (3), Adolescent (46), Adult (991), Elderly (298) and Unknown (64).

- Time to event onset was known for 1036 cases; in the remaining 366 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 ≤ 90 days: 138 subjects
    - ≥ 91 days to ≤ 180 days: 413 subjects
    - ≥ 181 days to ≤ 270 days: 272 subjects
    - ≥ 271 days to ≤ 360 days: 32 subjects
    - 438 days: 1 subject

  - Time to onset reported after the third dose.
    - day 1 to ≤ 90 days: 115 subjects

[160] Some cases reported more than 1 PT referring to a SARS-CoV-2 infection related event.

[161] In these cases reporting Suspected COVID-19, upon review, the infection was assessed to be confirmed.

  - ≥ 91 days to ≤ 180 days: 51 subjects
  - ≥ 181 days to ≤ 234 days: 11 subjects

- Time to onset reported after the fourth dose.
  - day 1, 4 days and 29 days: 3 subjects

- Reported COVID-19 infection related events (≥ 32 occurrences)[160]: Suspected COVID-19 (610), COVID-19 (527), Asymptomatic COVID-19 (239), and COVID-19 pneumonia (32).

- Outcome of COVID-19 infection related events: resolved/resolving (664), resolved with sequelae (4), not resolved (62), unknown (662), and fatal (24).

Not a vaccination failure cases (25,549 cases)

There were 25,549 cases reporting Drug ineffective that were indicative of occurrence of COVID-19 infection:

- in subjects who experienced COVID-19 infection from day 14 after receiving the first dose to day 6 after receipt of the second dose;

- in subjects who have not received the appropriate series of two doses or 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: Infant (1), Child (214), Adolescent (565), Adult (18,448), Elderly (4350) and Unknown (1971).

- Reported COVID-19 infection related events (>2 occurrences)[160]: COVID-19 (22,973), Suspected COVID-19 (2075), Asymptomatic COVID-19 (266), COVID-19 pneumonia (207), SARS-CoV-2 test positive (51), Breakthrough COVID-19 (44), Vaccine breakthrough infection (42), Post-acute COVID-19 syndrome (28), Multisystem inflammatory syndrome in children (7), Coronavirus infection (6), Coronavirus test positive, Multisystem inflammatory syndrome (4 each), and Pneumonia viral (3).

- Outcome of COVID-19 infection related events: resolved/resolving (3346), resolved with sequelae (160), not resolved (1245), unknown (20,746), and fatal (221).

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 25,549 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 (11,901 cases)

In 11,901 of the 51,028 cases, information on SARS-CoV-2 variants was provided.

- *Delta (India) variant[162] (11,274 cases)[163]*
  - Country of incidence (>3 occurrences): Austria (11,164), France (84), Germany (16), and US (4).
  - Lack of efficacy events: Vaccination failure (6591) and Drug ineffective (4683).
  - Outcome of COVID-19 infection related events[160]: resolved/resolving (50), resolved with sequelae (2), not resolved (23), unknown (11,156), and fatal (51).
- *Omicron variant[162] (606 cases)*
  - Country/region of incidence (>2 occurrences): Hong Kong (391), France (79), Germany (40), US (39), Japan (12), Spain (6), Austria (4), Belgium, Brazil, Mexico, and Norway (3 each).
  - Lack of efficacy events: Vaccination failure (404) and Drug ineffective (202).
  - Outcome of COVID-19 infection related events[160]: resolved/resolving (81), not resolved (11), unknown (503), and fatal (18).
- *Alpha (UK) variant[162] (19 cases)*
  - Country of incidence: Austria, Germany (5 each), France, Italy (4 each), and Poland (1).
  - Lack of efficacy events: Vaccination failure (16) and Drug ineffective (3).
  - Outcome of COVID-19 infection related events[160]: resolved/resolving (8), not resolved (1), unknown (10), and fatal (1).
- *Others (2 cases)*
  - In 2 other cases, variant was reported as Beta (South Africa[162]) and South African or Brazilian (as reported), respectively.

Literature

Review of the literature identified significant new information with regards to the use of BNT162b2 and lack of therapeutic efficacy. Please refer to Section 11 *Literature* and

[162] As per WHO Nomenclature (Countries in which earliest samples were documented were additionally listed, when applicable).

[163] Includes 30 cases reporting SARS-CoV-2 variant as Indian variant/lineage specified as B.1.617 and 6 cases reporting SARS-CoV-2 variant as AY lineages.

Section 17.2 *Newly Identified Information on Efficacy and Effectiveness* for the review of these articles.

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 38,130 cases, 8325 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

- 7960 cases reporting the PT Product administered to patient of inappropriate age (7958) and Contraindicated product administered (2) were found to be indicative of a potential medication error. These cases are referenced in Section 9.2 *Medication Errors*.
- 352 cases reported exposure in utero; these cases are referenced in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.
- 9 cases reported the event Intentional product use issue (6) and Intentional underdose (3). Three (3) of these cases were not reported with use of the BNT162b2 vaccine. In 1 case, only the intention of misuse was reported. These cases did not report any additional events potentially indicative of off label use. The remaining 5 cases are referenced in Section 16.3.4.3 *Abuse, Misuse and Drug Dependency*.
- 1 case reported the (fatal) PT Drug ineffective for unapproved indication with no additional events indicative of off-label use. This case is referenced in Section 16.3.4.7 *Unexpected Therapeutic Effect*.
- 3 additional cases did not report relevant off label use (i.e., off label use not reported with the BNT162b2 vaccine).

Clinical Trial Data

Not applicable.

Post-Authorisation Data

- Number of cases: 29,805 (5.9% of 507,683 cases, the total PM dataset), compared to: 22,533 (3.4%) cases retrieved in the PSUR #2. A general increase in cases reporting Interchange of vaccine products was noted (54.0% of PM cases from PSUR #2 versus 83.3% of PM cases retrieved during this reporting period).

- MC cases (6091), NMC cases (23,714).

- Country of incidence (≥2%): UK (10,172), Netherlands (6230), Germany (4368), France (1516), Poland (602)

- Subjects' gender: female (20,994), male (7831) and unknown (980).

- Subjects' age in years (n = 26,283), range: 0.01– 104 years, mean: 45.8 years, median: 44.0 years.

- Medical history (n = 12,399): the most frequently (≥2%) reported medical conditions include PT Disease risk factor (1663), COVID-19 (1591), Suspected COVID-19 (1448), Hypertension (1089), Breast feeding (1061), Asthma (746), Immunodeficiency (581), Hypothyroidism (340), Diabetes mellitus (319), Hypersensitivity (296), Steroid therapy (293), Depression (281), Drug hypersensitivity (279), Seasonal allergy (271).

- COVID-19 Medical history (n = 3001): the most frequently (≥2%) reported medical conditions included COVID-19 (1591) and Suspected COVID-19 (1448).

- Co-suspects (n = 1745 cases): the most frequently (≥2%) reported co-suspect vaccines/medications included COVID-19 vaccine MRNA (MRNA 1273) (681), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (420), Influenza vaccine (188), Influenza vaccine inact SAG 4V (80), Influenza vaccine inact SPLIT 4V (64), JNJ 78436735 (51), COVID-19 vaccine (50).

- Number of events: 174,381 (of which 32,211 were events of interest).

- Relevant event seriousness:[42] serious (10,382), non-serious (21,845).

- Most frequently reported relevant PTs (≥2%): Off label use (29,562) and Product use issue (2531). Of note, of the 29,805 cases, 696 did not report additional events. The majority of cases described off-label use as

  - intentionally used in unapproved populations such as those mentioned below:

    - It is unknown whether the BNT162b2 vaccine is excreted in human milk.

    - Administration of the vaccine in pregnancy should be considered when potential benefits outweigh any potential risks for the mother and foetus.

- Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

- The administration of the BNT162b2 vaccine should be postponed in individuals suffering from acute severe febrile illness.

- The safety and efficacy have not yet been established in individuals under 5 years of age. The safety and effectiveness of a booster dose of in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.

– alternative dosing or scheduling regimens (i.e., Full primary series not received, longer/shorter number of days between doses than recommended)

- The primary series of the BNT162b2 vaccine is administered as 2 doses at greater than or equal to 21 days (preferably 3 weeks) apart. Off label is currently considered when the 2nd dose of the vaccine is administered outside the 19-42 day range from the 1st dose.

– co-administration with other vaccines (i.e., influenza)

- No interaction studies have been performed

– administration of COVID-19 vaccines from different manufacturers and third/booster/extra doses.

– administration of COVID-19 vaccine formulations indicated for a different age group.

– usage of poor quality COVID-19 vaccines due to either preparation (i.e., dilution technique) and/or storage issues (i.e., used after the expiry or beyond use date).

Analysis by dose interval

Among these cases, 9 (all non-serious) reported administration of 3 doses of BNT162b2 with different time intervals than the recommended posology and included the relevant PTs[164] Off label use (9) and Product use issue (1).

- Upon review, there were no significant differences were identified in the occurrence of the most frequently relevant PTs and clinical co-reported AEs reported in those who received the 3 doses of vaccine at a different time interval than the recommended posology when compared to the population receiving BNT162b2 in unapproved

[164] More than 1 reported in 1 case.

conditions Clinical events reported more than once in this population included Headache (4), Pain, Pyrexia, and Vaccination site pain (2 each).

Literature

Review of the literature did not identify any significant new information with regards to the off-label use of BNT162b2.

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; no serious cases were retrieved in the PSUR #2.

Post-Authorisation Data

- Number of cases: 664 (0.1 % of 507,683 cases in the total PM dataset), compared to 844 cases (0.1%) retrieved in the PSUR #2.
- MC cases (76), NMC cases (588).
- Country of incidence (≥10 occurrences): Germany (297), US (71), Netherlands (64), UK (34), Australia (28), Canada (20), France (18), Japan (17) Belgium (14), Sweden (10); the remaining 91 cases were distributed among 30 countries.
- Subjects' gender: female (379), male (224), unknown (61).
- Subjects' age in years (n = 371), range: 7 – 96, mean: 53.2, median: 54.
- Medical history (n = 489): the most frequently (≥10 occurrences) reported medical conditions included the PTs Asthma (30), Psoriasis (29), Migraine, Seasonal allergy (24 each), Multiple sclerosis, Pain (21 each), Diabetes mellitus, Skin papilloma (15 each), Hypertension (13), Fatigue (12), Depression, Fibromyalgia, and Headache (10 each).
- COVID-19 Medical history (n = 33): PTs COVID-19 (25), Suspected COVID-19 (7), Post-acute COVID-19 syndrome (2), Coronavirus infection, SARS-CoV-2 test positive (1 each).
- Co-suspects (n = 28 cases): COVID-19 vaccine mRNA (mRNA 1273) (7), bupropion, COVID-19 vaccine (2 each), adalimumab, atogepant, bupropion/naltrexone, COVID-19

vaccine NRVV AD, hepatitis A vaccine, ibuprofen, influenza vaccine, JNJ 78436735, levonorgestrel/ethinyl estradiol, palbociclib, PF-07321332/ritonavir, pneumococcal 13-valent conjugate vaccine, sarilumab, senna alexandrina extract, sucralfate, tetanus vaccine, thyroid (1 each).

- Number of events: 1447 (of which 664 were events of interest).
- Relevant event seriousness: serious (11), non-serious (653).
- Relevant PTs: Therapeutic response unexpected (656), Therapeutic response changed (5), Therapeutic product effect increased (3).
- In most of the cases (when specified), the unexpected therapeutic effect included improvement in the following: pain, breathing, allergies, skin conditions (including warts and psoriasis), autoimmune/inflammatory diseases (e.g., arthritis, multiple sclerosis, ulcerative colitis), migraine/headache, infections (e.g., herpes and other viral infections, fungal infections), neoplasia (remission/regression of various cancers), movement/mobility, energy, hair growth/loss, menstruation, and general health/well-being (e.g., "felt better").
- Time to event onset (n = 146), range: <24 hours - 368 days, median: 1.5 days.
  - <24 hours: 50 events;
  - 1 day: 23 events;
  - 2-7 days: 35 events;
  - 8-14 days: 14 events;
  - 15-30 days: 9 events;
  - 31-180 days: 12 events;
  - >180 days: 3 events.
- Relevant event outcome: resolved/resolving (95), resolved with sequelae (1), not resolved (73), unknown (495).

Analysis by age group

- PM: Paediatric (3 [1 Child, 2 Adolescent]), Adults (285), Elderly (109), Unknown (267).
  - There was no meaningful difference between different age groups.

Literature

Review of the literature did not identify any significant new information regarding the use of BNT162b2 and unexpected therapeutic effects.

Conclusion

In most of the cases (when specified), the unexpected therapeutic effect included improvement in the following: pain, breathing, allergies, skin conditions (including warts and psoriasis), autoimmune/inflammatory diseases (e.g., arthritis, multiple sclerosis, ulcerative colitis), migraine/headache, infections (e.g., herpes and other viral infections, fungal

infections), neoplasia (remission/regression of various cancers), movement/mobility, energy, hair growth/loss, menstruation, and general health/well-being (e.g., "felt better"). In the majority of the cases, the subject experienced the unexpected therapeutic effect following the first dose (when recorded).

No significant new information was identified with regards the use of BNT162b2 and unexpected therapeutic effects.

16.3.5. Update on Special Patient Populations

Any new data identified during the reporting interval for use of BNT162b2 by special patient populations is analysed below.

16.3.5.1. Use in Elderly Patients

Of the 56,799 cases, 4 post-marketing cases were determined to be non-contributory and were not included in the discussion for the following reason:

- upon review, these 4 cases reported the PT Maternal exposure during pregnancy (4) in subjects greater than 65 years of age (in these 4 cases, it is most likely that the subjects' age was erroneously reported).

Clinical Trial Data

- Number of cases: 211 (BNT162b2 [180], blinded therapy [26], placebo [4], BNT162b2S01 [1]; (31.6 % of 668 cases in the total CT dataset), compared to 233 cases (32.3%) retrieved in the PSUR #2.
- Country of incidence: US (162), Argentina (26), Germany (9), Brazil (7), China (4), Israel (2), Dominican Republic (1).
- Subjects' gender: female (88), male (123).
- Subjects' age in years (n = 211), range: 65 – 87, mean: 73.1, median: 73.
- Medical history (n = 193): the most frequently (≥20 occurrences) reported medical conditions included the following HLGTs: Vascular hypertensive disorders (114), Lipid metabolism disorders (73), Joint disorders (63), Glucose metabolism disorders (incl diabetes mellitus) (51), Gastrointestinal motility and defaecation conditions (42), Appetite and general nutritional disorders (35), Allergic conditions (31), Depressed mood disorders and disturbances (28), Cardiac arrhythmias (26), Sleep disorders and disturbances (25), Coronary artery disorders, Thyroid gland disorders (24 each), Gastrointestinal therapeutic procedures (23), Bronchial disorders (excl neoplasms) (22), Anxiety disorders and symptoms, Prostatic disorders (excl infections and inflammations) (20 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 4 cases): amiodarone, amlodipine, atenolol, diltiazem, etoricoxib, furosemide, hydrochlorothiazide/triamterene, hydroxyzine, losartan, metformin, sulfamethoxazole/trimethoprim, tamsulosin (1 each).
- Number of events: 274.

- Most frequently (≥5 occurrences) reported PTs: Atrial fibrillation (11), Cerebrovascular accident, Osteoarthritis, Prostate cancer (9 each), Condition aggravated[165] (8), Acute kidney injury, Acute respiratory failure, Dyspnoea (5 each).
- Of the 274 events, the only related event was for BNT162b2 and coded to the PT Dehydration (1).
- Time to event onset: n = 247, range: from <24 hours to 504 days, median: 125 days.
  - <24 hours: 2 events;
  - 1 day: 3 events;
  - 2-7 days: no events;
  - 8-14 days: 3 events;
  - 15-30 days: 12 events;
  - 31-180 days: 179 events (20 of which had a fatal outcome);
  - >180 days: 48 events. (6 of which had a fatal outcome).
- Event outcome: fatal (27), resolved/resolving (185), resolved with sequelae (19), not resolved (43).

Post-Authorisation Data

- Number of cases: 56,584 (11.1% of 507,683 cases in the total PM dataset), compared to 87,982 cases (13.4%) retrieved in the PSUR #2.
- MC cases (28,690), NMC cases (27,894).
- Country of incidence (>500 occurrences): Germany (10,884), Austria (9277), France (7504), US (3203), UK (3119), Japan (2225), Netherlands (2140), Sweden (2091), Australia (1747), Italy (1596), Spain (1187), Malaysia (1025), Denmark (992), Belgium (984), Poland (804), Philippines (689), Slovenia (614), Norway (602), Finland (592), Canada (556); the remaining 4753 cases were distributed among 62 countries.
- Subjects' gender: female (33,348), male (22,179), unknown (1057).
- Subjects' age in years (n = 54,943), range: 65 – 120, mean: 73.9, median: 72.
- Medical history (n = 18,647): the most frequently (≥1000 occurrences) reported medical conditions included the following HLGTs: Vascular hypertensive disorders (6169), Glucose metabolism disorders (incl diabetes mellitus) (2721), Allergic conditions (2365), Bronchial disorders (excl neoplasms) (1789), Cardiac arrhythmias (1712), Lipid metabolism disorders (1683), Joint disorders (1580), Thyroid gland disorders (1409), Therapeutic procedures and supportive care NEC (1392), Lifestyle issues (1342), Coronary artery disorders (1226), Central nervous system vascular disorders (1081).

[165] The aggravated condition were: Adenocarcinoma pancreas, Back pain, Benign prostatic hyperplasia, Cardiac failure congestive, End stage renal disease, Gastrooesophageal reflux disease, Hypertrophic cardiomyopathy, Muscle rupture, and Supraventricular tachycardia (1 each).

- COVID-19 Medical history (n = 1489): COVID-19 (1150), Suspected COVID-19 (282), COVID-19 pneumonia (39), Exposure to SARS-CoV-2 (16), SARS-CoV-2 test positive (13), Asymptomatic COVID-19, Post-acute COVID-19 syndrome (8 each), Coronavirus infection (7), Occupational exposure to SARS-CoV-2 (1).
- Co-suspects (n = 1956 cases) the most frequently (≥10 occurrences) reported co-suspect medications included: COVID-19 vaccine (422), COVID-19 vaccine mRNA (mRNA 1273) (274), COVID-19 vaccine NRVV AD (258), influenza vaccine (154), adalimumab (151), influenza vaccine INACT SAG 4V (100), influenza vaccine INACT SPLIT 4V (58), pneumococcal polysaccharide vaccine 23-valent (32), apixaban (29), upadacitinib (24), influenza vaccine INACT SAG 3V (23), JNJ 78436735 (18), prednisone (17), mepolizumab (16), rivaroxaban (13), rituximab (12), casirivimab, imdevimab, influenza vaccine INACT SPLIT 3V (11 each), atorvastatin, ibrutinib, levothyroxine, risankizumab (10 each).
- Number of events: 167,970; the most frequently (>1000 occurrences) reported events were coded to the PTs were: COVID-19 (8394), Inappropriate schedule of product administration (5063), Fatigue (4864), Headache (4712), Drug ineffective (4627), Vaccination failure (4515), Pyrexia (4261), Off label use (3847), Myalgia (3431), Immunisation (3355), Arthralgia (3137), Interchange of vaccine products (2920), Dizziness (2815), Vaccination site pain (2798), Pain in extremity (2796), Malaise (2468), Dyspnoea (2455), Nausea (2155), Chills (2012), Asthenia (1966), Herpes zoster (1771), Pain (1706), Rash (1677), Pruritus (1194), Vomiting (1178), Diarrhoea (1175), Paraesthesia (1096), Chest pain (1089).
- Event seriousness:[42] serious (73,170), non-serious (94,882).
- Time to event onset (n = 119,721),[166] range: from <24 hours to 492 days, median: 2 days.
  - <24 hours: 37,098 events (733 of which had a fatal outcome);
  - 1 day: 19,235 events (440 of which had a fatal outcome);
  - 2-7 days: 21,444 events (674 of which had a fatal outcome);
  - 8-14 days: 9213 events (373 of which had a fatal outcome);
  - 15-30 days: 8260 events (395 of which had a fatal outcome);
  - 31-180 days: 21,670 events (991 of which had a fatal outcome);
  - >180 days: 2801 events (168 of which had a fatal outcome).
- Event outcome:[78] fatal (5367), resolved/resolving (52,311), resolved with sequelae (4003), not resolved (39,949), unknown (66,774).

[166] This number does not include 48,801 events for which administration and/or event onset dates were not provided or were incomplete; or events without a meaningful time to onset value as per reported information. Please note, multiple episodes of the same PT event were reported with different latencies within some cases hence the sum of latencies exceeds the total number of PT events.

Analysis by presence of comorbidities

- Number of elderly subjects with reported comorbidities: 10,304 (18.2% of the 56,584 cases in the total elderly dataset).

- Of the cases that reported medical histories, the percentage of cases reporting an AE with a fatal outcome is higher in subjects with comorbid conditions (72.1%) when compared to the percentage of cases involving an AE with a fatal outcome in subjects without comorbidities (27.9%).

- Upon review of the most frequently (≥200 occurrences) reported AEs in cases that recorded medical histories, the PT COVID-19 Pneumonia was the only event that had a significant proportional reporting ratio of >3:1 in the elderly population with comorbidities compared to the elderly population without comorbidities.

Literature

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

Conclusion

No significant differences in the reporting proportion of the most frequently reported AEs were noted between the elderly dataset and the non-elderly dataset, apart from the PTs indicative of lack of therapeutic effect, for which the reporting proportion is higher in the elderly population: COVID-19 (14.8% versus 8.8%) and Vaccination failure (7.9% versus 4.4%). This is expected due to age-related decline in immunity that results not only in increased susceptibility to infection, but also reduces the prophylactic efficacy of vaccinations[167].

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". Cases indicative of exposure to the vaccine during the mother's pregnancy or through breastfeeding were excluded.

- Of the 31,930 cases, 3 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

[167] Lord JM. The effect of aging of the immune system on vaccination responses. Hum Vaccin Immunother. 2013 Jun 1; 9(6): 1364–1367. Published online 2013 Apr 12. doi: 10.4161/hv.24696.

- in 2 cases the data reported (e.g., height, weight, clinical data) were not consistent with paediatric subjects;

- in 1 case, exposure to the vaccine occurred during the mother's pregnancy.

16.3.5.2.1. Paediatric Subjects <5 Years of Age[168]

Clinical Trial Data

- Number of cases: 62 (blinded therapy [43], BNT162b2 [18] and pre-randomisation[169] [1]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (9.3% of 668 cases, the total CT dataset), compared to 25 cases (3.5%) retrieved in the PSUR #2.
- Country of incidence of relevant cases: US (28), Poland (21), Brazil, Spain (4 each), Finland, and Germany (2 each).
- Subjects' gender: female (28), male (33).
- Subjects' age in years (n = 61), range: 0.58 – 4, mean: 2.4, median: 2.0.
- Medical history (n = 22): the most frequently reported (≥2): Chronic kidney disease, Renal transplant (4 each), Febrile convulsion, Gastrostomy, Urethral valves (3 each), Asthma Food allergy, Autism spectrum disorder, Biopsy kidney, Cough, Cystostomy, Eating disorder, Eczema, Heart transplant, Hypospadias, Orchidectomy, Orchidopexy, Pulmonary valves stenosis, Pyrexia, Reflux nephropathy, Respiratory disorder, Stem cell transplant, and Suture removal (2 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 1): Paracetamol (1).
- PTs reported in the relevant cases (n=67): PTs reported in more than 1 case: Febrile convulsion, Gastroenteritis, Gastroenteritis rotavirus (4 each), Bronchiolitis (3), Adenovirus infection, Anaphylactic reaction, Appendicitis, Dehydration, Humerus fracture, Lower respiratory tract infection, Metapneumovirus infection, Pneumonia, and Pyrexia (2 each).

All events were assessed as unrelated to BNT162b2 or blinded therapy.

- Time to event onset: n =66,[170] range: from 1 day to 298 days, median: 59 days.
  - 1 day: 2 events;

---

[168] The paediatric vaccine for individuals aged between 6 months and 4 years was approved first in the US on 17 June 2022; the administration of BNT162b2 in subjects < 5 years was unapproved during the reporting period of this PSUR.

[169] This case is not included in the analysis below.

[170] This number does not include 1 event for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- 2-7 days: 10 events;
- 8-14 days: 1 event;
- 15-30 days: 11 events;
- 31-298 days: 42 events.

- Duration of relevant events (n = 60 out of 61 occurrences with outcome of resolved/resolved with sequelae) [171], range: >1 day to 36 days, median: 4 days.

  - <24 hours: 6 events
  - 1 day: 10 events;
  - 2-7 days: 23 events;
  - 8-14 days: 16 events;
  - 15-36 days: 5 events.

- Event outcome: resolved/resolving (63), not resolved (3), resolved with sequelae (1).

Post-Authorisation Data

- Number of cases: 275[172] (0.5% of 507,683 cases, the total PM dataset), compared to 83 cases (0.01%) retrieved in the PSUR #2.
- MC cases (78), NMC cases (197).
- Country of incidence (≥1%): Germany (179), Iraq (28), US (18), Australia (15), France (9), Austria (7), Ireland, UK (4 each), Italy, and Philippines (3 each).
- Subjects' gender: female (119), male (142) and unknown (14).
- Subjects' age in years (n = 267), range: 0.01-4.50, mean: 2.4, median: 2.33.
- Medical history (n = 12): the reported medical conditions included Breast feeding, Cardiac disorder (2 each), Abnormal behaviour, Arrhythmia, Asthma, Atelectasis, Cardiomyopathy, Cytogenetic abnormality, Feeding disorder, Food allergy, Gait inability, Gastrooesophageal reflux disease, Hypersensitivity, Hypertension, Infection, Lactose intolerance, Lung disorder, Mite allergy, Pyelonephritis, Ventricular septal defect, and Weight gain poor (1 each).
- COVID-19 Medical history (n = 1): Suspected COVID-19 (1).
- Co-suspect vaccines (n = 2): influenza vaccine and influenza vaccine inactive split 3V (1 each).

[171] This number does not include 1 event for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[172] Cross-referenced with Section 16.3.4.6 *Off-Label Use*, since the administration of BNT162b2 was approved in subjects <5 years of age (≥ 6 months of age) only in the US since 17 June 2022.

- Number of events: 856. The most frequently reported PTs (>5): Product administered to patient of inappropriate age (202), Off label use (133), Vaccination site pain (88), Product use issue (75), Pyrexia (43), Fatigue (37), Headache, Rash, Vaccination site erythema (14 each), Arthralgia, Vaccination error (10 each), Diarrhoea (8), Malaise, Urticaria (7 each), Chest pain, Chills, Nausea, and Vomiting (6 each).
- Event seriousness[173]: (58), non-serious (799).
- Time to event onset: n =735[174], range: from <1 day to 28 days, median: <24 hours.
  - <1 day: 558 events;
  - 1 day: 87 events;
  - 2-7 days: 62 events;
  - 8-14 days: 8 events;
  - 15-28 days: 20 events.
- Duration of relevant events (n = 212 out of 268 occurrences with outcome of resolved/resolved with sequelae) [175], range: from <1 day to 62 days, median: 1 day.
  - <1 day: 53 events;
  - 1 day: 81 events;
  - 2-7 days: 72 events;
  - 8-14 days: 3 events;
  - 14-62 days: 3 events.
- Event outcome[78]: resolved/resolving (279), not resolved (87), resolved with sequelae (12), unknown (480).

16.3.5.2.2. Paediatric Subjects ≥5 Years and ≤ 11 Years of Age[176]

Clinical Trial Data

- Number of cases: 25 (blinded therapy [6] and BNT162b2 [19]), originated from Protocols C4591007, C4591007-OPENLABEL and C4591024 (3.7% of 668 cases, the total CT dataset), compared to 18 cases (2.5%) retrieved in the PSUR #2.
- Country of incidence: US (13), Brazil (6), Germany (3), Poland (2), and Spain (1).

---

[173] One case reported different seriousness for the same event.

[174] This number does not include 124 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[175] This number does not include 56 events with outcome resolved or resolved with sequalae for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[176] The administration of BNT162b2 in ≥ 5 years to ≤ 11 years population was approved by EMA on 25 November 2021.

- Subjects' gender: female (8), male (17).
- Subjects' age in years (n = 25), range: 5 – 11, mean: 7.7, median: 7.0
- Medical history (n = 21): the most frequently (≥2) reported medical conditions included Renal transplant (4), Dermatomyositis (3), Anal stenosis, Anoplasty, Asthma, Attention deficit hyperactivity disorder, Colostomy, Constipation, Currarino syndrome, Epilepsy, Factor V Leiden mutation, Inguinal hernia repair, Juvenile idiopathic arthritis, Malnutrition, Spinal cord operation, Spondylolisthesis, and Tumour necrosis factor receptor-associated periodic syndrome (2 each).
- COVID-19 Medical history (n = 1): COVID-19 (1).
- Co-suspect vaccines/medications: none.
- PTs (34): Gastroenteritis (3), Dermatomyositis, Intestinal obstruction, Pyrexia (2 each), Appendicitis, Asthma, Colitis, Condition aggravated, Constipation, Depression, Depression suicidal, Device related infection, Diarrhoea, Drug therapy, Febrile convulsion, Hypertension, Hyponatraemia, Influenza, Kidney transplant rejection, Large intestine benign neoplasm, Mental status changes, Myalgia, Myositis, Rhinovirus infection, Seizure, Small intestinal obstruction, Syncope, Tibia fracture, and Vomiting (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset: n = 34, range: 1 day to 282 days, median: 83 days.
  - 1 day: 1 event;
  - 2-14 days: 0 events;
  - 15-30 days: 3 events;
  - 31-90 days: 15 events;
  - 91-282 days: 15 events.
- Duration of relevant events (n = 30 out of 34 occurrences with outcome of resolved/resolved with sequelae) [177], range: 1 day to 10 days, median 3 days.
  - 1 day: 9 events;
  - 2-7 days: 18 events;
  - 8-10 days: 3 events.
- Event outcome: resolved/resolving (31), resolved with sequelae (3).

Post-Authorisation Data

- Number of cases: 9605 (1.9% of 507,683 cases, the total PM dataset), compared to 1227 cases (0.2%) retrieved in the PSUR #2.

[177] This number does not include 4 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- MC cases (6573), NMC cases (3032).
- Country of incidence (≥2%): US (2503), Australia (1428), Philippines (1264), Germany (1177), Japan (859), Italy (409), and Spain (386).
- Subjects' gender: female (3925), male (4133) and unknown (1547).
- Subjects' age in years (n = 8372), range: 5 – 11,25, mean: 8.4, median: 9.0.
- Medical history (n = 846): the most frequently (≥10) reported medical conditions included Asthma (158), Food allergy (62), Seasonal allergy (59), Attention deficit hyperactivity disorder (41), Hypersensitivity (34), Autism spectrum disorder, Epilepsy (30 each), Drug hypersensitivity (28), Rhinitis allergic (27), Eczema (26), Dermatitis atopic (23), Mite allergy (21), Allergy to animal (19), Constipation, Type 1 diabetes mellitus, Urticaria (15 each), Bronchospasm, Headache, Seizure (12 each), Obesity (11), Migraine (10).
- COVID-19 Medical history (n = 136): COVID-19 (121), Suspected COVID-19 (10), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (2 each), and Post-acute COVID-19 syndrome (1).
- Co-suspects (n = 44): the most frequently (>1) reported co-suspect vaccines/medications included influenza vaccine (8), adalimumab, COVID-19 vaccine (7 each), measles vaccine live (Enders-Edmonston)/ mumps vaccine live (Jeryl Lynn)/ rubella vaccine live (Wistar RA 27/3), varicella zoster vaccine live (Oka/Merck) (3 each), diphtheria vaccine toxoid/ pertussis vaccine acellular/tetanus vaccine toxoid, influenza vaccine inact split 3V, meningococcal vaccine B RFHBP, NADA, NHBA OMV, and sodium chloride (2 each).
- Number of events: 22,457.
- Event seriousness:[42] (3735), non-serious (18,725).
- Most frequently reported PTs (>3% of cases): Product administered to patient of inappropriate age (1338), Pyrexia (1289), Vaccination site pain (1213), Poor quality product administered (1063), Headache (976), Product administration error (753), Vomiting (733), Rash (556), Overdose (516), Product preparation error (429), Fatigue (425), Nausea (410), Abdominal pain (371), Dizziness (366), Chest pain (331), COVID-19 (309), Pain in extremity (293), and Underdose (290).
- Time to event onset (n = 16,236)[178], range: from <1 day to 385 days, median: <1 day.
  - <1 day: 8574 events;
  - 1 day: 3414 events;
  - 2 days: 1102 events;
  - 3-7 days: 1594 events;
  - 8-14 days: 593 events;
  - 15-30 days: 551 events;

[178] This number does not include 6242 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- 31-60 days: 273 events;
- 61-385 days: 135 events.

- Duration of relevant events (n = 3787 out of 7329 occurrences with outcome of resolved/resolved with sequelae) [179], range: from <1 day to 109 days, median 1 day.

  - <1 day: 1258 events;
  - 1 day: 955 events;
  - 2-7 days: 1263 events;
  - 8-14 days: 171 events;
  - 15-109 days: 140 events.

- Relevant event outcome: resolved/resolving (9811), resolved with sequelae (73), not resolved (3274), fatal (58), unknown (9257).
- Fatal cases: 20

  - Age: 5 years (1), 6 years (3), 7 years (4), 8 years (2), 9 years (1), 10 years (2), 11 years (5), unknown (2).
  - MC cases (17), NMC cases (3).
  - Gender: females (9), males (9), unknown (2).
  - Country: Philippines (6), Australia (4), Germany, Spain (3 each), Albania, Japan, Portugal, UK (1 each).
  - Fatal PTs (58): the most frequently (≥ 2) reported AEs included Dyspnoea (4), Cardiac arrest, Cardio-respiratory arrest, Pyrexia (3 each), Abdominal pain, Cough, COVID-19, Death, Headache, Myocarditis, Seizure, and Vomiting (2 each).
  - Medical history (n = 7): Autoimmune thyroiditis, Asphyxiating thoracic dystrophy, Brain malformation, Bronchitis, Bronchospasm, Cerebral palsy, Cognitive disorder, COVID-19, Dependence on respirator, Developmental delay, Dysphagia, Epilepsy, Gastrostomy, Hypoxic-ischaemic encephalopathy, Immunodeficiency, Intellectual disability, Joint dislocation, Kidney transplant rejection, Motor dysfunction, Myoclonic epilepsy, Neonatal asphyxia, Obstructive sleep apnoea syndrome, Pneumonia, Renal impairment, Renal transplant, Rhinitis allergic, Scoliosis, Seizure, Severe myoclonic epilepsy of infancy, Type 1 diabetes mellitus, and Varicella zoster virus infection (1 each).

    The 20 fatal cases are summarised below:

  - In 2 cases (1 MC and 1 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The limited information provided prevented any meaningful assessment.

[179] This number does not include 3542 events with outcome resolved or resolved with sequalae for which time to event onset partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- In 2 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

  - MC case; age: 11 years; gender: male; fatal PT: Acute respiratory failure, occurred 2 days after the 1st dose of BNT162b2; medical history: brain malformation, bronchitis, cognitive disorder, dysphagia, gastrostomy, joint dislocation, myoclonic epilepsy, obstructive sleep apnoea syndrome, pneumonia, scoliosis; autopsy: not performed.

  - MC case; age: 6 years; gender: female; fatal PTs: Renal impairment, Epilepsy, Apnoea, Varicella zoster virus infection, Seizure, Sudden death, Product administered to patient of inappropriate age, death occurred 7 days after the 1st dose of BNT162b2; medical history: developmental delay, epilepsy, immunodeficiency, renal impairment, seizure, severe myoclonic epilepsy of infancy, varicella zoster virus infection; autopsy: unknown if performed.

- In one case, the reporter concluded that the death "had nothing to do" with the administration of BNT162b2 and was due to natural causes:

  - MC case; age: 6 years; gender: male; fatal PTs: Myocarditis, Cardio-respiratory arrest, COVID-19, occurred 7 days after the 1st dose of BNT162b2; medical history: rhinitis allergic, autoimmune thyroiditis), type I diabetes mellitus); autopsy: performed, results are pending.

  - In the remaining 15 cases (13 MC and 2 NMC) reporting the following fatal PTs Dyspnoea (4), Cardiac arrest, Pyrexia (3 each), Abdominal pain, Cardio-respiratory arrest, Cough, Headache, Vomiting (2 each), Abdominal pain upper, Acute respiratory distress syndrome, Adverse event following immunisation, Arteriovenous malformation, Blood pressure decreased, Blood pressure immeasurable, Bradycardia, Cardiac failure acute, Cerebral haemorrhage, COVID-19, Cyanosis, Diarrhoea, Drug ineffective, haematemesis, Heart rate decreased, Immunisation, Influenza like illness, Multisystem inflammatory syndrome, Myocarditis, Nasopharyngitis, Nausea, Off label use, Pulmonary embolism, Respiratory failure, and Seizure (1 each), no confounding factors have been identified. In most cases (9) the limited information available does not allow a medically meaningful assessment; in the remaining cases (6) a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results provided evidence of a causal relationship.

16.3.5.2.3. Paediatric Subjects ≥12 Years of Age[180]

Clinical Trial Data

- Number of cases: 15 (BNT162b2 [14] and blinded therapy [1]) originated from Protocol C4591001 (2), C4591001-OPEN LABEL (10), C4591007-OPEN LABEL (1), C4591024 (1), and C4591031-OPEN LABEL (1) (2.2% of 668 cases, the total CT dataset), compared to 24 cases (3.3%) retrieved in the PSUR #2.
- Country of incidence: US (14) and Germany (1).
- Subjects' gender: female (7) and male (8).
- Subjects' age in years (n = 15), range: 12 – 17, mean: 14.6, median: 15.0.
- Medical history (n = 11): the most frequently (≥2) reported medical conditions included Anxiety (6), Seasonal allergy (4), Depression (3), Attention deficit hyperactivity disorder, Insomnia, and Rhinitis allergic (2 each).
- COVID-19 Medical history: None.
- Co-suspects (n = 1): aripiprazole, duloxetine (1 each).
- PTs (17): Suicidal ideation, Suicide attempt, Toxic shock syndrome (2 each), Addison's disease, Appendicitis, Constipation, Depression, Fractured skull depressed, Herpes zoster, Major depression, Mucocutaneous rash, Pectus excavatum, Subdural haematoma, and Syncope (1 each).
- All events were assessed as unrelated to BNT162b2 or blinded therapy.
- Time to event onset (n = 17), range: from 6 days to 284 days, median: 96 days.
  - 6 days: 1 event;
  - 7-30 days: no events;
  - 31-90 days: 7 events;
    91-284 days: 9 events.
- Duration of relevant events (n = 8 out of 8 occurrences with outcome of resolved/resolved with sequelae), range: from <1 day to 86 days, median 3.5 days.
  - <1 day: 1 event;
  - 1 day: 1 event;
  - 2-7 days: 5 events;
  - 86 days: 1 event.
- Event outcome: resolved/resolving (14), not resolved (2), resolved with sequelae (1).

[180] The administration of BNT162b2 in this subpopulation was approved by EMA on 31 May 2021.

Post-Authorisation Data

- Number of cases: 21,945 (4.3% of 507,683 cases, the total PM dataset), compared to 18,451 cases (2.8%) retrieved in the PSUR #2.
- MC cases (13,478), NMC cases (8467).
- Country of incidence (>2%): Germany (3333), Philippines (3026), Australia (2220), UK (1656), Austria (1645), Malaysia (1189), Taiwan, Province of China (1186), France (1061), US (1025), Italy (628), Netherlands (582), Japan (484), and Mexico (454).
- Subjects' gender: female (11,656), male (9813) and unknown (476).
- Subjects' age in years (n = 21,661), range: 12 - 17, mean: 14.7, median: 15.0.
- Medical history (n = 2837): the most frequently (>1%) reported medical conditions included Asthma (286), Hypersensitivity (210), Seasonal allergy (194), Food allergy (108), Attention deficit hyperactivity disorder (90), Drug hypersensitivity (74), Mite allergy (73), Epilepsy (62), Depression (51), Autism spectrum disorder (48), Allergy to animal (45), Anxiety, Migraine (40 each), Immunodeficiency, Obesity (39 each), Rhinitis allergic (37), Eczema (35), Non-tobacco user (34), Acne (33), Headache (31), and Dermatitis atopic (29).
- COVID-19 Medical history (n = 675): COVID-19 (457), Suspected COVID-19 (226), Asymptomatic COVID-19 (6), SARS-CoV-2 test positive (5), Post-acute COVID-19 syndrome (4), Coronavirus infection (3), and Exposure to SARS-CoV-2 (2).
- Co-suspects (n = 148): the most frequently (>2%) reported co-suspect vaccines/medications included COVID-19 vaccine (33), adalimumab (18), influenza vaccine (15), COVID-19 vaccine MRNA (MRNA 1273) (13), influenza vaccine inact split 4V, mestranol/norethisterone (8 each), HPV vaccine VLP RL1 9V (yeast) (7), HPV vaccine VLP RL1 2V (baculovirus) (5), HPV vaccine, infliximab (4 each), ibuprofen, and semaglutide (3 each).
- Number of events: 61,071.
- Relevant event seriousness:[42] serious (19,558), non-serious (41,530).
- Most frequently reported PTs (>2%): Headache (3495), Pyrexia (3395), Dizziness (2376), Chest pain (1956), Fatigue (1919), Vaccination site pain (1804), Nausea (1669), COVID-19 (1600), and Dyspnoea (1267).
- Time to event onset: (n = 45,162)[181], range: from <1 day to 476 days, median: 1 day.
  - <1 day: 18,167 events;
  - 1 day: 10,527 events;
  - 2-7 days: 7412 events;
  - 8-14 days: 2061 events;

[181] This number does not include 16,067 events for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- 15-30 days: 2003 events;
- 31-181 days: 4802 events;
- 182-476 days: 190 events.

- Duration of relevant events (n = 9201 out of 19,141 occurrences with outcome of resolved/resolved with sequelae) [182], range: <1 day to 329 days, median 1 day.
  - <1 day: 2914 events;
  - 1 day: 1832 events;
  - 2-7 days: 3247 events;
  - 8-14 days: 530 events;
  - 15-30 days: 317 events;
  - 31-181 days: 341 events;
  - 182-329 days: 20 events.

- Relevant event outcome: fatal (169), resolved/resolving (28,719), not resolved (12,336), resolved with sequelae (332), unknown (19,645).

Fatal cases (62)

- Age: 12 years (12), 13 years (13), 14 years (5), 15 years (6), 16 years (11), 17 years (9), unknown (6).
- MC cases (45), NMC cases (17).
- Gender: females (28), males (32), unknown (2).
- Country (≥ 2): Philippines (19), US (8), Malaysia, Poland (6 each), Germany (4), Austria, Brazil, Japan, Taiwan (Province of China), UK (2 each).
- Fatal PTs (169): the most frequently (≥ 3) reported AEs included Death (16), Dyspnoea (8), Pyrexia (7), Cardiac arrest (6), Myocarditis (5), Cardiac failure, Headache (4 each), Asthenia, Seizure, Shock, and Vomiting (3 each).
- Medical history (n = 13): Attention deficit hyperactivity disorder, Obesity (2 each), Abdominal pain, Agitation, Amenorrhoea, Asthma, Bedridden, Chest pain, Colloid brain cyst, Cough, Cystic fibrosis, Cyst removal, Decreased appetite, Depression, Diabetes insipidus, Dizziness, Drug hypersensitivity, Dyspnoea, Dyssomnia, Exercise adequate, Fatigue, Feeling abnormal, Fracture, Headache, Hereditary cerebral degeneration, Hypertension, Kawasaki's disease, Lipoedema, Liver disorder, Lymphoedema, Lymphostasis, Oral contraception, Osteogenesis imperfecta, Ovarian enlargement, Palpitations, Physical deconditioning, Pulmonary embolism, Pulmonary veno-occlusive disease, Seasonal allergy, Somatic symptom disorder, Substance abuser, Substance use, and Weight decreased (1 each).

[182] This number does not include 9940 events with outcome resolved or resolved with sequalae for which partial administration or event onset dates were reported or events without a meaningful time to onset value as per reported information.

The 62 fatal cases are summarised below:

- In 15 cases (9 MC and 6 NMC) reporting only Death as the fatal AE, neither cause of death nor information on autopsy was provided. The time to fatal event onset is available in 4 cases: 5 days, 7 days, 49 days, and 144 days (1 each). The limited information provided prevented any meaningful assessment.

- In 2 cases, the subjects did not die due to illness, but due to unfortunate accidents:

  - MC case; age: 17 years; gender: male; fatal PT: Fall, occurred 24 days after the vaccination; autopsy: unknown if performed.

  - MC case; age: 16 years; gender: male; fatal PT: Road traffic accident, occurred approximately 110 days after the 2nd dose of BNT162b2; autopsy: unknown if performed.

- In 6 cases, the underlying medical conditions could have predisposed to the occurrence of the fatal AEs:

  - MC case; age: 16 years; gender: female; fatal PT: Dyspnoea, occurred 3 days after the 1st dose of BNT162b2; medical history: bronchial asthma; autopsy: unknown if performed.

  - NMC case; age: 16 years; gender: female; fatal PTs: Dyspnoea (developed 6 days after the 1st dose of BNT162b2), Brain injury, Cardiac failure acute, Hypoxia, Cardiac failure (all developed 38 days after the 1st dose of BNT162b2), Sudden death, Pulmonary veno-occlusive disease, Pulmonary arterial hypertension (all developed 41 days after the 1st dose of BNT162b2), Brain oedema, Sudden cardiac death, Brain injury, Acute kidney injury, Pneumonitis, Epistaxis, Acute respiratory failure, Cardiac failure congestive (all unknown onset date); medical history: pulmonary veno-occlusive disease, amenorrhoea, cough, dyspnoea, fatigue, fracture, hypertension, lipoedema, lymphoedema, lymphostasis, osteogenesis imperfecta, ovarian enlargement; autopsy: not performed.

  - NMC case; age: 16 years; gender: female; fatal PTs: Pulmonary embolism, Cardiac arrest (all developed 2 days after the 3rd dose of BNT162b2); medical history: obesity, oral contraception, pulmonary embolism; autopsy: performed, results not provided.

  - MC case; age: 17 years; gender: male; fatal PTs Pneumococcal sepsis, Cardiac failure, Pneumonia pneumococcal (all occurred 92 days after the 2nd dose of BNT162b2); medical history: [redacted]agitation, attention deficit hyperactivity disorder, depression, dyssomnia, regular exercise. Autopsy results: the subject died after consumption of [redacted] from the beginning pneumonia and the influx of germs into the bloodstream as a result of cardiovascular failure. The [redacted] concentration determined in the blood and brain does not justify in itself a fatal intoxication in view of a long-

term intake with a tolerance effect but may have favoured the onset of death due to a substance-typical respiratory and circulatory depressive effect, also increased in combination with the effect of [redacted]. The findings obtained during the autopsy and the results of the chemical-toxicological examination can be reconciled with a protracted occurrence of death.

- MC case; age: 13 years; gender: female subject; fatal PTs: Malaise (developed 1 day after the 1st dose of BNT162b2, Lot number FJ1763), Palpitations, Chest pain (all occurred 5 days after the 1st dose of BNT162b2, Lot number FJ1763), Loss of consciousness, Pulseless electrical activity, Cardiac arrest (all occurred 64 days after the 1st dose of BNT162b2, Lot number FJ1763); medical history: Kawasaki's disease, palpitations, weight decreased, decreased appetite, feeling abnormal. Autopsy results showed that there was no possibility of myocarditis and angina pectoris, and there was no thrombus. Since symptoms such as episodes of palpitations had appeared before the vaccination, it was assessed that the vaccination was possibly related to the death, but the possibility of being the exacerbation factor could not be ruled out.

- MC case; age: 13 years; gender: male; fatal PTs Brain death, Condition aggravated (all occurred within 1 month of unknown dose number of BNT162b2, Lot number FG9428); medical history: colloid brain cyst; autopsy: unknown if performed.

– In the remaining 39 cases (30 MC and 9 NMC) reporting the following fatal PTs Pyrexia (7), Dyspnoea (6), Myocarditis (5), Cardiac arrest, Headache (4 each), Asthenia, Seizure, Shock, Vomiting (3 each), Cardiac failure, Cardiac infection, Cardiomegaly, Depressed level of consciousness, Diarrhoea, Dizziness, Hypoaesthesia, Multiple organ dysfunction syndrome, Myocardial infarction, Myocardial injury, Pneumonia, Toxic cardiomyopathy (2 each), Abdominal pain upper, Adverse event following immunisation, Agranulocytosis, Aneurysm ruptured, Anisocoria, Anuria, Atrioventricular block, B-cell type acute leukaemia, Brain injury, Cardiogenic shock, Cerebral haemorrhage, Chest discomfort, Chills,, Coma, Compartment syndrome, Completed suicide, Contusion, Cough, COVID-19, Death, Dehydration, Diabetic ketoacidosis, Enterovirus infection, Extensive swelling of vaccinated limb, Fallot's tetralogy, Gait inability, Haematemesis, Haemorrhage intracranial, Head banging, Hypertension, Immunisation, Loss of consciousness, Malaise, Meningitis meningococcal, Metabolic acidosis, Multi-organ disorder, Musculoskeletal stiffness, Nausea, Nervous system disorder, Off label use, Pain in extremity, Peripheral swelling, Pleural effusion, Pruritus, Pulse absent, Pulseless electrical activity, Rash, Rash pruritic, Renal failure, Respiratory arrest, Rhinovirus infection, Sepsis, Septic shock, Slow response to stimuli, Stress cardiomyopathy, Sudden death, Thrombosis, Unresponsive to stimuli, Vaccination failure, Vaccination site pain, and Ventricular tachycardia (1 each), no confounding factors have been identified. In 19 cases the limited information available does not allow a medically meaningful assessment, in the remaining 20 cases a causality between the vaccination and the occurrence of the fatalities cannot be ruled out, based on the temporal relationship, although no laboratory data or autopsy results provided evidence of a causal relationship.

Analysis by presence of comorbidities

- Number of subjects with reported comorbidities: 960 (3.0% of 31,927 cases, the total paediatric dataset).

- Upon review, there was no significant differences in the occurrence of the most frequently reported AEs in the subjects with comorbidities compared to the population without underlying diseases was identified.

Analysis of confounders and risk factors

- Among the 31,927 cases involving paediatric subjects, 4423 included one or more confounders that prevented a clear causality assessment: co-suspect and/or multiple concomitant drugs (1286 cases), underlying medical history and/or comorbidities (4037 cases) or predisposing factors (e.g., asthma, cardiac disorders, depression, diabetes, menstrual disorders, renal disease, respiratory disorders, seizures/epilepsy) (503 cases).

Literature

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

Conclusion

No relevant differences in the occurrence of the most frequently reported events, case seriousness and case outcomes were identified among the 3 paediatric age groups presented above. Additionally, no significant differences in the reporting proportion of the most frequently reported AEs were noted between the paediatric dataset and the non-paediatric dataset, apart from the PTs Vomiting (6.1% versus 2.0%) and Product administered to patient of inappropriate age (5.8% versus 1.3%).

No new significant safety information was identified based on the review of the cases reported in the overall paediatric population. The most frequently reported AEs[183] 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.

16.3.5.3. Use in Pregnant/Lactating Women[184]

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.

[183] For the CT cases, the analysis was focused on AEs assessed as related to BNT162b2 or blinded therapy.

[184] Exposure *in utero* cases are included.

In the final AR of the 4th SMSR (01 March 2021 – 31 March 2021), the MAH was requested to present data according to annex 3 of the "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)".

These requests are addressed within the section, providing a cumulative review of pregnancy and lactation cases originating from clinical trials along with incremental pregnancy and incremental lactation cases from CTs, and incremental pregnancy and lactation cases from PM and presenting the data according to annex 3 of the "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

Search criteria - "Selects Pregnancy cases from the data set. Pregnancy cases are identified as cases where:

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

Clinical Trial Data

Cumulative review (Pregnancy Cases)

- Number of pregnancy cases: 697 (28.7% of the total 2426 cases from the CT dataset). These 697 cases represent 669 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 28 pregnancies). Cases originated from clinical studies C4591001 (155), C4591015 (120), C4591001-OPENLABEL (91), C4591031-OPENLABEL (7), C4591031 (6), C4591020 (2), C4591017 (1), BNT162-01-OPENLABEL (1), BNT162-17 (2), and C4591006 (328) and study treatment was reported as BNT162B2 (466), blinded therapy (188), placebo (42) and BNT162C2 (1).
- Country of incidence: Japan (322), US (200), Brazil (49), Argentina (46), South Africa (44), Spain (19), UK (12), Germany (3) and Turkey (2).
- Of the 597 mother cases, 431 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The frequently reported pregnancy related events (>1 occurrence) were coded to the PTs Maternal exposure before pregnancy (272), Maternal exposure during pregnancy (139), Maternal exposure timing unspecified (12), Exposure during pregnancy (6), Drug exposure before pregnancy (2).

- One hundred sixty-six (166) mother cases, 139 serious and 27 non-serious, reported additional clinical events, which occurred in the vaccinated mothers.
    - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (57), Abortion spontaneous (46), Maternal exposure before pregnancy (30), Pre-eclampsia (7), Cephalo-pelvic disproportion (6), Abortion missed, Foetal death, Postpartum haemorrhage, Premature separation of placenta (4 each), Abortion threatened, Delivery, Ectopic pregnancy, Gestational hypertension, Premature delivery, Premature labour (3 each), Abortion incomplete, Hyperemesis gravidarum, Maternal exposure via partner during pregnancy, Miscarriage of partner, Uterine disorder (2 each).
    - Other reported clinical events were coded to the PTs COVID-19 (9), Anaemia (2), Abdominal wall haematoma, Cholelithiasis, Dehydration, Drug eruption, Endometritis, Lower respiratory tract infection, Osteoarthritis, Pneumonia, Pruritis, Pyelonephritis, Urinary tract infection, Urinary tract procedural complication, Vascular pseudoaneurysm, Venous thrombosis limb (1 each).
    - Of the 58 cases reporting spontaneous abortion or abortion related events, in 25 cases the mother had a medical history of spontaneous abortion, alcohol/tobacco use during pregnancy, ectopic pregnancy, obesity, diabetes mellitus, uterine disorder, depression or anembryonic gestation, which might have contributed to the event and in 33 cases there was limited information regarding the mother's obstetric history, which precluded meaningful assessment.
    - Of the 19 cases reporting elective termination, in 10 cases, the mother had a medical history of spontaneous abortion, induced abortion, alcohol/tobacco use and in the remaining 9 cases there was limited information regarding mother's obstetric history which precluded meaningful assessment.
    - In 3 cases reporting foetal death/stillbirth the mother had a medical history of amniotic cavity infection, HIV infection and/or spontaneous abortion, which might have contributed to the event.
    - In 3 cases reporting ectopic pregnancy, in 1 case, the mother had a medical history of tobacco use which might have contributed to the event, and in the remaining 2 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful assessment.
- Hundred (100) baby/foetal cases, 98 serious and 2 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: Thirty-one (31) of these cases reported 39 congenital anomalies that were coded to the PTs Atrial septal defect (4), Ankyloglossia congenital, Hypoxic-ischaemic encephalopathy, Neonatal hypotension, Trisomy 21 (2 each), Cleft lip, Coma neonatal, Congenital rubella syndrome, Congenital skin dimples, Congenital skin disorder, Craniosynostosis, DiGeorge's syndrome, Gnathoschisis, Microcephaly, Neonatal pneumothorax, Neonatal intestinal perforation, Neonatal seizure, Nervous system disorder, Newborn persistent pulmonary hypertension, Osteochondrodysplasia, Patent ductus arteriosus,

Polydactyly, Pyelonephritis acute, Renal failure neonatal, Renal tubular necrosis, Sepsis neonatal, Sex chromosome abnormality, Syndactyly, Thanatophoric dwarfism, Thrombocytopenia neonatal, Ventricular septal defect, Vesicoureteric reflux (1 each). Of these 31 cases, information regarding trimester of exposure was available in 17 cases. Of these 17 cases, in 12 cases foetus was exposed during the 3rd trimester, in 4 cases foetus was exposed during the 2nd trimester, and in 1 case exposure occurred during the 1st trimester. Of these 31 cases, in 5 cases the mother of the baby was on multiple concomitant medications, alcohol use, advanced age of the mother (i.e., 43 years) and/or had a medical history of *in vitro* fertilization which increases the chance of gene mutation. In the remaining 26 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

- Pregnancy outcome: Still birth without foetal defect: During the reporting period there was 1 case reporting stillbirth without foetal defect. The event reported in this case was coded to the PT Neonatal respiratory distress syndrome. The information regarding trimester of exposure was unknown. In this case the mother of the baby had underlying medical history of amniotic cavity infection, which might have led to the development of the reported event.
- Pregnancy outcome: Live birth without congenital anomaly: Sixty-eight (68) cases reported live birth babies without congenital anomaly. Of these 68 cases, information regarding trimester of exposure was available in 40 cases. Of these 40 cases, in 23 cases, foetus was exposed during the 3rd trimester, in 14 cases foetus was exposed during the 2nd trimester, and in 3 cases exposure occurred during the 1st trimester. The frequently reported events (>1 occurrence) in these 68 cases were coded to PTs Jaundice neonatal (11), Foetal distress syndrome (8), Premature baby (6), Neonatal pneumonia, Neonatal respiratory distress, Bronchiolitis, Neonatal respiratory distress syndrome, Hyperbilirubinaemia neonatal (3 each), Foetal hypokinesia, Neonatal tachypnoea, Dehydration, Gastroenteritis, Patent ductus arteriosus, Anaemia neonatal, Sepsis neonatal, Hypoglycaemia neonatal, Meconium aspiration syndrome (2 each). In all these 68 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

Of the 697 cases, 658 cases provided pregnancy outcomes, which are provided in Table 67 below. Pregnancy outcome was pending or not provided in the remaining 39 cases.

Table 67. Clinical Trial Data: Pregnancy Outcome - Cumulative Reporting Interval

Pregnancy outcome	Prospective cases 564 (80.9% of pregnancy cases)					Retrospective cases 94 (13.5% 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	1	0	0	0
Spontaneous abortion	0	20	0	0	23	0	5	1	0	6
Elective termination (foetal defects)	0	0	0	0	0	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	14	0	0	2	0	2	0	0	1
Stillbirth with foetal defects	0	0	1	0	0	0	0	0	0	0
Stillbirth without foetal defects	0	0	0	0	2	0	0	0	0	1
Live birth with congenital anomaly	0	1	24	0	13	0	3	0	0	4
Live birth without congenital anomaly	0	97	99	0	267	0	11	16	0	43
Total	***0***	***132***	***124***	***0***	***308***	***0***	***22***	***17***	***0***	***55***

Cumulative review (Lactation cases)

- Number of lactation cases: 141 (5.8% of the total 2426 cases from the CT dataset). All these 141 cases were non-serious. Of these 141 cases, 140 cases reported only exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical events. In the remaining case the clinical event was coded to the PT Respiratory syncytial virus infection. In this case there was limited information regarding mother's obstetric history, which precluded meaningful causality assessment.

Incremental review (CT cases)

- Number of pregnancy cases: 41 (6.1% of the total 668 cases from the CT dataset). These 41 cases represent 37 unique pregnancies (2 cases [a mother case and a foetus/baby case] for 4 pregnancies). Cases originated from clinical studies C4591015 (24), C4591001-OPENLABEL (10), C4591001, C4591031-OPENLABEL (3 each), C4591031 (1) and study treatment was reported as blinded therapy (27), and BNT162b2 (14).
- Country of incidence: South Africa (15), Brazil (11), US (6), Argentina (5), Spain (3), UK (1).
- Twenty-three (23) serious maternal cases reported additional clinical events, which occurred in the vaccinated pregnant females.
    - The frequently reported pregnancy related events (>1 occurrence) reported in these cases were coded to the PTs Maternal exposure during pregnancy (8), Abortion spontaneous (7), Cephalo-pelvic disproportion (3), Abortion missed, Maternal exposure before pregnancy (2 each).
    - Other reported clinical events were coded to the PTs Abdominal wall haematoma, COVID-19, Pneumonia, Urinary tract infection (1 each).
    - Of the 11 cases reporting spontaneous abortion or abortion related events, in 4 cases, the mother had a medical history of spontaneous abortion or had underlying condition of obesity, which might have contributed to the event and in 7 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.
- Eighteen (18) serious baby/foetal cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: Five (5) of these cases reported 5 congenital anomalies that coded to the PTs Congenital rubella syndrome, DiGeorge's syndrome, Pyelonephritis, Syndactyly, Trisomy 21 (1 each). Of these 5 cases, information regarding trimester of exposure was available in 2 cases and in these 2 cases foetus was exposed during the 2nd trimester in 1 case and the 3rd trimester in the remaining case. Of these 5 cases, in 1 case reporting Trisomy 21, the age of the mother was 43 years and advanced maternal age is a risk factor for Trisomy 21. In the remaining 4 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.
    - Pregnancy outcome: Live birth without congenital anomaly: Thirteen (13) cases reported live birth babies without congenital anomaly. Of these 13 cases, information

regarding trimester of exposure was available in 7 cases. Of these 7 cases, in 5 cases, foetus was exposed during the 2nd trimester and in 2 cases foetus was exposed during the 1st and the 3rd trimester each. The frequently reported clinical events (>1 occurrence) in these 13 cases were coded to the PTs Foetal distress syndrome (3), Meconium aspiration syndrome, Gastroenteritis, Jaundice neonatal (2 each). In all these 13 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

Of the 41 cases, 38 cases provided pregnancy outcomes, which are provided in Table 68 below. Pregnancy outcome was pending or not provided in the remaining 3 cases.

Table 68. Clinical Trial Data: Pregnancy Outcome during the Reporting Interval

Pregnancy outcome	Prospective cases 38 (92.7% of pregnancy cases)					Retrospective cases 0 (0% of pregnancy cases)				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	0
Spontaneous abortion	0	2	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	0	0	0	0	0	0	0	0
Live birth with congenital anomaly	0	0	2	0	3	0	0	0	0	0
Live birth without congenital anomaly	0	1	15	0	7	0	0	0	0	0
Total	***0***	***3***	***17***	***0***	***18***	***0***	***0***	***0***	***0***	***0***

Post-Authorisation Data

Incremental review (Pregnancy cases)

- Number of pregnancy cases: 3642 (0.7% of 507,683 cases, the total PM dataset), compared to 5239 cases (0.8%) retrieved in the PSUR #2. These 3642 cases represent 3419 unique pregnancies (2 cases [a mother case and a foetus/baby case] or 3 cases [a mother case and 2 foetus/baby cases for twins] were created for 223 pregnancies).
- Country of incidence (>100 occurrences): Germany (837), UK (475), Netherlands (461), Philippines (309), France (302), Sweden (162), Australia (110).
- Of the 3320 mother cases, 535 cases reported exposure to vaccine in utero without the occurrence of any clinical event. The pregnancy exposure events were coded to the PTs Maternal exposure during pregnancy (355), Maternal exposure timing unspecified (116), Maternal exposure before pregnancy (52), Exposure during pregnancy (7), Drug exposure before pregnancy (4), Foetal exposure during pregnancy (1).
- There were 2785 mother cases of which 1479 were serious and 1306 were non-serious reporting additional clinical events, which occurred in the vaccinated pregnant females. Additional pregnancy related events reported in these cases (≥50 occurrences) were coded to the PTs Abortion spontaneous (566), Labour pain (151), Vaginal haemorrhage (78), Heavy menstrual bleeding (50)[185]. Other frequently reported (>100 occurrences) clinical events were coded to the PTs Headache (410), Vaccination site pain (407), Fatigue (363), Pyrexia (206), Malaise (194), Myalgia (192), Nausea (178), Chills (156), Pain in extremity (135). The distribution of clinical events that were not pregnancy related (>100 occurrences) was similar in the pregnant mothers when compared with non-pregnant women of childbearing age.
- Three hundred twenty-two (322) baby/foetal cases, 283 serious and 39 non-serious. Cases are classified according to pregnancy outcome.
    - Pregnancy outcome: Live birth with congenital anomaly: Thirty-nine (39) of these cases reported 72 congenital anomalies that were coded to the PTs Foetal malformation (4), Atrial septal defect, Congenital anomaly, Ventricular septal defect (3 each), Congenital cystic lung, Congenital hydronephrosis, Congenital skin dimples, Exomphalos, Foetal cardiac disorder, Foetal chromosome abnormality, Foetal growth restriction, Kidney malformation, Pulmonary valve stenosis congenital (2 each), Anal atresia, Ankyloglossia congenital, Arnold-Chiari malformation, Cleft lip, Cleft palate, Cloacal exstrophy, Congenital amputation, Congenital foot malformation, Congenital haematological disorder, Congenital hand malformation, Congenital heart valve disorder, Congenital musculoskeletal disorder, Congenital musculoskeletal disorder of limbs, Congenital musculoskeletal disorder of spine, Congenital oral malformation, Cryptorchism, Double outlet right ventricle, Dysmorphism, Enlarged foetal cisterna magna, Fallot's tetralogy, Foetal arrhythmia, Foetal growth abnormality, Growth retardation, Heart disease congenital, Heart valve incompetence, Hepatic cytolysis,

[185] Few additional events reported were coded to PTs Pre-eclampsia (20), Amniotic cavity infection (1).

Hypospadias, Meningomyelocele, Neonatal deafness, Neonatal infection, Polydactyly, Pulmonary artery stenosis congenital, Pulmonary sequestration, Renal aplasia, Renal disorder, Renal dysplasia, Renal failure, Renal fusion anomaly, Renal hypertrophy, Spina bifida, VACTERL syndrome (1 each). Of these 39 cases, information regarding trimester of exposure was available in 19 cases. Of these 19 cases, in 13 cases foetus was exposed during the 1st trimester, in 4 cases foetus was exposed during the 2nd trimester, and in 2 case exposure occurred during the 3rd trimester. Of these 39 cases, in 2 cases the mother of the baby was an asymptomatic gene carrier or had familial risk factors. In the remaining 37 cases, there was limited information regarding mother's obstetric history, which precluded meaningful causality assessment.

- Pregnancy outcome: Spontaneous abortion: Thirty-seven (37) cases reported spontaneous abortion. Of these 37 cases, information regarding trimester of exposure was provided in 17 cases. Of these 17 cases, in 15 cases, foetus was exposed during the 1st trimester, in 2 cases foetus was exposed during the 2nd and the 3rd trimester each. The most frequently reported events (>1 occurrence) in these 37 cases other than exposure related events were coded to PTs Foetal growth restriction (18), Congenital anomaly (8), Foetal heart rate abnormal (3), Cytogenetic abnormality, Foetal vascular malperfusion (2 each). Of these 37 cases, in 4 cases mother had underlying medical history (i.e., spontaneous abortion, induced abortion and/or tobacco abuse), which might have contributed to the reported events. In the remaining 33 cases, there was limited information regarding obstetric history or co-suspect medications of the mother, which precluded meaningful causality assessment.
- Pregnancy outcome: Elective termination: Twenty-three (23) cases reported elective termination of pregnancy. Of these 23 cases, 22 cases reported elective termination due to foetal defects and 1 case reported elective termination without foetal defects or unknown. Of these 23 cases, information regarding trimester of exposure was provided in 8 cases. Of these 8 cases, in 7 cases foetus was exposed during the 1st trimester, in 1 case, foetus was exposed during the 2nd trimester. The most frequently reported events (>1 occurrence) in these 23 cases other than exposure related events were coded to the PTs Heart disease congenital (4), Foetal malformation (3), Congenital central nervous system anomaly, Abortion induced (2 each). Of these 23 cases, in 5 cases mother had underlying medical history (i.e., spontaneous abortion, and/or gestational diabetes), which might have contributed to the reasons for elective termination of foetus. In the remaining 18 cases, there was limited information regarding obstetric history or co-suspect medications of mother, which precluded meaningful assessment.
- Pregnancy outcome: Stillbirth: Twenty-one (21) cases reported foetal death/neonatal death. Of these 21 cases, 15 cases reported stillbirth with foetal defects and remaining 6 cases reported stillbirth without foetal defect. Of these 21 cases, information regarding trimester of exposure was provided in 6 cases. Of these 6 cases, in 3 cases foetus was exposed during the 1st trimester, in the remaining 3 cases, foetus was exposed during the 2nd trimester. The most frequently reported events (>1 occurrence) in these 21 cases other than exposure related events were coded to the

PTs Premature baby (7), Foetal hypokinesia (5), Foetal death, Foetal heart rate abnormal (4 each), Foetal growth restriction (3). Of these 21 cases, in 5 cases the mother had underlying medical history (i.e., spontaneous abortion, and/or obesity), which might have contributed to the reported event. In the remaining 16 cases, there was limited information regarding obstetric history or co-suspect medications of mother, which precluded meaningful causality assessment.

- Pregnancy outcome: Live birth without congenital anomaly: Two hundred two (202) cases reported live birth babies without congenital anomaly. Of these 202 cases, information regarding trimester of exposure was available in 58 cases. Of these 58 cases, in 26 cases, foetus was exposed during the 3rd trimester, in 20 cases foetus was exposed during the 2nd trimester, and in 12 cases exposure occurred during the 1st trimester. The frequently reported events (≥5 occurrence) in these 202 cases other than exposure related events were coded to PTs Premature baby (74), Foetal growth restriction (22), Foetal hypokinesia (12), Jaundice neonatal (9), Foetal heart rate abnormal, Congenital anomaly, Foetal distress syndrome (7 each), Immunisation (6), Neonatal respiratory distress syndrome, Breech presentation (5 each). Of these 202 cases, in 1 case reporting cerebral thrombosis and cerebral haemorrhage foetal the baby was delivered using vacuum extractor, which might have led to development of reported event. In the remaining 201 cases, there was limited information regarding the mother's obstetric history, which precluded meaningful causality assessment.

Of the 3642 cases, 1898 cases provided pregnancy outcomes, which are provided in Table 69 below. Pregnancy outcome was pending or not provided in the remaining 1744 cases.

Table 69. Post-Authorisation Data: Pregnancy Outcome during the Reporting Interval[a]

Pregnancy outcome	Prospective cases 1032 (28.3% of pregnancy cases)					Retrospective cases 866 (23.8% 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	1	0	0	0	0	1	0	0	1
Spontaneous abortion	0	14	1	0	25	0	149	13	0	281
Elective termination (foetal defects)	0	0	0	0	2	0	10	3	0	24
Elective termination (no foetal defects or unknown)	0	0	0	0	1	0	4	2	0	2
Stillbirth with foetal defects	0	0	0	0	0	0	4	7	0	15
Stillbirth without foetal defects	0	1	2	0	2	0	3	10	0	13
Live birth with congenital anomaly	0	14	2	0	10	0	5	10	0	11
Live birth without congenital anomaly	0	100	240	0	617	0	29	89	0	180
Total	***0***	***130***	***245***	***0***	***657***	***0***	***205***	***134***	***0***	***527***

a. 19 December 2021 through 18 June 2022.

Incremental review (Lactation cases)

- Number of lactation cases: 3771 (0.7% of 507,683 cases, the total PM dataset), compared to 2670 cases (0.4%) retrieved in the PSUR #2.
  - Breast feeding baby cases: 3119, of which:
  - Two thousand six hundred eighty-nine (2689) cases reported exposure to vaccine during breastfeeding (PT Breast feeding, Exposure via breast milk and Maternal exposure during breast feeding) without the occurrence of any clinical events.
  - Four hundred thirty (430) cases, 66 serious and 364 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 (76), Diarrhoea (56), Crying (38), Poor feeding infant (34), Immunisation (33), Fatigue (26), Somnolence (25), Infant irritability (22), Rash (21), Vomiting (19), Irritability (16), Abdominal pain, Malaise (15 each), Rhinorrhoea (14), Restlessness (13), Body temperature increased (12), Faeces discoloured, Insomnia (11 each).
- Breast feeding mother cases: 652, of which:
  - Sixty-nine (69) mother cases who were breast feeding their baby while taking the vaccine were reported without the occurrence of any clinical events.
  - Five hundred eighty-three (583) cases, 75 serious and 508 non-serious, reported clinical events in mothers who were breast feeding; the frequently reported clinical events (>20 occurrences) were coded to the PTs Headache (93), Fatigue (86), Pyrexia (68), Vaccination site pain (60), Myalgia (54), Malaise (46), Immunisation (44), Chills (42), Pain in extremity (34), Nausea (31), Lymphadenopathy (30), Arthralgia (24), Dizziness, Influenza like illness, Interchange of vaccine products, Pain (21 each).

Literature

During the reporting period an article including new significant information regarding the use of BNT162b2 in pregnant/lactating women was identified. Please refer to Section 11 *Literature* for details.

Conclusion

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

16.3.5.4. 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.

Clinical Trial Data

- Number of cases: 259 (blinded therapy [36], BNT162b2, BNT162b2S01 [219, 1] and placebo [3]) (38.3% of 668 cases, the total CT dataset), compared to 286 cases (39.7%) retrieved in the PSUR #2.
- Country of incidence: US (188), Argentina (29), Germany (19), Brazil (13), China, South Africa, Spain (2 each), Dominican Republic, India, Israel, and Turkey (1 each).
- Subjects' gender: female (112), and male (147).
- Subjects' age (n = 259), range: 10 months – 87 years, mean: 57 years, median: 63 years.
- Medical history (n = 259): the most frequently (> 20 occurrences) reported medical conditions included Hypertension (117), Type 2 diabetes mellitus (71), Hypothyroidism (43), Obesity (42), Gastrooesophageal reflux disease, Osteoarthritis (41 each), Seasonal allergy (39), Anxiety, Depression (36 each), Hypercholesterolaemia (34), Asthma (33), Hyperlipidaemia (32), Insomnia (24), and Chronic obstructive pulmonary disease (23).
- COVID-19 Medical history: COVID-19 (3), COVID-19 immunisation (2)
- Co-suspects (n = 7 cases): amlodipine, metformin (2 each), amiodarone, aripiprazole, atenolol, diltiazem, duloxetine, furosemide, hydrochlorothiazide/triamterene, hydroxyzine, losartan, metoprolol, semaglutide, tamsulosin, and warfarin (1 each).
- Number of relevant events: 341.
- Most frequently reported relevant PTs (≥4): Condition aggravated (13), Atrial fibrillation, Cerebrovascular accident, Pneumonia (8 each), Acute kidney injury, Dyspnoea,

Gastroenteritis, Osteoarthritis (5 each), Acute respiratory failure, Chest pain, Coronary artery disease, Pancreatic carcinoma, and Pulmonary embolism (4 each).

- Event outcome: fatal (18), resolved/resolving (251), resolved with sequelae (16), not resolved (55), and unknown (1).

Post-Authorisation Data

- Number of cases: 38,528 (7.6 % of 507,683 cases, the total PM dataset), compared to 66,813 cases (10.2%) retrieved in the PSUR #2.
- MC cases (13,011), NMC cases (25,517).
- Country of incidence (≥ 212 occurrences): France (7282), Germany (6733), UK (5557), US (3168), Sweden (1948), Italy (1560), Japan (1146), Austria (1066), Norway (1030), Netherlands (969), Spain (946), Denmark (670), Canada (603), Finland (543), Belgium (539), Czech Republic (460), Greece (393), Ireland (366), Estonia (275), Iraq, Portugal (272), Switzerland (260), Taiwan (246), Croatia (239), and Brazil (212).
- Subjects' gender: female (26,999), male (10,838) and unknown (691).
- Subjects' age in years (n = 36,076), range: 3 – 107 years, mean: 52.8 years, median: 53.0 years.
- Medical history (n = 38,528): the most frequently (≥1100 occurrences) reported medical conditions included: Asthma (7896), Hypertension (6254), Hypothyroidism (3732), Diabetes mellitus (3121), Seasonal allergy (2067), Type 2 diabetes mellitus (2001), Drug hypersensitivity (1971), Autoimmune thyroiditis (1752), Immunodeficiency (1647), Hypersensitivity (1633), Rheumatoid arthritis (1408), Food allergy (1239), Chronic obstructive pulmonary disease (1201), and Breast cancer (1121).
- COVID-19 Medical history: the most frequently (≥13 occurrences) reported COVID-19 (1922), Suspected COVID-19 (695), Post-acute COVID-19 syndrome (71), COVID-19 pneumonia (60), SARS-CoV-2 test (25), Asymptomatic COVID-19 (16), Coronavirus infection (13).
- Co-suspects (n = 976 cases): the most frequently (>10 occurrences) reported co-suspect vaccines/medications included COVID-19 vaccine (471), COVID-19 Moderna vaccine (326), COVID-19 AstraZeneca vaccine (263), Influenza vaccine (107), adalimumab (90), ocrelizumab (62), quadrivalent influenza vaccine (39), COVID-19 JNJ vaccine (34), levothyroxine, mycophenolate (20 each), apixaban, methotrexate (19 each), casirivimab, rituximab, tacrolimus (13 each), ibrutinib (12), and pneumococcal vaccine (11).
- Number of events: 38,528.
- Event seriousness: serious (82, 607), non-serious (78,808).
- Most frequently reported relevant PTs (>10%): Headache (5518), Fatigue (5412), Pyrexia (3989), Off label use (3951).
- Reported event outcome: fatal (1081), resolved/resolving (19,899), resolved with sequelae (1540), not resolved (15,122), unknown (20,250).

Conclusion

The reporting proportion of not resolved cases (38.8%), cases resolved with sequelae (3.1%), and fatal cases (2.8%) in subjects with comorbidities is slightly higher than the reporting proportion observed in the overall population (31.6% for outcome of not resolved, 1.8% for outcome of resolved with sequelae, and 0.6% for fatal outcome). This is expected, considering the presence of the underlying diseases and/or poor intercurrent conditions.

No safety signals have emerged that would be considered specific to this population. Evaluation of cases 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); Malignancy related therapeutic and diagnostic procedures (SMQ Narrow); Malignant or unspecified tumours (SMQ Narrow); HLGT: Immunodeficiency syndromes (Primary Path); HLT: Retroviral infections (Primary Path); PTs: Allogenic bone marrow transplantation therapy; Allogenic stem cell transplantation; Autologous bone marrow transplantation therapy; Autologous haematopoietic stem cell transplant; Bone marrow transplant; Cord blood transplant therapy; Heart transplant; Liver transplant; Lung transplant; Pancreas islet cell transplant; Renal transplant; Small intestine transplant; Stem cell transplant.

Clinical Trial Data

- Number of cases: 110 (BNT162b2 [90], blinded therapy [18], and BNT162B2S01, placebo [1 each]) (16.5% of 668 cases, the total CT dataset), compared to 110 cases (15.3%) retrieved in the PSUR #2.
- Country of incidence: US (78), Argentina (15), Germany (9), Brazil (5), South Africa (2), and Dominican Republic (1).
- Subjects' gender: female (58), and male (52).
- Subjects' age in years (n = 110), range: 2–85 years, mean: 56.4 years, median: 64.5 years.
- Medical history (n = 110): the most frequently (≥5 occurrences) reported relevant medical conditions included Hysterectomy (14), Cholecystectomy (10), Basal cell carcinoma (8), Colon cancer, HIV infection, Prostate cancer, Tonsillectomy (7 each), Benign prostatic hyperplasia, Breast cancer, Thyroidectomy (6 each), Breast conserving surgery (5).
- COVID-19 Medical history: COVID-19 (1).
- Co-suspects (n = 21): The reported co-suspect agents included amiodarone, amlodipine, diltiazem, hydroxyzine, losartan, metoprolol, tamsulosin (1 each).
- Number of events: 156.

- Most frequently reported clinical PTs (>2%): Condition aggravated (8), Atrial fibrillation (4), Cerebrovascular accident (4), Gastroenteritis (4), Osteoarthritis (4), Pneumonia (4), Acute kidney injury (3), Peritonitis (3), Pyrexia (3).
- BNT162b2 related events coded to the PT: None of the events were assessed as related to BNT162b2 and/or blinded therapy by the Sponsor or investigator.
- Time to event onset: (n = 145 events),[186] range: from <24 hours to ≤540 days, median: 113 days.
  - <24 hours: 1 event;
  - 1 day: 2 events;
  - 2-7 days: 1 event;
  - 8-14 days: 1 event;
  - 15-30 days: 10 events;
  - 31-181 days: 113 events;
  - ≥182 days: 17 events.
- Duration of event: (n = 95 of 102 events with outcome of resolved/resolved with sequelae), range: <24 hours to 122 days, median: 9 days
  - < 24 hours: 3 events;
  - 1 day: 9 events;
  - 2-7 days: 31 events;
  - 8-14 days: 13 events;
  - 15-30 days: 17 events;
  - 31-122 days: 22 events.
- Reported event outcome: fatal (10), resolved/resolving (119), resolved with sequelae (6), not resolved (20), and unknown (1).

Post-Authorisation Data

- Number of cases: 8815 (1.7% of 507,683 cases, the total PM dataset), compared to 14,657 cases (2.2%) retrieved in the PSUR #2.
- MC cases (3474), NMC cases (5341).
- Country of incidence: France (2200), UK (2070), Germany (1085), US (726), Italy (314), Sweden (312), Japan (212), Austria (192), Spain (158), Netherlands (156), Denmark

[186] This number does not include 2 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

(131), Belgium (119), Canada (116), Norway (112); the remaining 912 cases were distributed among 53 countries.

- Subjects' gender: female (5967), male (2628) and unknown (220).
- Subjects' age in years (n = 8073), range: 5 – 100, mean: 58.2, median: 60.0.
- Medical history (n = 8815). The most frequently (≥200 occurrences) reported relevant medical conditions included Immunodeficiency (1647), Breast cancer (1121), Thyroidectomy (566), Neoplasm malignant (466), Hysterectomy (407), Chemotherapy (377), Prostate cancer (330), Radiotherapy (272), Chronic lymphocytic leukaemia (243), Neoplasm (239).
- COVID-19 Medical history (n = 689): COVID-19 (418), Suspected COVID-19 (249), COVID-19 pneumonia (22), Post-acute COVID-19 syndrome (15), SARS-CoV-2 test positive (4), Asymptomatic COVID-19, Exposure to SARS-CoV-2 (3 each), Coronavirus infection, Coronavirus test positive (2 each).
- Co-suspects (n = 608): The most frequently (≥10 cases) reported co-suspect vaccines/medications included COVID-19 vaccine NRVV AD (113), COVID-19 vaccine (101), COVID-19 vaccine MRNA (95), Influenza vaccine (23), prednisone (20), mycophenolate mofetil (18), adalimumab (16), casirivimab/ imdevimab, tacrolimus (13 each), Influenza vaccine inact split 4V, JNJ 78436735, nivolumab, ocrelizumab (10 each).
- Number of events: 38,399.
- Event seriousness[42]: serious (21,926), non-serious (16,507).
- Most frequently reported clinical PTs (≥3%): Immunisation[43] (1248), Interchange of vaccine products (1223), Headache (1096), Fatigue (1030), Pyrexia (827), COVID-19 (740), Pain in extremity (686), Dyspnoea (605), Arthralgia (589), Myalgia (535), Dizziness (516), Pain (510), Nausea (488), Asthenia (478), Lymphadenopathy (456), Malaise (420), Chills (401), Chest pain (389), Vaccination site pain (374), Palpitations (326), Paraesthesia (313), Vomiting (292), Condition aggravated (254), Tachycardia (246).
- Time to event onset (n = 23,969 events),[187] range: from <24 hours to ≤540 days, median: 1 day.
  - <24 hours: 8672 events;
  - 1 day: 4064 events;
  - 2-7 days: 4107 events;
  - 8-14 days: 1711 events;
  - 15-30 days: 1749 events;

[187] This number does not include 103 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

- 31-181 days: 2935 events.
- ≥182 days: 731 events.

- Duration of event (n = 3184 of 6987 events with outcome of resolved/resolved with sequelae) [188], range: <24 hours to 200 days, median: 3 days.
  - <24 hours: 396 events;
  - 1 day: 569 events;
  - 2-7 days: 1129 events;
  - 8-14 days: 383 events;
  - 15-30 days: 284 events;
  - 31-181 days: 401 events.
  - ≥182 days: 22 events.
- Event outcome[78]: fatal (1006), resolved/resolving (10,930), resolved with sequelae (821), not resolved (8997), unknown (16,862).

Analysis by age group

- CT Data: Paediatric (16), Adults (39), and Elderly (55).
  - A meaningful comparison between the different age groups is not possible due to the low number of cases.
- PM Data: Paediatric (96), Adults (4828), Elderly (3198) and Unknown (693).
  - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the events coded to the PTs Headache, Lymphadenopathy, Palpitations and Tachycardia.
  - A higher reporting proportion of events coded to the PT Headache was observed in the adult population (16.6% [752 cases] in adults vs 8.2% [251 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Lymphadenopathy was observed in the adult population (7.4% [334 cases] in adults vs 2.6% [78 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Palpitations was observed in the adult population (5.2% [234 cases] in adults vs 2.1% [64 cases] in elderly) compared to the elderly population. A higher reporting proportion of events coded to the PT Tachycardia was observed in the adult population (4.1% [185 cases] in adults vs 1.5% [46 cases] in elderly) compared to the elderly population.

[188] This number does not include 66 events for which partial administration and/or events without a meaningful time to onset/cessation value as per reported information.

- No comparison was made to the paediatric population considering the 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 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.

Clinical Trial Data

- Number of cases: 102 (BNT162b2 [86], blinded therapy [14], and placebo [2]) (15.3% of 668 cases, the total CT dataset), compared to 101 cases (14.0%) retrieved in the PSUR #2.
- Of the 102 cases, the most frequently reported PTs (≥3%) included: Condition aggravated (6, 5.9%) and Atrial fibrillation (4, 3.9%).
- Event outcome: fatal (10), resolved/resolving (93), resolved with sequelae (3), and not resolved (24).
- In 6 cases (reporting 10 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Acute myeloid leukaemia, Adenocarcinoma pancreas, Cardiac failure congestive, Cardio-respiratory arrest, Completed suicide, Condition aggravated, COVID-19, Death, Pneumonia, and Sudden cardiac death (1 each). Of note, limited information regarding the cause of death was provided in 1 case (PT Death). Half (3 of 6 cases) of the fatal cases involved elderly subjects. The medical history reported included hypothyroidism, (3), colitis ulcerative, diabetes mellitus, narcolepsy, neuropathy peripheral (1 each).
- BNT162b2 related events coded to the PT Dehydration (1). Time to onset of event is 1 day and the event outcome is reported as resolved. None of the events were related to blinded therapy.

Post-Authorisation Data

- Number of cases: 21,000 (4.1% of 507,683, the total PM dataset), compared to 35,514 cases (5.4%) retrieved in the PSUR #2.
- MC cases (6424), NMC cases (14,576).
- Of the 21,000 cases, the most frequently reported clinical PTs (>3%) included: Fatigue (3103, 14.8%), Headache (3082, 14.7%), Pyrexia (2207, 10.5%), Immunization (1750, 8.3%), Pain in extremity (1680, 8.0%), Arthralgia (1675, 8.0%), Interchange of vaccine products (1568, 7.5%), Myalgia (1535, 7.3%), Dizziness (1478, 7.0%), Dyspnoea (1385,

6.6%), Vaccination site pain (1360, 6.5%), COVID-19 (1344, 6.4%), Nausea (1308, 6.2%), Pain (1226, 5.8%), Malaise (1180, 5.6%), Chills (1174, 5.6%), Asthenia (1083, 5.2%), Chest pain (932, 4.4%), Paraesthesia (929, 4.4%), Lymphadenopathy (896, 4.3%), Condition aggravated (813, 3.9%), Palpitations (794, 3.8%), Tachycardia (646, 3.1%), and Hypoaesthesia (640, 3.1%).

- Event seriousness: serious (39,651), non-serious (43,889).
- Event outcome: fatal (1295), resolved/resolving (27,683), resolved with sequelae (2277), not resolved (25,409), unknown (27,206).
- In 409 cases (reporting 1295 relevant events with a fatal outcome), the reported causes of death (≥ 20 occurrences) were coded to the PTs Death (63), Immunisation (44), Cardiac arrest, COVID-19 (36 each), COVID-19 pneumonia (33), Dyspnoea (23), Cardio-respiratory arrest (22), Interchange of vaccine products, Sudden death (21 each), and Cardiac failure (20). Of note, in 84 cases, limited information regarding the cause of death was provided (PTs Death and Sudden death). Immunisation and Interchange of vaccine products are discussed in the Section 16.3.4.6 *Off Label Use.* Most (326 of 409 cases) of the fatal cases involved elderly subjects. The most frequently (≥10 occurrences) reported medical history included diabetes mellitus (169), hypothyroidism (53), rheumatoid arthritis (36), type 1 diabetes mellitus (20), pulmonary fibrosis (15), rheumatic disorder (13), colitis ulcerative, psoriasis, and thyroid disorder (10 each).
- The most frequently reported clinical events observed in subjects with autoimmune or inflammatory disorders were consistent with those observed in the overall population.

Exacerbation or Flare-up

A focused analysis on exacerbation or flare of autoimmune or inflammatory disorders was conducted using PTs of interest (i.e., condition aggravated, disease progression), rather than all events.

- Of the 1117 cases that reported PTs indicative of exacerbation or flare, 345 cases were determined to be non-contributory and were not included in the discussion for the following reasons:
  - The events referred to an exacerbation/progression of an underlying condition that was not an autoimmune or inflammatory disorder (e.g., pain, arrhythmia, elevated blood pressure/hypertension, deep vein thrombosis, renal disease, migraine, fatigue/tiredness).

Therefore, 772 cases are included in the analysis below.

Clinical Trial Data

- Number of cases: 1 case (BNT162b2) (0.1% of 668 cases, the total CT dataset), compared to 1 (0.1%) retrieved in the PSUR #2.

- In a case from [redacted], a 6-year-old male subject experienced a worsening of the dermatomyositis (PTs Condition aggravated and Dermatomyositis) approximately 87 days after receiving the second dose of the BNT162b2. During the hospitalisation, he was treated with methylprednisolone, albendazole, hydroxychloroquine, vitamin D, without any complications and recovered from the reported events. The events were considered unrelated to BNT162b2.

Post-Authorisation Data

- Number of cases: 771 (0.2% of 507,683 cases, the total PM dataset), compared to 750 (0.1%) retrieved in the PSUR #2.
- MC cases (274), NMC cases (497).
- Country of incidence: France (185), Germany (126), UK (118), Netherlands (54), Italy (51), US (35), Austria (23); the remaining 179 cases were distributed among 34 countries.
- Subjects' gender: female (584), male (180) and unknown (7).
- Subjects' age in years (n = 736), range: 9 – 90 years, mean: 50.7 years, median: 51 years.
- Relevant medical history: the most frequently (>20 occurrences) reported medical conditions included: Autoimmune thyroiditis (79), Hypothyroidism (53), Rheumatoid arthritis (49), Psoriasis (34), Pericarditis (29), Colitis ulcerative, Diabetes mellitus, Multiple sclerosis (28 each), Autoimmune disorder, Basedow's disease (27 each), Ankylosing spondylitis, Systemic lupus erythematosus (26 each), Immune thrombocytopenia (25), Sjogren's syndrome (22), Crohn's disease (21), Arthritis, and Psoriatic arthropathy (20 each).
- COVID-19 Medical history (n = 61): COVID-19 (43), Suspected COVID-19 (20), Post-acute COVID-19 syndrome (5), and SARS-CoV-2 test positive (1).
- Co-suspect vaccines/medications: Influenza vaccine (5), COVID-19 Vaccine MRNA (MRNA) 1273) (3), Adalimumab, COVID-19 Vaccine NRVV AD (CHADOX1 NCOV-19) (2 each), acyclovir, colchicine, Hepatitis B vaccine, hydroxychloroquine, ocrelizumab, and pneumococcal vaccine polysacch 23V (1 each).
- Number of events: 4633 (of which 782 were events of interest ie, exacerbation/flare AEs).
- Relevant event seriousness:[42] serious (521), non-serious (266).
- Most frequently reported relevant PTs (≥2%): Condition aggravated (548), Disease recurrence (200), and Concomitant disease aggravated (22).
- Time to event onset (n = 424)[189], range: from 1 day to 164 days, median: 4 days.
  - <24 hours: 65 events (0 of which had a fatal outcome);
  - 1 day: 67 events;

[189] This number does not include 7 events for which partial administration and/or events without a meaningful time to onset/cessation value as per reported information.

- 2-7 days: 129 events
- 8-14 days: 61 events;
- 15-30 days: 42 events;
- 31-180 days: 60 events;

- Duration of relevant events (n = 41 out of 112 occurrences with outcome of resolved/resolved with sequelae) [190], range: 1 day to 160 days, median 17 days.

  - <24 hours: 2 events;
  - 1 day: 4 events;
  - 2 - 7 days: 6 events;
  - 8-14 days: 1 events;
  - 15-31 days: 11 events;
  - 32-181 days: 17 events;

- Relevant event outcome: fatal (4), resolved/resolving (224), resolved with sequelae (18), not resolved (332), unknown (208).

  In 4 cases (reporting 4 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Disease recurrence (3), and Condition aggravated (1). Three of the 4 cases involved elderly subjects. The medical history reported included arthritis, autoimmune hepatitis, Miller Fisher syndrome, and thrombotic thrombocytopenic purpura.

Analysis by age group

- CT: Paediatric (1).

- PM: Paediatric (19), Adults (572), Elderly (155) and Unknown (25).

  - Exacerbation and/or flare of underlying autoimmune or inflammatory disorders occurred more frequently in the adult population, which is likely due to autoimmune disorders being more common in adults and the fact that adults are the largest group of vaccinated individuals reporting adverse events.

Conclusion

Overall, there were 772 cases (1 CT case and 771 PM cases [0.2% of the overall dataset]) that reported exacerbation/flares in subjects with autoimmune or inflammatory disorders following administration of BNT162b2. Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders occurred more frequently in the adult population which is likely due to the fact that the largest group of vaccinated individuals reporting AEs are in this age group. Also, the autoimmune or inflammatory disorders often occur during adulthood.

[190] This number does not include 1 event for which partial administration and/or events without a meaningful time to onset/cessation value as per reported information.

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: 153 (BNT162b2 [125], blinded therapy [25], and placebo [3]) (22.9% of 668 cases, the total CT dataset), compared to 176 cases (24.4%) retrieved in the PSUR #2.
- Country of incidence: US (123), Argentina (11), Germany (9), Brazil (3), China, Spain (2 each); the remaining 3 cases were distributed among 3 countries.
- Subjects' gender: female (56), male (97).
- Subjects' age in years (n = 153), range: 0.83 – 87 years, mean: 59.6 years, median: 64 years.
- Medical history (n = 153): the most frequently (≥5 occurrences) reported relevant medical conditions included Type 2 diabetes mellitus (71), Asthma (33), Chronic obstructive pulmonary disease (23), Diabetes mellitus (14), Cardiac failure congestive, Chronic kidney disease (10 each), Pulmonary embolism (7), and Bronchitis chronic (5).
- COVID-19 Medical history: COVID-19 (2).
- Co-suspects (n = 33 cases): The reported co-suspect agents included metformin (2), amiodarone, amlodipine, aripiprazole, atenolol, diltiazem, duloxetine, furosemide, hydrochlorothiazide/triamterene, hydroxyzine, losartan, semaglutide, tamsulosin, warfarin (1 each).
- Number of events: 187.
- Most frequently reported clinical PTs (>2%): Condition aggravated, Pneumonia (6 each), Cerebrovascular accident, Dyspnoea (5 each), and Coronary artery disease (4).
- BNT162b2 related events were coded to the PT: Dehydration (1). Time to onset of event is 1 day and the event outcome is reported as resolved. None of the events were related to blinded therapy.

- Time to event onset: (n = 131),[191] range: from 1 day to 178 days, median: 106 days.
  - <24 hours: 2 events (none had a fatal outcome)
  - 1 day: 1 event;
  - 2-7 days: 6 events;
  - 8-14 days: 0 events;
  - 15-30 days: 9 events;
  - 31-180 days: 113 events.

- Duration of relevant events (n = 78 out of 103 occurrences with outcome of resolved/resolved with sequelae), range: 1 day to 78 days, median 5 days.
  - <24 hours: 4 events;
  - 1 day: 7 events;
  - 2 - 7 days: 43 events;
  - 8-14 days: 8 events;
  - 15-31 days: 10 events;
  - 32-181 days: 6 events.

- Reported event outcome: fatal (13), resolved/resolving (128), resolved with sequelae (10), not resolved (36), and unknown (0).

- In 9 cases (reporting 13 relevant events with a fatal outcome), the reported causes of death were coded to the PTs Death (2), Adenocarcinoma pancreas, Cardiac failure congestive, Cardio-respiratory arrest, Completed suicide, Condition aggravated, COVID-19, Drowning, Pneumonia, Pulmonary embolism, Respiratory failure, and Sudden cardiac death (1 each). Of note, in 2 cases, limited information regarding the cause of death was provided (PT Death). Most (5 of 9 cases) of the fatal cases involved elderly subjects. The most frequently (>1 occurrence) reported medical histories included type 2 diabetes mellitus (6) and Asthma (2).

Post-Authorisation Data

- Number of cases: 18,276 (3.6% of 507,683, the total PM dataset), compared to 33,889 cases (5.2%) retrieved in the PSUR #2.
- MC cases (6964), NMC cases (11,312).
- Country of incidence: France (3532), Germany (3124), UK (2189), US (1520), Sweden (1062), Japan (765), Italy (616), Austria (471), Norway (448), Spain (442), Denmark (408), Netherlands (396), Finland (305), Canada (260), Belgium (240), Czech Republic (234), Estonia (222), Iraq (220), Ireland (196), Greece (164), Taiwan, province of China

[191] This number does not include 39 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

(144), Portugal (143), Switzerland (136), Poland (102); the remaining 937 cases were distributed among 54 countries.

- Subject's gender: female (11,576), male (6436), and unknown (264).
- Subject's age in years (n = 17,342), range: 3 - 107 years, mean: 54.1 years, median: 55 years.
- Medical history (n = 18,276): the most frequently (≥75 occurrences) reported relevant medical conditions included Asthma (7896), Diabetes mellitus (3121), Type 2 diabetes mellitus (2001), Chronic obstructive pulmonary disease (1201), Type 1 diabetes mellitus (649), Cardiac failure (616), Chronic kidney disease (608), Pulmonary embolism (564), Renal failure (343), Parkinson's disease (247), Dementia (242), Hypokinesia (168), Cognitive disorder (166), Dementia Alzheimer's type (146), Bronchitis chronic (133), Renal disorder (117), Bronchiectasis (107), Asthma exercise induced (100), Cardiac failure chronic (81), Cardiac failure congestive (77), Bronchospasm, IgA nephropathy (76 each), and Hepatic cirrhosis (75).
- COVID-19 Medical history (n = 1226): COVID-19 (912), Suspected COVID-19 (268), COVID-19 pneumonia (38), Post-acute COVID-19 syndrome (36), SARS-CoV-2 test positive (13), Coronavirus infection (8), Asymptomatic COVID-19 (5), and Exposure to SARS-CoV-2 (1).
- Co-suspects (n = 929 cases): The most frequently (>5 occurrences) reported co-suspect vaccines/medications included COVID-19 vaccine (250), COVID-19 vaccine MRNA (MRNA 1273) (141), COVID-19 vaccine NRVV AD (CHADOX1 NCOV-19) (129), influenza vaccine (58), influenza vaccine inact split 4V (24), ocrelizumab, prednisone (19 each), JNJ 78436735, mycophenolate mofetil (15 each), apixaban (14), influenza vaccine inact SAG 4V (13), tacrolimus (12), adalimumab (11), rituximab (9), prednisolone (8), atorvastatin, levothyroxine, methotrexate (7 each), allopurinol, clopidogrel, influenza vaccine inact SAG 3V, and pregabalin (6 each).
- Number of events: 70,918
- Relevant event seriousness:[42] serious (34,905), non-serious (36,098).
- Most frequently reported (≥3%) clinical PTs: Headache (2624, 15.0%), Fatigue (2570, 14.6%), Pyrexia (2012, 11.5%), Dyspnoea (1797, 10.2%), Immunisation (1533, 8.7%), COVID-19 (1446, 8.2%), Interchange of vaccine products (1383, 7.9%), Pain in extremity (1366, 7.8%), Dizziness (1255, 7.2%), Myalgia (1212, 6.9%), Arthralgia (1179, 6.7%), Vaccination site pain (1173, 6.7%), Nausea (1146, 6.5%), Malaise (1073, 6.1%), Asthenia (970, 5.5%), Chills (925, 5.3%), Pain (907, 5.2%), Chest pain (826, 4.7%), Palpitations (668, 3.8%), Lymphadenopathy (614, 3.5%), Paraesthesia (602, 3.4%), Cough (585, 3.3%), and Vomiting (561, 3.2%).

- Time to event onset (n = 46,814),[192] range: from 1 day to 180 days, median: 2 days.
  - <24 hours: 16,088 events (334 of which had a fatal outcome);
  - 1 day: 9793 events;
  - 2-7 days: 9384 events;
  - 8-14 days: 3231 events;
  - 15-30 days: 3313 events;
  - 31-180 days: 5005 events.

- Duration of relevant events (n = 8391 out of 16,690 occurrences with outcome of resolved/resolved with sequelae) [193], range: 1 day to 181 days, median 3 days.
  - <24 hours: 1255 events;
  - 1 day: 1660 events;
  - 2 - 7 days: 3221 events;
  - 8-14 days: 760 events;
  - 15-31 days: 578 events;
  - 32-181 days: 917 events.

- Relevant event outcome[78]: fatal (2258), resolved/resolving (24,735), resolved with sequelae (1867), not resolved (19,410), unknown (23,001).

- In 801 cases (reporting 2258 relevant events with a fatal outcome), the reported cause of death (≥26 occurrences) was coded to the PTs Death (144), Immunisation (92), COVID-19 (91), COVID-19 pneumonia (80), Cardiac arrest (62), Cardiac failure, Dyspnoea (50 each), Interchange of vaccine products (49), Sudden death (42), Cardio-respiratory arrest (40), Pulmonary embolism (38), Pneumonia (34), Respiratory failure (29), Pyrexia (28), and Myocardial infarction (26). Of note, in 186 cases, limited information regarding the cause of death was provided (PTs Death and Sudden death). Most (689 of 801 cases) of the fatal cases involved elderly subjects. The most frequently (≥20 occurrences) reported medical history included diabetes mellitus (169), type 2 diabetes mellitus (117), cardiac failure (113), chronic obstructive pulmonary disease (95), dementia (83), chronic kidney disease (72), asthma (55), cognitive disorder, pulmonary embolism (39 each), renal failure (38), Parkinson's disease (35), dementia Alzheimer's type (31), Cardiac failure chronic (27), and type 1 diabetes mellitus (20).

Analysis by age group

- CT Data: Paediatric (12), Adults (67), Elderly (74)).

[192] This number does not include 1005 events for which partial administration and/or event onset dates were reported or events without a meaningful time to onset value as per reported information.

[193] This number does not include 221 events for which partial administration and/or events without a meaningful time to onset/cessation value as per reported information.

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

- PM Data: Paediatric (625), Adults (11,157), Elderly (5906) and Unknown (588).

  - No significant difference was observed in the reporting proportion of frequently (≥3%) reported events between adult and elderly population except for the event coded to PT Lymphadenopathy.
  - A higher reporting proportion of events coded to PT Lymphadenopathy was observed in the adult population (4.7% [520 cases] in adults vs 1.0% [59 cases] in elderly) compared to the elderly population.
  - No comparison was made to the paediatric population considering the limited number of cases.

Conclusion

The reporting proportion of not resolved cases (36.1%) and cases resolved with sequelae (3.1%) in frail subjects is similar to the reporting proportion observed in the overall population (31.7% for outcome of not resolved, 1.9% for outcome of resolved with sequelae). The reporting proportion of cases reporting fatal outcome (4.4%) in frail subjects is higher than the reporting proportion of cases reporting fatal outcome in the overall population (0.6%). This is expected, considering that most of the cases reporting a fatal outcome (64.4%) among the frail subjects involved subjects over 75 years of age who, due to their advanced age and underlying comorbidities, are more likely to die than younger individuals. Underlying comorbidities are likely to be contributory to their deaths.

The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity). It has not been systematically studied in frail individuals with severe comorbidities but there is much post-authorisation data in this population as they have generally been targeted as high priority for vaccination. No safety signals have emerged that would be considered specific to this population.

16.3.5.8. Interactions with other Vaccines

Search criteria - HLT Interactions.

- Of the 146 cases, 143 cases were determined to be non-contributory and were not included in the discussion for the following reasons:

  - in 1 case, the subject did not experience an interaction, but rather the reporter was inquiring about whether or not a drug interaction could potentially occur;
  - in 32 cases, the drug possibly interacting with BNT162b2 was not specified;
  - in 3 cases, alcohol (1), or herbal (2) interaction occurred;
  - in 1 case BNT162b2 was not involved in the interaction;
  - in 106 cases (of which 58 were serious), the subjects experienced drug interactions with the following medications rather than another vaccine (≥2): adalimumab (9), mycophenolate (6), upadacitinib (5), prednisone (4), budesonide, levetiracetam (3

each), botulinum toxin type A, capecitabine, ciclosporin, clozapine, corticosteroid nos, ethinylestradiol/ levonorgestrel, hyaluronic acid, infliximab, levothyroxine, methylphenidate, ocrelizumab, and venlafaxine (2 each).

Three of the 146 cases reported an interaction with another vaccine and are discussed below.

Clinical Trial Data

There were no relevant serious clinical trial cases reported during the reporting period, as in the PSUR #2.

Post-Authorisation Data

- Number of cases: 3 (0.0006% of 507,683 cases, the total PM dataset), compared to 18 (0.003%) retrieved in the PSUR #2.
- MC case (2), NMC case (1).
- Country of incidence: Finland, France, UK (1 each).
- Subjects' gender: female (3).
- Subjects' age in years (n =2), 61 and 68 years.
- Medical history (n = 3): Ankylosing spondylitis, Dermatitis, and Polychondritis (1 each).
- COVID-19 Medical history: none.
- Co-suspect vaccines (n = 3 cases): COVID-19 Vaccine Novavax, Pneumococcal vaccine Pneumovax and COVID-19 Vaccine AstraZeneca (1 each).
- Other co-suspects (n = 1 case): Methotrexate.
- Number of events: 26 (of which 3 were events of interest).
- Relevant event seriousness: serious (1), non-serious (2).
- Relevant PTs: Drug interaction (3).
- Co-reported AEs: Interchange of vaccine, Off label use, Pyrexia (2 each), Asthenia, Blood pressure decreased, Chills, COVID-19 Immunisation, Dermatitis, Dizziness, Eating disorder, Fall, Feeling hot, Hypersensitivity, Hypoasthesia, Illness, Nausea, Vaccination site induration, Vaccination site plaque, Vaccination site pruritus, and Vomiting (1 each). Of note, the following AEs may be associated with the interactions with other vaccines: Asthenia, Chills, Fall, Feeling hot, Hypersensitivity, Vomiting, Vaccination stie induration, and Vaccination site plaque, Vaccination site pruritus. The outcome of these events was unknown or not resolved.
- Time to event onset: not available in the 3 cases.
- Relevant event outcome: resolving (1), unknown (2).

Analysis by age group comorbidities and dose

No comparison between the different age groups and presence of comorbidities was performed due to the limited number of cases.

Conclusion

Among the overall 146 cases, 143 were considered not relevant, as a drug interaction did not occur in 1 case, the interacting agents was not specified in 32 cases, BNT162b2 was not involved in 1 case and in the remaining 110 cases, the interaction occurred with alcohol, herbal or medications rather than another vaccine.

There were 3 cases in the overall post-marketing dataset that involved a vaccine interaction. The most frequently co-reported event (>2 occurrences) other than off label use and interchange of vaccines PTs was Pyrexia, which is consistent with the known reactogenicity of the vaccine and listed in Section 4.8 Undesirable effects of the CDS.

There is no indication of a safety signal noted based on the review of these cases.

16.4. Characterisation of Risks

As reported in Section 16.1 *Summary of Safety Concerns*, on 08 July 2022 (after the DLP of this PSUR), the MAH submitted the EU RMP version 5.1 to remove the important identified risk of anaphylaxis from the list of safety concerns in accordance with CHMP recommendation received on 10 March 2022 with the positive opinion for the Type II Variation 87 (EMEA/H/C/005735/II/0087) and based on the accumulation of post-authorisation safety information.

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

16.4.1. Characterisation of Important Identified and Potential Risks

A typical medicinal product has multiple risks associated with it and individual risks vary in terms of severity, effect on individual patients, and public health impact.

What constitutes an important risk depends upon several factors including the impact on the individual subject, the seriousness of the risk and its severity, and the impact on public health. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered. Risks may be related to nonclinical or clinical safety or quality issues. The intended purpose and impact of the product e.g., whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease must also be considered when characterising risks.

The following were considered in characterising risk(s) of this product:

- frequency of risk;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life or could lead to serious consequences if left untreated);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (ie, predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

Internal and external datasets were used to populate the table below with available data. In addition to literature searches for the drug itself and its class, external data sources were consulted.

Please see Appendix 8 for the characterisation of the important identified and important potential risks of BNT162b2, consistent with Part II, Module SVII of the BNT162b2 EU RMP version 5.0 adopted on 10 March 2022.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer. The risks for BNT162b2 are well managed. No special investigations to further characterise any of these risks are necessary.

Summary information from clinical trials and post-marketing sources received by the MAH through 18 June 2022 is provided in Section 16.4.1.1 and Section 16.4.1.2.

16.4.1.1. Cumulative Characterisation of Important Identified Risks

Table 70. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
Anaphylaxis	• No. of cases: 8 (of which 4 involved blinded therapy) • No. of SAEs: 8 • Relevant PTs: Anaphylactic reaction (6), Anaphylactic shock, Anaphylactoid reaction (1 each).	• No. of cases: 8483 • Relevant PTs: Anaphylactic reaction (7345), Anaphylactic shock (1224), Anaphylactoid reaction (202), Anaphylactoid shock (8). • Frequently reported additional PTs (>300 occurrences): Dyspnoea

Table 70. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
	• Related SAEs: Anaphylactoid reaction (1) with an outcome of resolved. • Related case gender: female • Related case age: 17 years Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and anaphylaxis.	(1924), Nausea (1125), Pruritus (1029), Dizziness (931), Erythema (870), Rash (819), Cough (795), Headache (782), Urticaria (779), Tachycardia (698), Throat tightness (615), Malaise (551), Blood pressure increased (537), Pyrexia (490), Vomiting (484), Blood pressure decreased (468), Feeling abnormal (460), Oropharyngeal discomfort (436), Palpitations (423), Chest discomfort (409), Hypoaesthesia (398), Paraesthesia (392), Fatigue (382), Hypersensitivity (361), Wheezing (354), Loss of consciousness (330), Hypotension (329), Chills (325), Heart rate increased (305), Pallor (301), and Swollen tongue (301). • Subjects' gender: female (6720), male (1395) and unknown (368). • Subjects' age in years (n = 7763), range: 5 – 104 years, mean: 44.1 years, median: 43.0 years. • Age group: Paediatric (325), Adults (6543), Elderly (909) and Unknown (706). • Case source: Spontaneous (8285), Literature (166), Non-interventional study (25), Solicited (7). • Event seriousness: serious (8779) • Event outcome: Fatal (57), Not resolved (580), Resolved with sequelae (148), Resolved/resolving (6338), Unknown data (1667). Based on the cumulative PM data, no new significant safety information was identified for BNT162b2 and anaphylaxis.
Myocarditis and Pericarditis	*Myocarditis* • No. of cases: 4 of BNT162b2 • No. of SAEs: 4 • The relevant PTs: Myocarditis, Myopericarditis (2 each) • Related SAEs: Myopericarditis (2), Myocarditis (1). *Pericarditis* • No. of cases: 3 of BNT162b2 • No. of SAEs: 3	Cumulatively, there were 20,256 cases of Myocarditis and Pericarditis: 12,327 cases reported myocarditis and 9896 cases reported pericarditis (in 1967 of these 20,256 cases, the subjects developed both myocarditis and pericarditis). *Myocarditis* • No. of cases: 12327 • Relevant PTs: Myocarditis (10390), Myopericarditis (1803), Carditis

Table 70. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
	• The most common PTs: Pericarditis (3) • Related SAEs: None. Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and myocarditis/pericarditis.	(180), Eosinophilic myocarditis (8), Hypersensitivity myocarditis (5), Autoimmune myocarditis (4), Giant cell myocarditis, Immune-mediated myocarditis (2 each). • Frequently reported additional PTs (≥500 occurrences): Chest pain (4226), Dyspnoea (2659), Fatigue (2080), Palpitations (2009), Pericarditis (1964), Pyrexia (1838), Tachycardia (1375), Chest discomfort (1262), Headache (1046), Immunisation (886), Off label use (846), Troponin increased (788), Dizziness (714), Interchange of vaccine products (691), Inappropriate schedule of product administration (585), Malaise (557), Asthenia (511), Nausea (502). • Subjects' gender: female (4203), male (7709) and unknown (415). • Subjects' age in years (n = 11,150), range: 6 – 102 years, mean: 35 years, median: 31 years. • Age group: Paediatric (1836), Adults (8543), Elderly (866) and Unknown (1082). • Case source: Spontaneous (12,071), Literature (217), Clinical study (27), Solicited (12) • Event seriousness: serious (12,394) • Event outcome:[78] Fatal (188), Not resolved (3639), Resolved with sequelae (296), Resolved/resolving (4780), Unknown data (3501). <u>*Pericarditis*</u> • No. of cases: 9896. • Relevant PTs: Pericarditis (9824), Pleuropericarditis (75), Pericarditis constrictive (16), Pericarditis adhesive (1). • Frequently reported additional PTs (≥2%): Chest pain (4153), Dyspnoea (2535), Myocarditis (1848), Fatigue (1714), Palpitations (1610), Pyrexia (1150), Tachycardia (1102), Chest discomfort (1027), Headache (776), Pericardial effusion (714), Immunisation (671), Off label use (603), Dizziness (555), Interchange of vaccine products (523), Malaise

Table 70. Cumulative Characterisation of Important Identified Risks

Risks	Clinical Study Data	Post-Marketing Data
		(441), Myalgia (386), Nausea (379), Pain (376), Arthralgia (361), Pain in extremity (357), Asthenia (340), Inappropriate schedule of product administration (337), Paraesthesia (276), Syncope (262), Chills (238), Electrocardiogram abnormal (232), Cough (228), Heart rate increased (227), Angina pectoris (213), and Lethargy (208). • Subjects' gender: female (4619), male (5062) and unknown (215). • Subjects' age in years (n = 9188), range: 2 – 98 years, mean: 39.5 years, median: 37.0 years. • Age group: Paediatric (685), Adults (7657), Elderly (893), and Unknown (661). • Case source: Spontaneous (9806), Literature (45), Clinical study (41), Other solicited sources (4). • Event seriousness: serious (9916). • Event outcome:[78] Fatal (32), Not resolved (3418), Resolved with sequelae (147), Resolved/resolving (3647), Unknown data (2676). Based on the accumulating data from post-authorisation use of the vaccine, including the consistent findings from passive and active surveillance databases of increased occurrences of myocarditis and pericarditis following vaccination with BNT162b2, myocarditis and pericarditis have been added as ADRs in section 4.8 Undesirable effects, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022, after the DLP.

16.4.1.2. Cumulative Characterisation of Important Potential Risks

Table 71. Cumulative Characterisation of Important Potential Risks

Risks	Clinical Study Data	Post-Marketing Data
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	There were no cases reporting COVID-19 infection associated with one of the PTs utilized to identify potential severe or atypical cases of COVID-19.	• No. of cases: 3472. • Relevant PTs most frequently reported (≥2%): Drug ineffective (1952), Vaccination failure (1520), COVID-19 pneumonia (1428), Dyspnoea (1062), Diarrhoea (498),

Table 71. Cumulative Characterisation of Important Potential Risks

Risks	Clinical Study Data	Post-Marketing Data
	Based on the cumulative CT data, no new significant safety information was identified for BNT162b2 and VAED/VAERD.	Vomiting (239), Nausea (191), Respiratory failure (184), Myocarditis (174), Abdominal pain (150), Pulmonary embolism (129), Hypoxia (123), Acute respiratory distress syndrome (115), Cardiac failure (96), Acute kidney injury, Tachypnoea (94 each). • Frequently reported additional PTs (>100 occurrences): COVID-19 (2132), Pyrexia (683), Cough (547), Fatigue (385), Headache (379), Asthenia (330), Suspected COVID-19 (296), Malaise (182), Chest pain (175), Myalgia (172), Oxygen saturation decreased (163), Pain (159), Dizziness (144), Chills (141), Decreased appetite (124), Anosmia (121), Arthralgia (119), Oropharyngeal pain (118), Ageusia (111), Off label use (110), Pneumonia (106), and Immunisation (103). • Subjects' gender: female (1735), male (1662) and unknown (75). • Subjects' age in years (n = 3331), range: 5 – 104 years, mean: 65.8 years, median: 71.0 years. • Age group: Paediatric (50), Adults (1292), Elderly (1994) and Unknown (136). • Case source: Spontaneous (3393), Literature (26), Non-interventional study (53) • Relevant event seriousness: serious (7324), non-serious (1017) • Relevant event outcome: Fatal (1413), Not resolved (1261), Resolved with sequelae (80), Resolved/resolving (2784), Unknown data (2815). Based on the cumulative PM data individual review of cases, no new significant safety information was identified for BNT162b2 and the potential risk of VAED/VAERD.

16.4.2. Description of Missing Information

Table 72 describes missing information associated with the use of BNT162b2.

Table 72. Description of Missing Information

Topic	Description
Use in pregnancy and while breast feeding	The safety profile of the vaccine in pregnant and/or breastfeeding women was not studied in the pivotal clinical trial and the maternal clinical trial was terminated early due to participant recruitment difficulties. Many pregnant women have chosen to be vaccinated despite the lack of clinical trial safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.3 *Use in Pregnant/Lactating Women*.
Use in immunocompromised patients	The vaccine is being studied in ongoing clinical trials of individuals with immunocompromised conditions. Cases involving use of BNT162b2 in immunocompromised patients received during the reporting interval are summarised 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 (e.g., hypertension, obesity), however, it has not been studied in frail individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population. Cases involving use of BNT162b2 in frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) received during the reporting interval are summarised 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 clinical trial 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 summarised 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.*
Long term safety data	At the time of the initial submission, 2-month post dose 2 safety data were available for approximately half of the patients who have received BNT162b2 mRNA vaccine in Study C4591001. The pivotal clinical study is ongoing and ongoing non-interventional safety studies will collect longer term post-marketing safety data.

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.[194]

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.[195] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[195] 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,[196] were included as were participants with known stable infection with HIV, HCV, or HBV.[195]

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.

[194] As per information reported in the CDS version 13.0 dated 10 May 2022, in effect at the end of the reporting period. Since 17 June 2022, BNT162b2 is approved in individuals 6 months of age and older, as the paediatric Tris/Sucrose presentation - maroon cap was approved in the US.

[195] Ref #12 of the CDS. Global Emergency Use Authorisation Application, Section 6.2.1.2.

[196] Ref #21 of the CDS. Global Emergency Use Authorisation, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01.

Table 73. 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*,[197]			
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[198]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Timec (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Timec (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).

[197] 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.

[198] Ref #54 of the CDS. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 73. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Age Subgroup – Participants without Evidence of Infection and Participants with or without Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided CI for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 74 and Table 75.

Table 74. 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[199]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2 [f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk [g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)

[199] Ref #55 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population.

Table 74. 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[199]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
65 and older and 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.

Table 75. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days after Dose 2, by Risk Status – Participants with or without* Evidence of Infection prior to 7 Days after Dose 2 – Evaluable Efficacy (7 Days) Population during the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2 [f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk [g]			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese [h]			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Table 75. 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 76) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the TRADENAME and placebo groups.

Table 76. 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[200,201]			
	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[202,203]			
	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:[204]

- 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);

---

[200] 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.

[201] 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.

[202] 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.

[203] 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.

[204] Ref #61 of the CDS. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy.

Table 76. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants with or without* prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition after Dose 1 or from 7 Days after Dose 2 in the Placebo-Controlled Follow-up

- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[204]

- 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.[205]
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.[205]
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 77.

[205] Ref #62 of the CDS. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations.

Table 77. 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*,[206]			
	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[207]			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1110 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by RT-PCR and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In C4591001 an analysis of SARS-CoV-2 neutralising titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses comparing adolescents 12 to 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n = 190) was non-inferior to the

[206] 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.

[207] 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.

immune response in participants 16 through 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titers at 1 month after Dose 2. The GMT ratio of the adolescents 12 to 15 years of age group to the participants 16 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the GMR >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 through 25 years of age.[208]

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 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 from the 6-month interim analysis of study C4591031 (16 years and older participants)

Study C4591031 Substudy A evaluated BNT162b2 boosting strategies across different population of participants (e.g., age groups). In the 6-month interim report for Substudy A efficacy analysis of a single booster dose of BNT162b2 30 µg from 7 days after booster dose during the blinded placebo-controlled follow-up period was evaluated; also incidence of

[208] 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.

COVID-19 cases through the entire study follow-up period in participants who received BNT162b2 initially or subsequently after unblinding was analysed.

Demographics of participants in the evaluable efficacy populations without evidence of infection prior to 7 days after booster vaccination were similar in the BNT162b2 and placebo groups. This analysis population had similar demographics compared to the overall safety population, as did the evaluable efficacy population participants with or without evidence of infection prior to 7 days after booster vaccination and the all-available efficacy population.

For participants without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population, the median duration of blinded follow-up after booster vaccination was 2.8 months as of the data cutoff date and was similar to the safety population. Of these participants originally randomized to the BNT162b2 group, the total exposure from booster vaccination to the data cutoff date was ≥6 months for most participants (99.0%).

Follow-up times after booster vaccination for participants with or without evidence of infection prior to 7 days after booster vaccination in the evaluable efficacy population were similar to the evaluable efficacy population.

After unblinding, in the all-available efficacy population there were 7 cases meeting severe criteria; all occurred after 20 December 2021, when the Omicron variant was the predominant strain, in participants who were baseline SARS-CoV-2 negative. In original BNT162b2 participants, there were 5 severe cases: 3 met the FDA definition, 1 met the CDC definition, and 1 met both definitions. In placebo participants who later received BNT162b2, there were 2 severe cases that met the FDA definition.

These results indicate that a booster dose of BNT162b2 30 μg given ≥6 months after the primary 2-dose series of BNT162b2 30 μg vaccination provided protection against COVID-19, and protection was strongest during the Delta variant wave, and sustained up to 4 months after vaccination; longer term protection against Delta variant relative to placebo cannot be estimated from this study due to unblinding and crossover of placebo control participants. For the same reason, RVE of boosted to non-boosted participants during the Omicron variant wave cannot be estimated in this study. Although the IR during Omicron wave is much higher than that of Delta wave, the IR in those participants that were 'later' vaccinated is lower than those participants that were 'early' vaccinated, which implies better protection against Omicron with recent vaccination.

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 enrolled 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.[209]

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 78. 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. [209]

Table 78. 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).

[209] 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.

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 79.[210]

[210] Ref #73 of the CDS. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults.

Table 79. 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 80.[210]

Table 80. 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 immunogenicity in children 5 through <12 years of age – after booster dose

Administration of a booster (third) dose of BNT162b2 10-µg to children 5 through <12 years of age in Study C4591007 elicited robust neutralizing titers against the wild-type variant of SARS-CoV-2 in an evaluable immunogenicity population of 67 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

Observed GMTs at 1-month post-Dose 3 were substantially increased (2720.9) compared with those at 1-month post-Dose 2 (1253.9) and prior to booster (Dose 3) vaccination (271.0).

The GMR for participants with available titers at 1-month post-Dose 3 compared to those with available titers at 1-month post-Dose 2 was 2.17 (2-sided 95% CI: 1.76, 2.68).

The observed proportion of participants who achieved seroresponse (ie, ≥4-fold rise in SARS-CoV-2 neutralizing titers from pre-Dose 1, or ≥4 × LLOQ for a pre-Dose 1 measurement <LLOQ) was high (100.0%) at 1-month post-Dose 2, waned by pre-Dose 3 (77.6%), and was increased at 1 month after Dose 3 (98.5%). The difference in seroresponse rates at 1-month post-Dose 3 compared with at 1-month post-Dose 2 was -1.5% (2-sided 95% CI: -8.0%, 2.4%).

Additionally, based on the FFRNT (a supportive assay), a third (booster) dose of BNT162b2 10-µg elicited neutralizing titers against a recombinant SARS-CoV-2 Omicron variant and recombinant wild-type (reference) strain of SARS-CoV-2 in an evaluable immunogenicity population of 29 children 5 to <12 years of age who were without evidence of SARS-CoV-2 infection.

The observed 1-month post-Dose 2, neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively which increased at 1-month post-Dose 3 to 614.4 and 1702.8 and, respectively, representing an increase from post-two-dose primary series to post-booster vaccination of 22-fold for Omicron and 5-fold for the reference strain.

The GMR of neutralizing titers against Omicron versus the reference strain at 1-month post-Dose 2 was 0.09 (2-sided 95% CI: 0.07, 0.10) and increased to 0.36 (2-sided 95% CI: 0.28, 0.47) at 1-month post-Dose 3, representing a fold-rise from 1-month post-Dose 2 to 1-month post-Dose 3 that was 4-times higher for the Omicron titers than for the reference strain titers obtained in the FFRNT assay.

The immune response associated with a booster (third) dose of BNT162b2 10-µg administered approximately 6 months after the second dose to children 5 to <12 years of age is expected to confer protection against COVID-19 including disease caused by Omicron. This is in the context of previously observed immunogenicity and efficacy results across pediatric, adolescent, and adult populations in the clinical development program and available real-world data, which have collectively shown that a booster (third) dose of BNT162b2 substantially increases the magnitude and breadth of neutralization and provides protection against symptomatic SARS-CoV-2 infection caused by variants including Omicron.

Efficacy and immunogenicity in children 6 months to <5 years of age – after 3 doses

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pediatric study in healthy children from 6 months to <12 years of age. The pediatric vaccination series for children 6 months to <5 years of age was initially planned as a two-dose series given 3 weeks apart; however, based on emerging clinical and real-world data, the protocol was amended to add a third dose given at least 8 weeks after the second dose at the age-appropriate dose level.

Immunobridging (i.e., effectiveness) data were analyzed from approximately 4500 children across the 6 months to <5 years of age groups who were randomized 2:1 to receive three

doses of BNT162b2 3 µg or placebo with median follow-up of approximately 2 months after Dose 3 (inclusive of blinded and open-label periods).

Immunobridging Results

Immunobridging success criteria were met for both age groups, comparing the GMR and seroresponse for each C4591007 group who received three doses of BNT162b2 3-µg to adults 16 to 25 years of age in C4591001 who received two doses of BNT162b2 30-µg. Note, the CI lower bounds of the GMRs were ≥1, indicating statistical significance.

- For children 2 to <5 years of age, the GMR for titers at 1-month post-Dose 3 of BNT162b2 3-µg compared to young adults 16 to 25 years of age at 1-month post-Dose 2 of BNT162b2 30-µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.30 (2-sided 95% CI: 1.13, 1.50) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -1.5%, 4.2%).

- For children 6 months to <2 years of age, the GMR for titers at 1-month post-Dose 3 of BNT162b2 3-µg compared to young adults 16 to 25 years of age at 1-month post-Dose 2 of BNT162b2 30-µg, all of whom were without evidence of prior SARS-CoV-2 infection, was 1.19 (2-sided 95% CI: 1.00, 1.42) and the difference in proportions who achieved seroresponse was 1.2% (2-sided 95% CI: -3.4%, 4.2%).

Wild-type Strain SARS-CoV-2 Neutralization

Three doses of BNT162b2 elicited robust immune responses to wild-type SARS-CoV-2 in children who received 3-µg doses and in young adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.7) was increased prior to Dose 3 (401.1) and then substantially increased at 1-month post-Dose 3 (1535.2). The GMFR at 1-month post-Dose 3 was 73.3 and the seroresponse rate was 100%.

- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.8) was increased prior to Dose 3 (317.0) and was substantially increased at 1-month post-Dose 3 (1406.5). The GMFR at 1-month post-Dose 3 was 68.4 and the seroresponse rate was 100%.

Patterns observed for children in wild-type SARS-CoV-2 neutralization at 1-month post-Dose 3 were generally comparable to young adults 16 to 25 years of age at 1-month post-Dose 2.

Omicron Variant SARS-CoV-2 Neutralization

Three doses of BNT162b2 increased neutralizing titers to Omicron and Delta variants of SARS-CoV-2 in children who received 3-µg doses and in adults who received 30-µg doses.

- For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, FFRNT assay results showed neutralizing titers

against a recombinant Omicron variant increased from before Dose 3 (14.0) to 1-month post-Dose 3 (82.5). This represents a 5.9-fold increase in Omicron neutralizing titers from before Dose 3 to 1-month post-Dose 3.

- For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, FFRNT assay results showed neutralizing titers against a recombinant Omicron variant increased from before Dose 3 (16.3) to 1-month post-Dose 3 (127.5). This represents a 7.8-fold increase in Omicron neutralizing titers from before Dose 3 to 1-month post-Dose 3.

- Substantial increases in titers against a recombinant Delta variant and a wild-type reference strain were also observed after the second and third doses in both pediatric age groups.

Efficacy

Descriptive efficacy analyses for Phase 2/3 Study C4591007 populations of children 6 months to <2 years of age were based on symptomatic COVID-19 cases accrued from Dose 1 to a data cutoff date of 29 April 2022. These represent available data for a still-actively enrolling study.

Observed Vaccine Efficacy Across Total Population of Children 6 Months to <5 Years

VE was estimated across the total population of participants 6 months to <5 years of age randomized 2:1 to receive BNT162b2 3-µg vs placebo, which included 992 BNT162b2 recipients and 464 placebo recipients who received three doses of study intervention.

Based on COVID-19 cases confirmed from at least 7 days post-Dose 3 to the cutoff date, observed VE was 80.3% (2-sided 95% CI: 13.9%, 96.7%). Based on cases from Dose 1 onwards, observed VE was 25.5% (2-sided 95% CI: 7.7%, 39.6%).

RVE based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) vs 4 cases reported at least 7 days after Dose 2 (original placebo group unblinded to receive BNT162b2) during the calendar interval of 07 February 2022 to 29 April 2022 was 76.2% (2-sided 95% CI: -0.5%, 95.1%). Note that this time period corresponds to when Omicron was the dominant SARS-CoV-2 variant.

Observed Vaccine Efficacy in Each Age Group

VE was estimated for each age group based on COVID-19 cases confirmed at least 7 days post-Dose 3 or from Dose 1 to the data cutoff date. Observed VE from Dose 1 onwards, or from at least 7 days after Dose 3, was not meaningfully impacted by excluding cases involving coinfection with other respiratory pathogens.

In the 2 to <5 years of age group, VE was estimated from a population of 1835 BNT162b2 recipients and 915 placebo recipients of whom 606 and 280, respectively, received three doses. Based on cases confirmed from at least 7 days post-Dose 3 to the cutoff date, observed

VE of 82.3% (2-sided 95% CI: -8.0%, 98.3%). From Dose 1 onwards, observed VE of 32.6% (2-sided 95% CI: 10.8%, 48.8%)

In the 6 months to <2 years of age group, VE was estimated from a population of 1178 BNT162b2 recipients and 598 placebo recipients of whom 386 and 184, respectively, received three doses. Based on cases confirmed from at least 7 days post-Dose 3 to the cutoff date, observed VE of 75.5% (2-sided 95% CI: -370.1%, 99.6%). From Dose 1 onwards, observed VE of 14.0% (2-sided 95% CI: -21.2%, 38.4%).

Relative Vaccine Efficacy of Three Doses vs Two Doses in Each Age Group

For children 2 to <5 years of age, RVE during the calendar interval of 07 February 2022 to 29 April 2022 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) vs 4 cases reported at least 7 days after Dose 2 (original placebo group unblinded to receive BNT162b2) was 84.0% (2-sided 95% CI: -11.8%, 98.6%).

For children 6 months to <2 years of age, RVE during the calendar interval of 07 February 2022 to 29 April 2022 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) vs 2 cases reported at least 7 days after Dose 2 (original placebo group unblinded to receive BNT162b2) was 59.4% (2-sided 95% CI: -459.5%, 97.1%).

Omicron-specific VE for the time period 01 December 2021 to 06 February 2022.

Given that the US Food and Drug Administration initially authorized a third dose of the vaccine for individuals aged 65 years and older and individuals at high risk of severe COVID-19 on 22 September 2021, early estimates of VE against Omicron are likely enriched for high-risk populations, including patients who are immunocompromised. Indeed, the analysis using data from the early portion of the Omicron wave showed early signs of waning effectiveness of the BNT162b2 mRNA COVID-19 vaccine against Omicron variant-related hospital and emergency department admission at 3 months or longer after receipt of a third dose in US adults aged 18 years and older.

Updated findings primarily show two things. First, waning effectiveness against Omicron-related hospitalisation observed at ≥3 months after a third dose of vaccine during the initial study period (data cutoff of 06 February 2022) was less pronounced after excluding individuals who were immunocompromised; original VE ≥3 months after a third dose of 55% (95% CI: 28−71) against hospitalisation vs 74% (95% CI: 52−86) after excluding individuals who were immune-compromised. Second, extending the analysis period through 18 March 2022, which captures the entire Omicron wave and results in the inclusion of more individuals who became eligible for booster doses on 29 November 2021, diminished the evidence of waning vaccine protection after a third dose. Specifically, after extending the analysis period, waning of VE against Omicron-related outcomes was no longer apparent, particularly in the immunocompetent population.

Thus, patients who were immunocompromised likely drove much of the observed waning seen in our initial report. Another explanation may be differences in severity of illness among patients admitted to the hospital or emergency department over time, which could result from

increasing levels of immunity due to natural infection and/or increased at-home COVID-19 testing during the updated study period[211]

A more recent study by the same group, found that three doses of BNT162b2 conferred high protection against hospital and emergency department admission due to both the delta and omicron variants in the first 3 months after vaccination. However, 3 months after receipt of a third dose, waning was apparent against SARS-CoV-2 outcomes due to the omicron variant, including hospital admission. Additional doses of current, adapted, or novel COVD-19 vaccines might be needed to maintain high levels of protection against subsequent waves of SARS-CoV-2 caused by the omicron variant or future variants with similar escape potential. (2) [212].

The UK health security agency released the COVID-19 vaccine surveillance report up to 16 June 2022, showing that BNT162b2 vaccine efficacy against symptomatic COVID-19 is lower and wanes faster for Omicron.[213]

Tarof et al. also highlights vaccines have been effective against severe Omicron illness[211,212] however waning against Omicron hospitalisation is observed >9m after the second vaccination dose and duration of protection >6m post-boost is unknown and could trigger higher rates of lack of efficacy, defined by breakthroughs and re-infections by the current Omicron subvariants BA.4 and BA.5.

A recent publication from Israel[214] reports a low neutralisation efficiency against BA.4 and BA.5 even in sera obtained from BA.1-recovered from health care workers who previously received three or four vaccine doses. These findings suggest that an Omicron-specific vaccination might be indicated.

Hansen et al. evaluated the risk of reinfection, vaccine protection, and severity of infection with the BA.5 Omicron subvariant and they found a high protection against BA.5 from prior Omicron infection in triple-vaccinated individuals, and similar vaccine effectiveness for BA.5

---

[211] Tartof SY, Slezak JM, Puzniak L. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: a retrospective cohort study. The Lancet Regional Health – Americas 2022;9: 100198 Published on line 14 February 2022.

[212] Tartof SY, Slezak JM, Puzniak L. Durability of BNT162b2 vaccine against hospital and emergency department admission due to the omicron and delta variants in a large health system in the USA: a test-negative case-control study. Lancet Respir Med 2022; 10:689-99.

[213] UK Health Security Agency. COVID-19 vaccine surveillance report: week 24. 16 June 2022. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1083443/Vaccine-surveillance-report-week-24.pdf. Accessed July 29, 2022.

[214] Kliker L, Zuckerman N, Atari N et al. COVID-19 vaccination and BA.1 breakthrough infection induce neutralising antibodies which are less efficient against BA.4 and BA.5 Omicron variants, Israel, March to June 2022. www.eurosurveillance.org submitted on 12 Jul 2022 / accepted on 28 Jul 2022 / published on 28 Jul 2022

infection as currently for BA.2. BA.5 infection was associated with an increased risk of hospitalisation which needs confirmation and continued surveillance as hospitalisations were low and stable during the study period.[215] Adapted vaccines can help slow virus circulation and emergence of variants of concern.

Three doses of BNT162b2 conferred high protection against hospital and emergency department admission due to both the Delta and Omicron variants in the first 3 months after vaccination. However, 3 months after receipt of a third dose, waning was apparent against SARS-CoV-2 outcomes due to the omicron variant, including hospital admission.[212]

Additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high levels of protection against subsequent waves of SARS-CoV-2 caused by the omicron variant or future variants with similar escape potential.[212]

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 and older. Efficacy also appears largely independent of risk factors (having at least 1 of the CMI categories) and obesity. Efficacy is also high against severe disease after the first dose. This is anticipated to deliver effective prevention of COVID-19 in the community and reduced hospitalisation, severe morbidity and death from COVID-19. Section 17.2 describes the newly identified information on efficacy and effectiveness of the 2-month and 6-month interim analysis of study C4591031 and on efficacy in children 6-month 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

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.[216] The number of infected cases

---

[215] Hansen CH, Friis NU, Bager P et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish nation-wide population-based study. Lancet pre-print https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4165630.

[216] 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.

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.[217]

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[218].

As of 05 April 2022, the overall number of people who had been infected with SARS-CoV-2 was over 475 million worldwide[219], an increase of 268 million since 15 August 2021.[220]

Table 77 shows the incidence and prevalence as of 05 April 2022 for the US, UK, and EU-27 countries. In the EU and the UK, by 05 April 2022 the total number of confirmed cases had accumulated to over 148 million people, or 28,895 per 100,000 people (from 41 million, or 8074 per 100,000 by 15 August 2021). Across countries in the EU, the number of confirmed cases ranged from 13,859 to 50,185 cases per 100,000 people. Cyprus and Romania reported the lowest incidence rates while Netherlands, Slovenia, and Denmark reported the highest.[219]

In the US, the number of confirmed cases had reached over 81 million (24,482 per 100,000 people) by 05 April 2022.[219] This is an increase from 37 million (11,236 per 100,000) by 15 August 2021.[220]

---

[217] World Health Organization. 2020. Coronavirus Disease 2019 (COVID-19) Situation Report – 11.

[218] Worldometers.info 2022a. Worldometer COVID-19 Data. https://www.worldometers.info/about/. Accessed January 14, 2022

[219] Worldometers.info 2021c. Reported Cases and Deaths by Country or Territory. https://www.worldometers.info/coronavirus/#countrieshttps://www.worldometers.info/coronavirus/#countries. Accessed April 05, 2022.

[220] Worldometers.info 2021b. Reported Cases and Deaths by Country or Territory. https://www.worldometers.info/coronavirus/#countrieshttps://www.worldometers.info/coronavirus/#countries. Accessed August 15, 2021.

Table 81. Incidence, Prevalence, and Mortality of COVID-19 as of 05 April 2022

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	475,374,204	5,988	58,426,026	736	6,124,782	77	7,938,283,964[a]
EU-27	127,222,565	28,544	13,224,809	2,967	1,052,505	236	445,707,924
UK	21,359,681	31,177	1,931,030	2,819	165,780	242	68,511,272
EU-27 + UK	148,582,246	28,895	15,155,839	2,947	1,218,285	237	514,219,196
US	81,867,963	24,482	15,018,006	4,491	1,008,679	302	334,405,890
EU-27 Countries							
Austria	3,912,606	43,012	252,955	2,781	16,061	177	9,096,500
Belgium	3,881,523	33,238	289,217	2,477	30,908	265	11,678,061
Bulgaria	1,141,859	16,653	173,569	2,531	36,608	534	6,856,744
Croatia	1,103,662	27,178	7,321	180	15,634	385	4,060,882
Cyprus	444,174	13,859	318,853	3,617	951	52	1,222,769
Czech Republic	3,838,868	35,731	51,306	478	39,755	370	10,743,816
Denmark	2,924,746	50,185	51,848	890	5,798	99	5,827,966
Estonia	560,233	42,183	69,637	5,243	2,475	186	1,328,099
Finland	907,786	16,339	858,532	15,453	3,254	59	5,555,812
France	26,025,500	39,717	2,267,053	3,460	142,655	218	65,526,762
Germany	21,908,379	26,003	4,369,710	5,186	130,969	155	84,253,677
Greece	3,096,135	29,961	257,121	2,488	27,746	268	10,333,792
Hungary	1,860,159	19,342	97,280	1,012	45,611	474	9,617,343
Ireland	1,474,374	29,286	154,166	3,062	6,799	135	5,034,484
Italy	14,877,144	24,669	1,274,305	2,113	159,909	265	60,305,943
Latvia	804,288	43,483	31,740	1,716	5,657	306	1,849,641
Lithuania	1,033,547	38,918	51,071	1,923	8,925	336	2,655,708
Luxembourg	219,390	34,076	18,113	2,813	1,041	162	643,829
Malta	82,845	18,675	7,969	1,796	649	146	443,605
Netherlands	7,935,106	46,131	1,227,890	7,138	22,037	128	17,201,349
Poland	5,971,998	15,810	522,946	1,384	115,395	305	37,773,933
Portugal	3,604,114	35,527			21,693	214	10,144,581
Romania	2,864,473	15,066	192,684	1,013	65,129	343	19,012,700
Slovakia	1,732,096	31,699	85,628	1,567	19,462	356	5,464,279
Slovenia	978,134	47,038	34,930	1,680	6,512	313	2,079,439
Spain	11,551,574	24,690	530,130	1,133	102,541	219	46,786,531
Sweden	2,487,852	24,368	28,835	282	18,331	180	10,209,679

a. World population based on https://www.worldometers.info/world-population/#:~:text=7.9%20Billion%20(2022),Nations%20estimates%20elaborated%20by%20Worldometer

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested, as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported.[221] Further, as at-home rapid testing kits have become more readily

[221] Worldometers.info 2021d. Worldometer COVID-19 Data. https://www.worldometers.info/coronavirus/about/. Accessed August 24, 2021.

available[222] and formal testing resources reach capacity due to the Omicron variant, the true estimate of cases is estimated to be larger than formally reported counts, the true estimate of cases is estimated to be larger than formally reported counts. The numbers should therefore be interpreted with caution. While there is limited information on number of cases attributable to specific variants, recent case counts are likely to reflect the Omicron variant, which is currently the predominant strain in many countries, including the US[223] Omicron BA1.1 was responsible for 57.3%, BA.2 is responsible for 34.9%, and B1.1.529 was responsible for 7.9% of all SARS-CoV-2 specimens sequenced by the CDC during the week ending 19 March 2022.[223]

The main existing treatment options:

Through 18 June 2022, other COVID-19 vaccines were authorised[224] in the European Union including COVID-19 Vaccine (inactivated, adjuvant), Spikevax (EU/1/20/1507), JCOVDEN (EU/1/20/1525), Vaxzevria (EU/1/21/1529), Nuvaxovid (EU/1/21/1618).

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[225,226,227,228] 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.[228] One recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic.[228] The most common symptoms of

[222] 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

[223] CDC (2022). Variant Proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 24 March 2022.

[224] According to the Union Register of Medicinal Products https://ec.europa.eu/health/documents/community-register/html/ Accessed on 20 July 2022.

[225] Pollock A M, Lancaster J. Asymptomatic transmission of COVID-19. BMJ 2020; 371:m4851 doi:10.1136/bmj.m4851.

[226] 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.

[227] 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.

[228] 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.

COVID-19 are fever, cough, and shortness of breath for both children and adults.[229,230] 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%.[231]

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.[232,233] 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.[233] 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.[233,234]

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 22 March 2022, there were 4,580,996 total hospital admissions for patients with confirmed COVID-19 in the US.[235] For the week ending 20 March 2022, 9.3 per 100 000 population (country range: 2.7–42.8) were hospitalised due to COVID-19 in 17 countries of the EU/EEA with available data.[236] As of 24 March 2022, 0.1% -1.5% of children who tested positive for

---

[229] 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.

[230] 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.

[231] 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

[232] 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.

[233] 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.

[234] 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

[235] CDC 2021i. COVID Data Tracker New Hospital Admissions. https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions. Accessed 25 March 2022.

[236] ECDC (2022). ECDC Country Overview Report: Week 11, 2022. https://www.ecdc.europa.eu/en/COVID-19/country-overviews. Accessed 27 March 2022.

COVID-19 have been hospitalised (for any diagnosis) based on data reported from 25 states and New York City reporting, and 0.00%-0.01% of children with COVID-19 have died based on data reported from 46 states, New York City, Puerto Rico and Guam.[237]

The most common symptoms in patients are fever (42-80%), shortness of breath (35-71%), fatigue (33-62%), cough (77-84%), chills (63%), myalgias (63%), headache (59%), and diarrhea (33%)[238,239,240,241] COVID-19 patients also commonly experience gustatory disorders (44%) and olfactory disorders (53%).[242] 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.[240] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[243,244,239] with 31% of children hospitalised experiencing severe COVID-19 that necessitates intensive care or invasive ventilation or ends in death. Risk factors for severe COVID-19 in hospitalised children include presence of a comorbid condition, younger age, and male sex.[245] More than 75% of patients hospitalised with COVID 19 require supplemental oxygen.[246]

---

[237] 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 26 March 2022.

[238] Gold 2020b. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and clinical outcomes of adult patients hospitalised with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020;69(18):545-50

[239] Hur K, Price CPE, Gray EL, et al. Factors associated with intubation and prolonged intubation in hospitalised patients with COVID-19. [published correction appears in Otolaryngol Head Neck Surg. 2020 Jul;163(1):NP1]. Otolaryngol Head Neck Surg 2020;163(1):170-8.

[240] Burke RM, Killerby ME, Newton S, et al. Case Investigation Form Working Group. Symptom profiles of a convenience sample of patients with COVID-19 - United States, January-April 2020. MMWR Morb Mortal Wkly Rep 2020; 69(28):904-8. doi: 10.15585/mmwr.mm6928a2. PMID: 32673296; PMCID: PMC7366851.

[241] Nowak B, Szymański P, Pańkowski I, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med 2020;130(5):407-11.

[242] Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2020 Jul;163(1):3-11. doi: 10.1177/0194599820926473. Epub 2020 May 5. PMID: 32369429.

[243] 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.

[244] 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

[245] Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA network open. 2021;4(4):e215298

[246] 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.

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.[232] In 12 countries of the EU/EEA with available data, 0.7 per 100,000 population (country range 0.1-4.1) were in the ICU due to COVID-19 for the week ending 20 March 2022.[247],[248] A recent meta-analysis found that, of patients <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.[226] A study of 82 cases in three pediatric hospitals noted that older children and those with higher body mass index or multiple comorbidities were more likely to receive respiratory support.[249]

Mortality

As of 27 March 2022, there were 974,277 deaths reported in the US for all age groups among 79,766,087 individuals positive for COVID-19 (1.2% of cases)[250] As of the week ending on 20 March 2022, the mortality rate was 29.6 per million population (country range: 7.1–119.0) in the EU.[247,251] As of 27 March 2022, the UK has seen 165,046 deaths from COVID-19 in all age groups among 20,848,913 cases (0.8% of cases).[252] According to a recent meta-analysis of paediatric studies published through October 2020, the mortality for pediatric patients is 0.1-2%[253,226] 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. [254]

[247] ECDC (2022)- country overview report. ECDC Country Overview Report: Week 11, 2022. https://www.ecdc.europa.eu/en/COVID-19/country-overviews. Accessed 27 March 2022.

[248] ECDC 2021f. Situation Report Week 37 Individual Indicators. https://covid19-surveillance-report.ecdc.europa.eu/#individual-indicators-week-37. Accessed 23 September 2021

[249] 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.

[250] COVID Data Tracker as of 27Mar2022. https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed on 27 March 2022.

[251] ECDC 2021d. Situation Report. https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea. Accessed on 17 August 2021.

[252] JHU COVID Map 2022. https://coronavirus.jhu.edu/ united-kingdom. Accessed on 27 March 2022.

[253] Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. MMWR Morb Mortal Wkly Rep. 2021 Jan 22;70(3):88-94. doi: 10.15585/mmwr.mm7003e1. PMID: 33476314; PMCID: PMC7821770.

[254] 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.

Mortality data are also presented from Worldometers, an independent organisation that publishes current, reliable COVID-19 statistics online.[218] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 05 April 2022, the overall SARS-CoV-2 mortality for the EU + UK was 1,218,285 deaths, or 237 per 100,000 people. Reported mortality among EU countries and the UK ranged from 52 to 534 deaths per 100,000. Cyprus and Finland reported the lowest mortality; Croatia, Hungary, and Bulgaria reported the highest.[219]

In the US, as of 05 April 2022, the mortality was 1,008,697 deaths (2302 per 100,000 people). Mortality in the US was higher than that of the UK (242 per 100,000).[219]

Overall reported mortality among hospitalisedhospitalised COVID-19 patients varies from 12.8% to 26% in the EU and UK and US[244,255,256,257]

Complications of COVID-19 and Post-acute COVID

Recent evidence has shown that a range of persistent symptoms can remain long after the acute SARS-CoV-2 infection. This condition has been called long COVID or post-acute COVID by some recognised research institutes; a universally accepted definition of long COVID has yet to be established.

Studies have shown that long COVID can affect the whole spectrum of people with COVID-19, from those with very mild acute disease to the most severe forms.

Studies around the world have reported various incidence rates for long COVID with different follow-up examination times after the acute infection, including 76% of people at 6 months, 32.6% at 60 days, 87% at 60 days, and 96% at 90 days. These finding are not fully corroborative, but they show that a substantial proportion of people who have had COVID-19 may develop long COVID.[258]

[255] Gold JAW, Rossen LM, Ahmad FB, et al. Race, ethnicity, and age trends in persons who died from COVID-19 - United States, May-August 2020. MMWR Morb Mortal Wkly Rep 2020; 69(42):1517-21.

[256] Jones S, Mason N, Palser T, et al. Trends in risk-adjusted 28-day mortality rates for patients hospitalised with COVID-19 in England. J Hosp Med. Published Online First February 5, 2021. DOI: 10.12788/jhm.3599.

[257] Rao GG, Allen A, Papineni P, et al. London North West Healthcare Trust COVID-19 Research Group. Cross-sectional observational study of epidemiology of COVID-19 and clinical outcomes of hospitalised patients in North West London during March and April 2020. BMJ Open 2021;11(2):e044384. doi: 10.1136/bmjopen-2020-044384. PMID: 33602712; PMCID: PMC7896375.

[258] Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. BMJ, 10.1136/bmj.n1648 on 26 July 2021.

Assuming at least 10% of COVID-19 survivors develop long COVID, it is estimated that 5 million people are facing long COVID globally.[259]

This illness is poorly understood as it affects COVID-19 survivors at all levels of disease severity, even younger adults, children, and those not hospitalised. While the precise definition of long COVID may be lacking, the most common symptoms reported in many studies are fatigue and dyspnoea that last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues.

Presently, there is limited literature discussing the possible pathophysiology, risk factors, and treatments in long COVID, which the current review aims to address. In brief, long COVID may be driven by long-term tissue damage (e.g., lung, brain, and heart) and pathological inflammation (e.g., from viral persistence, immune dysregulation, and autoimmunity). The associated risk factors may include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific biomarkers (e.g., D-dimer, CRP, and lymphocyte count), although more research is required to substantiate such risk factors.[259]

Several studies are evaluating a potential impact of SARS Cov-2 vaccination on long COVID:

Ayoubkhani et al. described that a first dose of COVID-19 vaccine was associated with a reduction in long COVID symptoms 12.8% decrease (95% confidence interval −18.6% to −6.6%, P<0.001), and evidence suggested a sustained improvement after a second dose, with an initial 8.8% decrease (95% confidence interval −14.1% to −3.1%, P=0.003) in the odds of long COVID, with a subsequent decrease by 0.8% per week (−1.2% to −0.4% per week, P<0.001), at least over the median follow-up of 67 days in this study.

No evidence was found of differences in this relationship by sociodemographic characteristics, health related factors, vaccine type, or duration from infection to vaccination.

Although causality cannot be inferred from this observational evidence, vaccination may contribute to a reduction in the population health burden of long COVID.[260]

Furthermore, Kuodi et al.[261] showed that two doses of BNT162b2 vaccine reduced the risk of the most common long COVID symptoms after COVID-19 infection, in a cross-sectional study preformed between 15 March 2020–15 November 2021. They found that patients who

[259] Yung SJ. Long COVID or post-COVID-19 syndrome:putative pathophysiology, risk factors, and treatments. Infectious diseases 2021; VOL 0, No. 0, 1-18.

[260] Ayoubkhani D, Bermingham C, Pouwels KB, et al Trajectory of long covid symptoms after COVID-19 vaccination: community based cohort study. 10.1136/bmj-2021-069676 on 18 May 2022.

[261] Kuodi P, et al. medRxiv. Published online 17 January 2022. doi:10.1101/2022.01.05.22268800.

received 2 doses of BNT162b2 were 54% to 82% less likely to report 7 of the 10 most commonly reported symptoms compared with unvaccinated patients (all P<0.04).

Post COVID has also been described in children, a national survey in the UK found 7-8% of children with COVID-19 reported continued symptoms >12 weeks.[262]

Long COVID can appear after mild to severe infections, and after MIS-C. Most common symptoms: similar to adults and include fatigue, headache, insomnia, trouble concentrating, muscle and joint pain, and cough. Impact on quality of life: limitations of physical activity, feeling distressed about symptoms, mental health challenges, decreased school attendance/participation.

Post-COVID conditions may be less likely to occur after vaccine breakthrough in adolescents.[263,264]

Persons who were previously vaccinated were less likely to have symptoms between 12 and 20 weeks after infection compared to persons who were unvaccinated (OR 0.22; 95% 0.20, 0.25) with a lower occurrence of post-COVID conditions after infection compared to persons who were unvaccinated.[263,264]

Further research is needed, but vaccination may contribute to a reduction in the population health burden of long COVID.

18.2. Benefit-Risk Analysis Evaluation

Based on the safety data presented in Section 16 and the benefits presented in Section 17, this section presents an overall qualitative evaluation of the benefit risk analysis of BNT162b2 in prevention of COVID-19 infection. With respect to benefit, the nature, clinical importance, duration, efficacy profile, and pharmacokinetic benefits of BNT162b2 were considered. With respect to the risks, data from clinical trials, post-marketing, and literature sources were considered as well as important potential and identified risks, if applicable.

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

[262] Office for National Statistics United Kingdom. (2021) Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021.

[263] Simon et al. Preprint posted online 18 November 2021. MedRxiv. doi:10.1101/2021.11.17.21263608.

[264] Tarquetet al. *Brain Behav Immun*. 2022;103:154-162.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

Non-interventional (observational) study data:

a) There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.

b) Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also inherent limitations.

Post-marketing data:

a) Reports originate from multiple sources (consumer and healthcare professional) and they can be poorly characterised from a medical perspective.

b) Limited or incomplete information is common, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.

c) Difficult to 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 82.

Based on pharmacovigilance monitoring activities, there has been no new safety information contributing importantly to the risks of BNT162b2.

Table 82. 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.	The risk is communicated through the CDS, Sections 4.4 *Special warnings and precautions for use*, 4.8 *Undesirable effects*, Appendix A and Appendix B and in the EU SmPC, Sections 4.4 *Special warnings and precautions for use* and 4.8 *Undesirable effects*. It is being monitored through routine pharmacovigilance. 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.	During the reporting period an unpublished presentation including significant information on myocarditis was reviewed. Please refer to Section 11 *Literature* for details.	The risk is communicated through the CDS in the Section 4.4 *Special warnings and precautions for use* and EU SmPC in the Section 4.8 *Undesirable effects*. It is also included as an Important identified risk in the EU RMP and in the US PVP. Considering the accumulating data from post-authorisation use of the vaccine, myocarditis and pericarditis have been added as ADRs in the Section 4.8 *Undesirable effects*, in Appendix A and Appendix B of the CDS v. 14.0, made effective on 26 July 2022, after the DLP. .
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/effectiveness data for BNT162b2, the overall benefit-risk profile of BNT162b2 remains favourable for all age groups in which it is authorised.

Table 83. 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 and immunogenicity 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 in addition to those in place are warranted at this time.

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.