PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 02-DEC-2021

Date of Superseded CDS: 19-Oct-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 9

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2,72]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use): This is a multidose vial and must be diluted before use. One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute): This is a multidose vial. One vial (2.25 mL) contains 6 doses of 0.3 mL (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years): This is a multidose vial and must be diluted before use. One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.2 mL) contains 10 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3,72]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use): Concentrate for dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute): Dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years): Concentrate for dispersion for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 5 years of age and older.[4,49,73]

4.2. Posology and method of administration

Posology

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*
Or
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

Individuals 12 years of age and older

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) are administered intramuscularly as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

A booster dose (third dose) of TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.[71]

Doses of TRADENAME (Dilute Before Use) concentrate for dispersion for injection (30 micrograms/dose) and TRADENAME (Do Not Dilute) dispersion for injection (30 micrograms/dose) vaccine are considered interchangeable.

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) intended for individuals ages 12 years and older cannot be used for individuals age 5 years to <12 years.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series or the booster dose (third dose) has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series and for any additional doses.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) 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.[73]

TRADENAME (for age 5 years to <12 years) cannot be used in individuals 12 years of age and older.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 5 years of age have not yet been established. The safety and effectiveness of a booster dose (third dose) of TRADENAME 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.[71]

Geriatric population

Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50] The safety and effectiveness of a booster dose (third dose) of TRADENAME in individuals 65 years of age and older is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

After dilution, vials of TRADENAME (Dilute Before Use) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead -volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

Vials of TRADENAME (Do Not Dilute) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

After dilution, vials of TRADENAME (for age 5 years to <12 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 5 through <12 years of age

Low dead-volume syringes and/or needles can be used to extract 10 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

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.[69]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through less than 12 years of age.[73]

Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose (third dose) of TRADENAME approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.[71]

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age – after 2 doses

In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have been followed for at least 2 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Children 5 through <12 years of age – after 2 doses[73]

In an analysis of Study 3 Phase 2/3, 2,268 participants (1,518 TRADENAME 10 mcg; 750 placebo) were 5 through <12 years of age. Of these, 2,158 (95.1%) (1,444 TRADENAME 10 mcg and 714 placebo) participants have been followed for at least 2 months after the second dose. The safety evaluation in Study 3 is ongoing.

The most frequent adverse reactions in children 5 through <12 years of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

Participants 18 years of age and older – after booster dose (third dose)[71]

A subset from Study 2 Phase 2/3 participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose (third dose) of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a]
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.[71]

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥30 kg/m^2)
   - Diabetes (Type 1, Type 2, or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	**TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]

First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	**TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* 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.

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta = r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 10 and Table 11.

Table 10. 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[55]

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)
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 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.

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 confidence interval (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 $\geq 95^{th}$ percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥ 30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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)

Table 11. 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[56]

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]
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)

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.

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 confidence interval (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 $\geq$30 kg/m^2 or BMI $\geq$95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI $\geq$30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19 - after 2 doses

Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);

- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all-available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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 – after 2 doses

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cut-off date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

Immunogenicity in children 5 through <12 years of age – after 2 doses[73]

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomized, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no

serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 14.

Table 14: 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[73]

		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 15.

Table 15: 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[73]

		Pfizer-BioNTech COVID-19 Vaccine		5 Through <12 Years / 16 Through 25 Years	
		Study 3 10 mcg/Dose 5 Through < 12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253		
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.

Immunogenicity in participants 18 years of age and older – after booster dose (third dose)[71]

Effectiveness of a booster dose (third dose) of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose (third dose). In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose (third dose) compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose (third dose), based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 16 and Table 17).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose (third dose) to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 98.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: -0.7%, 3.7%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >-10%).

Table 16: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	210	2476.4 (2210.1, 2774.9)	753.7 (658.2, 863.1)	3.29 (2.76, 3.91)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. 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.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.
e. 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.

Table 17: Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[e])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	198	197 99.5 (97.2, 100.0)	194 98.0 (94.9, 99.4)	1.5 (-0.7, 3.7)	Y

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.
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 after receipt of booster dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster dose were included in the analysis.
a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.
g. 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.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3,74]

*[Editorial Guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose.**]*

TRADENAME (Dilute Before Use)
(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose.**]*

TRADENAME (Do Not Dilute)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose.**]*

TRADENAME (for age 5 years to <12 years)

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Tromethamine
Tromethamine hydrochloride
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

*[Editorial Guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)

Unopened vial

9 months at -90 °C to -60 °C.[63,70]

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for

injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute)[75]

Unopened vial

9 months when stored at -90 °C to -60 °C.[79]

TRADENAME (Do Not Dilute) may be received frozen at -90 °C to -60 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks within the 9month shelf life.[79]

Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at temperatures up to 30 °C.

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following first puncture.[77]

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 8 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)[75]

Unopened vial

9 months when stored at -90 °C to -60 °C.[79]

TRADENAME (for age 5 years to <12 years) may be received frozen at -90 °C to -60 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks within the 9-month shelf life.[79]

Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at temperatures up to 30 °C.

Vaccine may be stored at temperatures between 8 °C to 30 °C for up to 24 hours, including any time at these temperatures following dilution.[77]

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

6.4. Special precautions for storage[2,25,75]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)

TRADENAME (Do Not Dilute) and TRADENAME (for age 5 years to <12 years) can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the original expiry date (EXP). Alternatively, the vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after "EXP".

The vaccine may be received frozen at -90 °C to -60 °C or at -25 °C to -15 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt. Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at room temperature (up to 30 °C).

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

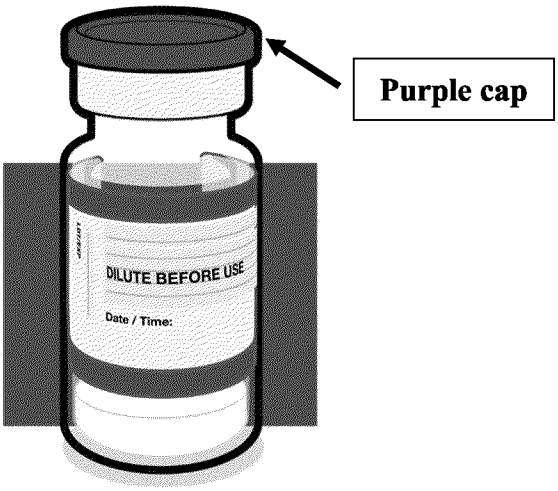
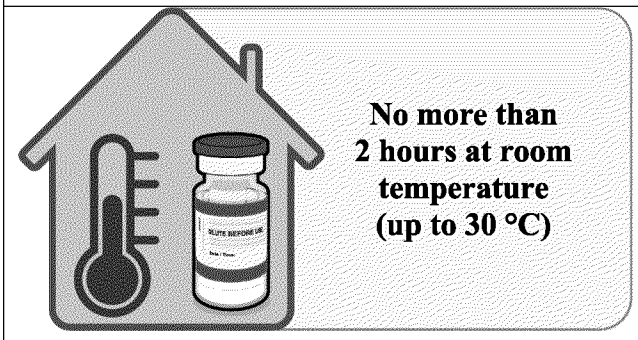
Information to be provided by local subsidiary.

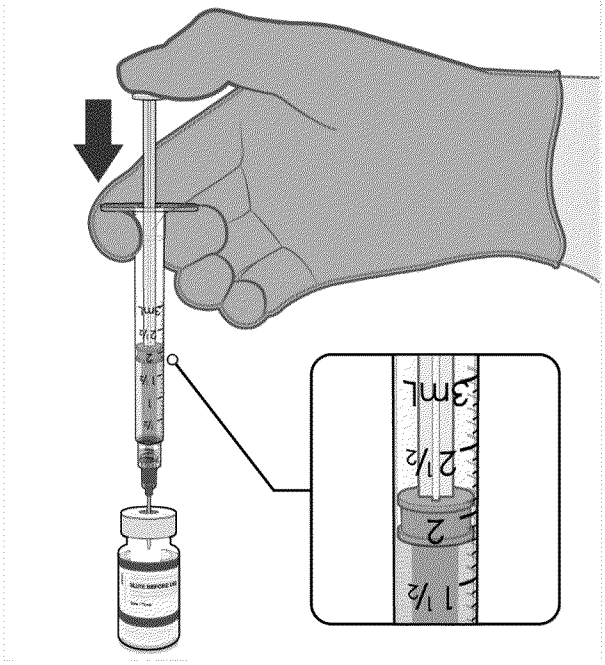
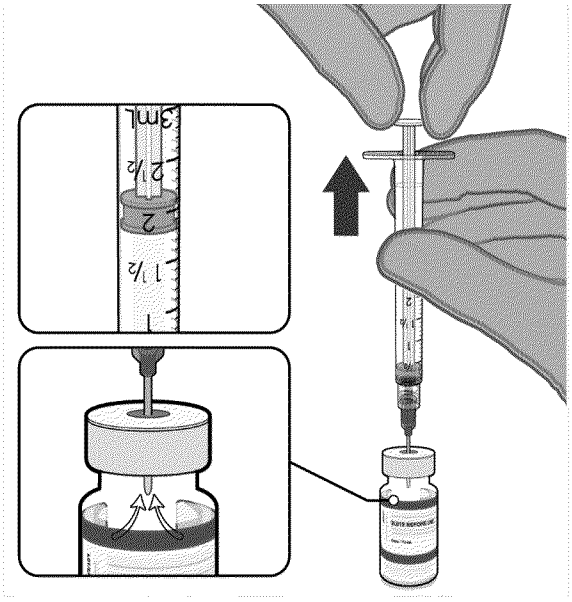
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63,75,77,78]

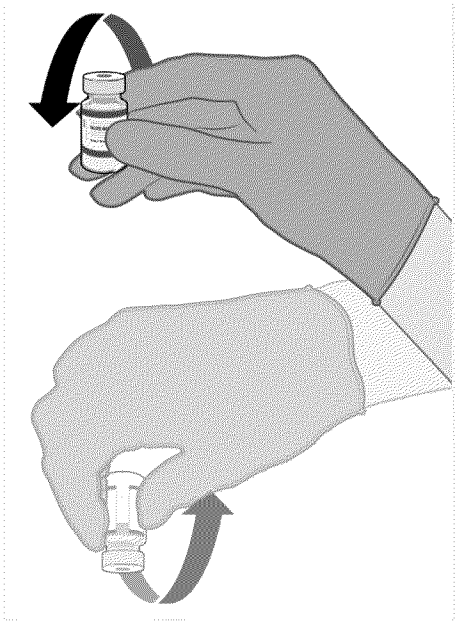
Handling instructions

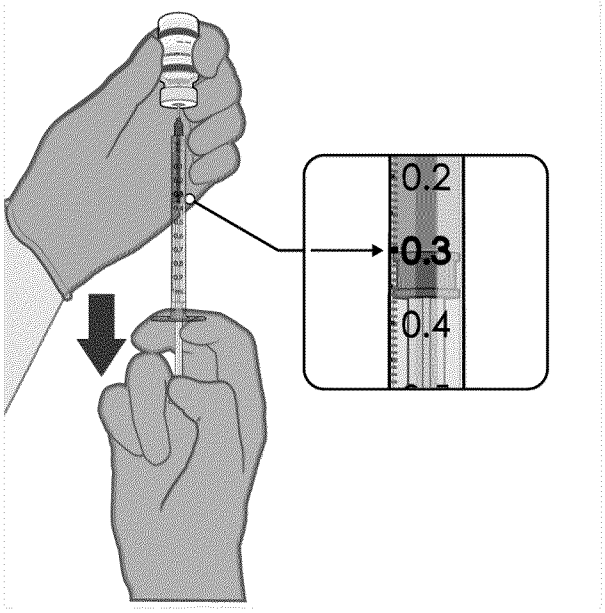
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

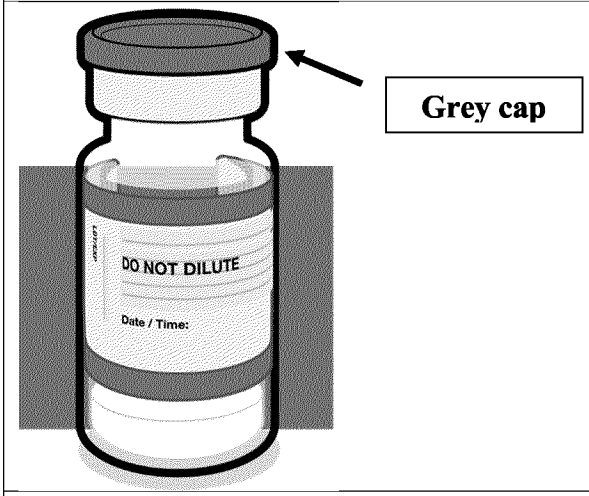
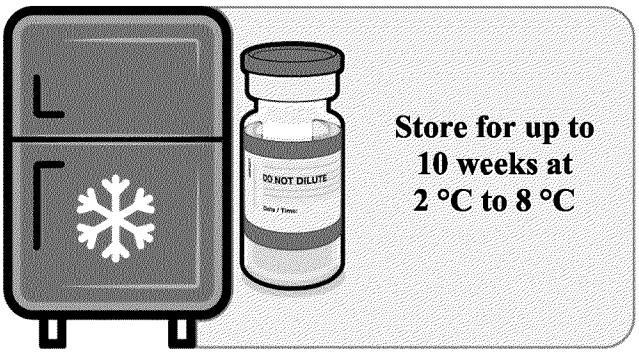
<table>
<tr><th colspan="2">TRADENAME (Dilute Before Use)</th></tr>
<tr><td colspan="2">DOSE VERIFICATION</td></tr>
<tr><td> 
</td><td>Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years).</td></tr>
<tr><td colspan="2">THAWING PRIOR TO DILUTION</td></tr>
<tr><td> 
</td><td>• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
• The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf life at 2 °C to 8 °C, up to 12 hours may be used for transportation.
• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
• Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.</td></tr>
</table>

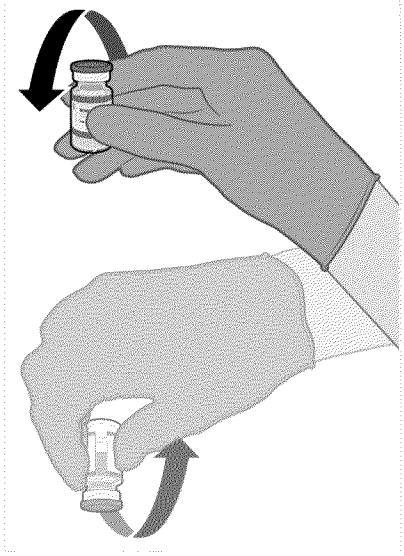
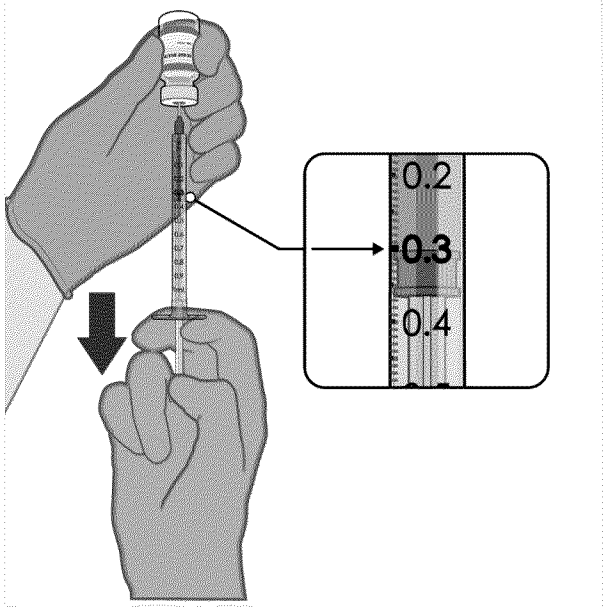
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.

TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ℃ to 30 ℃ and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

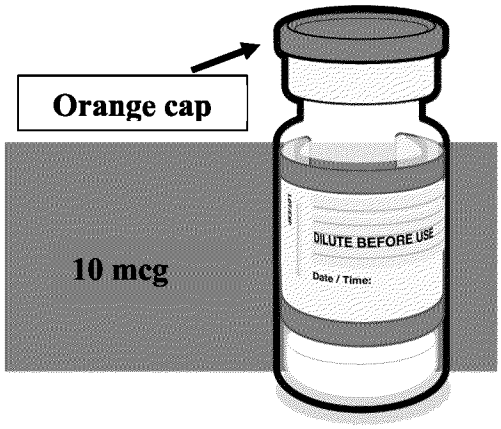
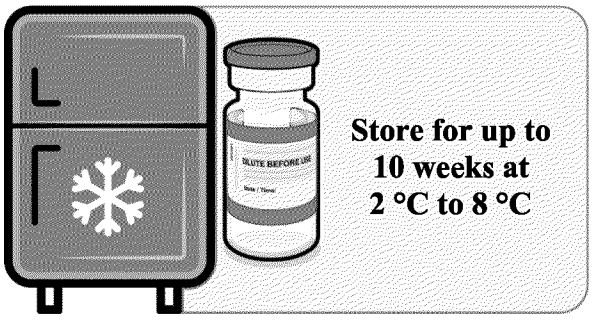
TRADENAME (Dilute Before Use)	
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL diluted vaccine**	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead-volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Discard any unused vaccine within 6 hours after dilution.

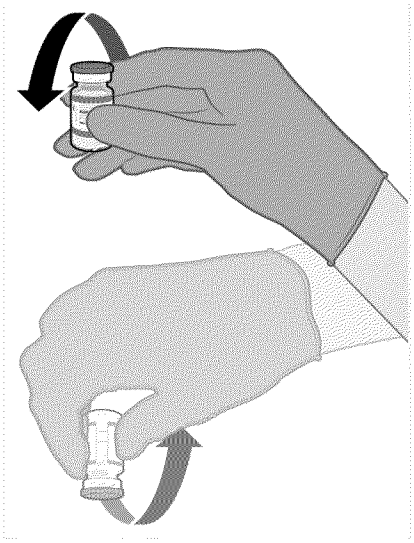
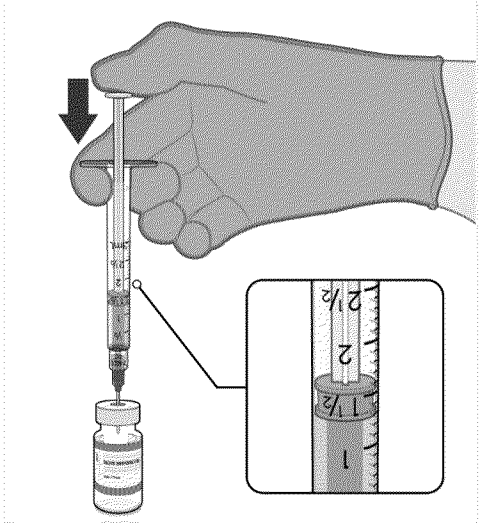
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

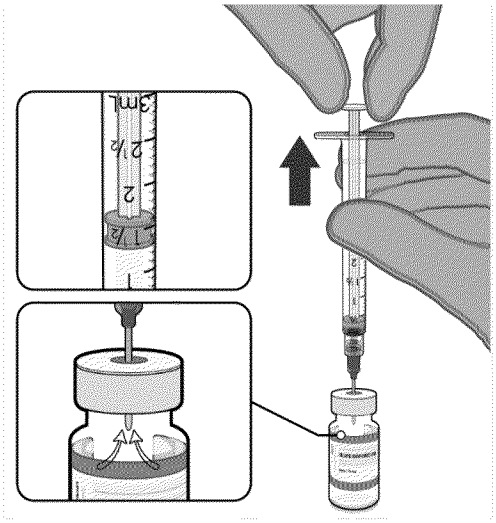
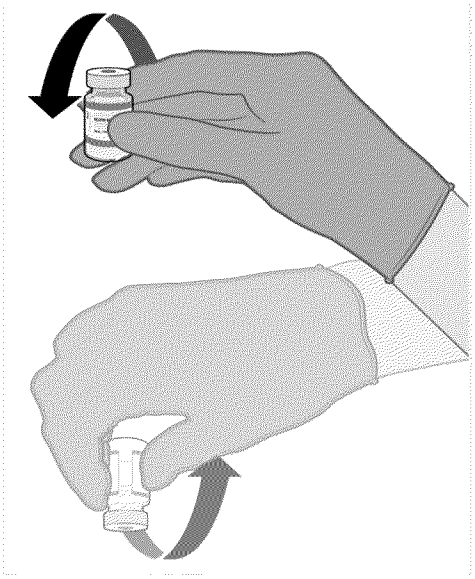
TRADENAME (Do Not Dilute)	
DOSE VERIFICATION	
	• Verify that the vial has a grey plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use. • Update the expiry date on the carton. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C. • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

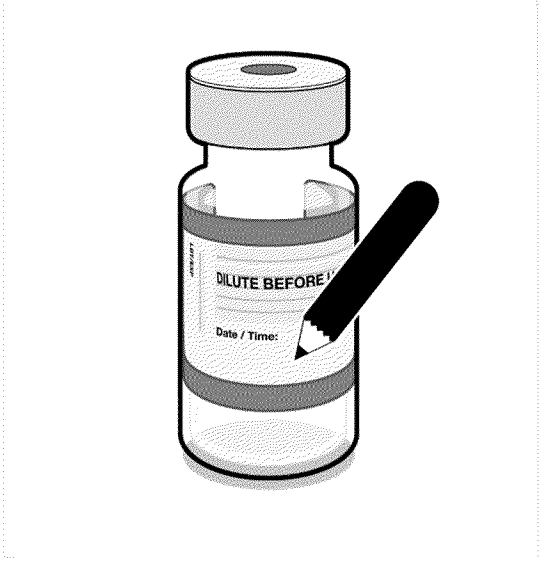
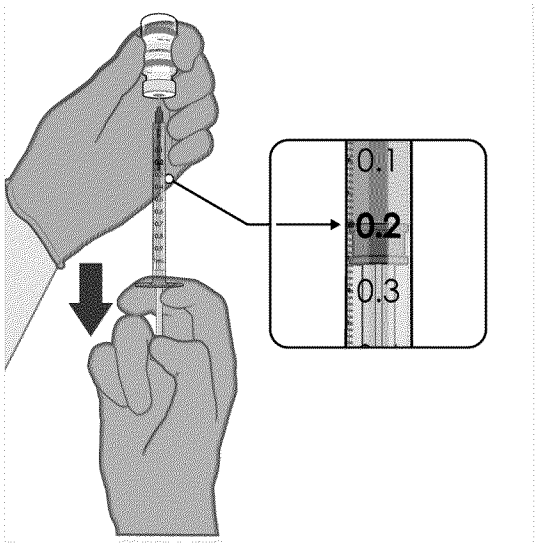
TRADENAME (Do Not Dilute)	
 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration are present.
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Discard any unused vaccine 12 hours after first puncture. Record the appropriate date/time on the vial.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose.**]*

TRADENAME (for age 5 years to <12 years)	
DOSE VERIFICATION	
	• Verify that the vial has an orange plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C. • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
DILUTION	
 **1.3 mL of 0.9% sodium chloride**	• The thawed vaccine must be diluted in its original vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 °C to 30 °C and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF TRADENAME	
 **0.2 mL diluted vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.2 mL of TRADENAME for children age 5 to 11 years. Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial. • Each dose must contain 0.2 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume. • Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), October 2021
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

– Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): 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
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. 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
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021
79. Module 3.2.P.8.1 Stability Summary and Conclusions – Tris-Sucrose, November 2021

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and nutrition disorders	Decreased appetite	39/21926 (0.2%)[a]
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)[a]
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis	31/21926 (0.1%)[a]
	Night sweats	17/21926 (0.1%)[a]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)[a]

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. A higher frequency of lymphadenopathy (5.2% vs. 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Cutoff date: 17June2021).

e. These adverse reactions were identified in the post-authorization period.

f. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age following the 2-dose series (13 March 2021 Data Cut-off Date) Table A-1: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see **Error! Reference source not found.**): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the 12 through 15 years of age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria and rash.

Table B-3. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Rash[a]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea[a] Vomiting[a]	Nausea			
Skin and subcutaneous tissue disorders						
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age 1 month after Dose 2 (Cutoff date: 13March2021) (see Table B-1): angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Table B-4. ADRs by System Organ Class and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness within each Frequency Category and System Organ Class: Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria[a,b]; Pruritus[a,b]; Rash[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea;[a] Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Injection site swelling; Injection site redness	Pyrexia	Malaise			

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see Table B-1): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, and rash

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[65]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

PRODUCT NAME: COVID-19 mRNA Vaccine

CDS Version History:

CDS version number	Effective date	Sections changed
8	19-Oct-2021	4.2 Posology and method of administration 4.8 Undesirable effects 5.1 Pharmacodynamic properties Appendix A Appendix B
7	08-Sept-2021	4.8 Undesirable effects Appendix A Appendix B
5	14-July-2021	4.4 Special warnings and precautions for use

1. NAME OF THE MEDICINAL PRODUCT

No safety changes during the reporting period

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

No safety changes during the reporting period

3. PHARMACEUTICAL FORM

No safety changes during the reporting period

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

No safety changes during the reporting period

4.2 Posology and method of administration

Version 8	Effective Date: 19-Oct-2021	PfLEET: 2021-0072943
Safety/Non-safety: Safety **Content change:** Posology		
*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose.**]* *Or* *[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose.**]*		

Individuals 12 years of age and older

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) are ~~is~~ administered intramuscularly ~~after dilution~~ as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

A booster dose (third dose) of TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.[71]

Doses of TRADENAME (Dilute Before Use) concentrate for dispersion for injection (30 micrograms/dose) and TRADENAME (Do Not Dilute) dispersion for injection (30 micrograms/dose) vaccine are considered interchangeable.

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) intended for individuals ages 12 years and older cannot be used for individuals age 5 years to <12 years.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series or the booster dose (third dose) has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series and for any additional doses.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose.**]*

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) 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.[73]

TRADENAME (~~F~~for age 5 years to <12 years) cannot be used in individuals 12 years of age and older.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

[…]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle ~~after dilution~~.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose.**]*

After dilution, vials of TRADENAME (Dilute Before Use) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose.**]*

Vials of TRADENAME (Do Not Dilute) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.

- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose.**]*

After dilution, vials of TRADENAME (for age 5 years to <12 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 5 through <12 years of age

Low dead-volume syringes and/or needles can be used to extract 10 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3 Contraindications

No safety changes during the reporting period

4.4 Special warnings and precautions for use

Version 5	Effective Date: 14-July-2021	PfLEET: 2021-0071083

Safety/Non-safety: Safety

Content change:

General recommendations

[…]

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.[69]

[…]

4.5 Interaction with other medicinal products and other forms of interaction
No safety changes during the reporting period

4.6 Fertility, pregnancy and lactation
No safety changes during the reporting period

4.7 Effects on ability to drive and use machines
No safety changes during the reporting period

4.8 Undesirable effects

Version 8	Effective Date: 19-Oct-2021	PfLEET: 2021-0072943

Safety/Non-safety: Safety

Content change:

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5~~12~~ years of age and older in 3~~2~~ clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through less than 12 years of age.[73]

[…]

Adolescents 12 through 15 years of age – after 2 doses

In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have

been followed for at least 2 months after the second dose ~~of TRADENAME~~.[41,42] The safety evaluation in Study 2 is ongoing.

[…]

Children 5 through <12 years of age – after 2 doses[73]

In an analysis of Study 3 Phase 2/3, 2,268 participants (1,518 TRADENAME 10 mcg; 750 placebo) were 5 through <12 years of age. Of these, 2,158 (95.1%) -(1,444 TRADENAME 10 mcg and 714 placebo) participants have been followed for at least 2 months after the second dose. The safety evaluation in Study 3 is ongoing.

The most frequent adverse reactions in children 5 through <12 years of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

[…]

Version 7	Effective Date: 08-Sep-2021	PfLEET: 2021-0072028

Safety/Non-safety: Safety

Content change:
Summary of safety profile

[…]

Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose (third dose) of TRADENAME approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.[71]

Participants 16 years of age and older – after 2 doses
[…]
The most frequent adverse reactions in participants 16 years of age and older that received 2 doses (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] […]

Adolescents 12 through 15 years of age – after 2 doses
[…]

The most frequent adverse reactions in adolescents 12 through 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Participants 18 years of age and older – after booster dose (third dose)[71]
A subset from Study 2 Phase 2/3 participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose (third dose) of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a.]
[…]	

a. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.[71]

4.9 Overdose
No safety changes during the reporting period

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Version 8	Effective Date: 19-Oct-2021	PfLEET: 2021-0072943

Safety/Non-safety: Safety

Content change:

[…]

Immunogenicity in children 5 through <12 years of age – after 2 doses[73]

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomized, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as

achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 14.

Table 14: 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[73]

		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 15.

Table 15: 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[73]

		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

~~Note:~~ * 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.

[…]

5.2 Pharmacokinetic properties
No safety changes during the reporting period

5.3 Preclinical safety data
No safety changes during the reporting period

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
No safety changes during the reporting period

6.2 Incompatibilities
No safety changes during the reporting period

6.3 Shelf life
No safety changes during the reporting period

6.4 Special precautions for storage
No safety changes during the reporting period

6.5 Nature and contents of container
No safety changes during the reporting period

6.6 Special precautions for disposal and other handling
No safety changes during the reporting period

7. REFERENCES

All new references can be found in the References section of the affected CDS.

PRODUCT NAME: COVID-19 mRNA Vaccine

Appendix A. Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)

Version 8	Effective Date: 19-Oct-2021	PfLEET: 2021-0072943

Safety/Non-safety: Safety

Content change:

Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 to <12 Years of Age (06 September -2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021)

b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).

c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).

d. These adverse reactions were identified in the post-authorization period.

e. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see **Error! Reference source not found.**): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.

Version 7	**Effective Date: 08-Sep-2021**	**PfLEET: 2021-0072028**

Safety/Non-safety: Safety

Content change:

Table A.3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]

	Chills	84/289- (29.1%)[c]
	Pyrexia	25/289- (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. A higher frequency of lymphadenopathy (5.2% vs. 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population- (Cutoff date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Cutoff date: 17June2021).

e. These adverse reactions were identified in the post-authorization period.

f. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age following the 2-dose series (13 March 2021 Data Cut-off Date) Table 1:-angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Appendix B. Adverse Drug Reactions (ADRs) and Council for International Organizations of Medical Sciences (CIOMS) Frequency Categories Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC

Version 8	Effective Date: 19-Oct-2021	PfLEET: 2021-0072943

Safety/Non-safety: Safety

Content change:

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. ~~Please note that t~~The following events were not reported in the 12 through 15 years of age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

b. The following events are categorized as hypersensitivity reactions: urticaria and rash.

Table B-3. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[*,64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Rash[a]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea[a] Vomiting[a]	Nausea			
Skin and subcutaneous tissue disorders						
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. -These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age 1 month after Dose 2 (Cutoff date: 13March2021) (see Table B-1): angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Table B-4. ADRs by System Organ Class and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness within each Frequency Category and System Organ Class: Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria[a,b]; Pruritus[a,b]; Rash[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					

Gastrointestinal disorders		Diarrhea;[a] Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Injection site swelling; Injection site redness	Pyrexia	Malaise			

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see Table B-1): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, and rash

Version 7	Effective Date: 08-Sep-2021	PfLEET: 2021-0072028

Safety/Non-safety: Safety

Content change:

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. Please note that the following events were not reported in the 12 through 15 years of age group in Study C4591001 (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria and, ~~pruritus,~~ rash~~, and angioedema~~.

Table B-3. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Rash[a]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea[a] Vomiting[a]	Nausea			
Skin and subcutaneous tissue disorders						
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

o These adverse reactions were identified in the post-authorization period.

PRODUCT NAME: COVID-19 mRNA Vaccine

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

No safety changes during the reporting period

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 19-MAY-2021

Date of Superseded CDS: 20-Apr-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 4

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2]

This is a multidose vial and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see Section 6.6.

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3]

Concentrate for solution for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 12 years of age and older.[4,49]

4.2. Posology and method of administration

Posology

Individuals 12 years of age and older
TRADENAME is administered intramuscularly after dilution as a series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

There are no data available on the interchangeability of TRADENAME with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population
The safety and efficacy of TRADENAME in individuals under 12 years of age have not yet been established.

Geriatric population
Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

After dilution, vials of TRADENAME contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 12 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12]

Participants 16 years of age and older
In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age
In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have been followed for at least 2 months after the second dose of TRADENAME.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older
In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)

- Obesity (body mass index ≥30 kg/m^2)
- Diabetes (Type 1, Type 2, or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	**TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).

Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* 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.

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 Tables 10 and 11.

Table 10. 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[55]

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)
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)

Table 10. 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[55]

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]
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 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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 11. 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[56]

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 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.

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 confidence interval (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 $\geq$30 kg/m^2 or BMI $\geq$95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI $\geq$30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3]

(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

Unopened vial

6 months at -90 °C to -60 °C.

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage[2,25]

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

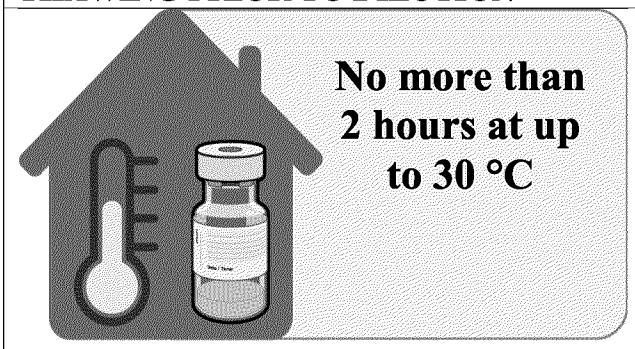
6.5. Nature and contents of container

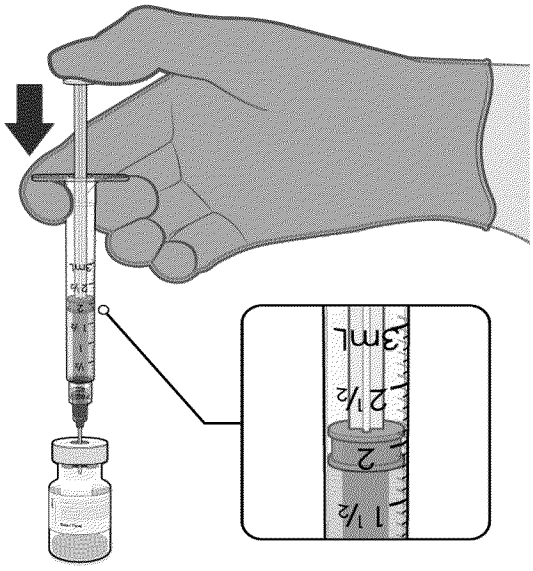
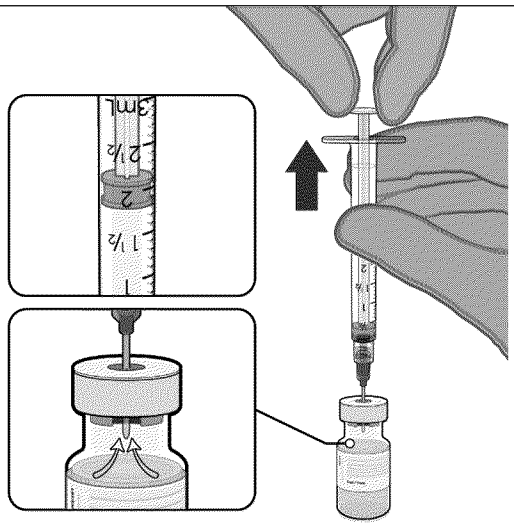
Information to be provided by local subsidiary.

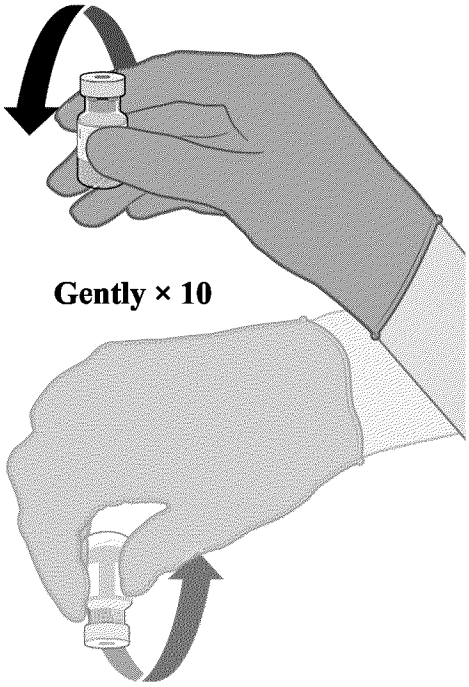
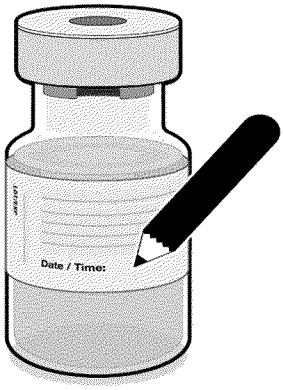
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63]

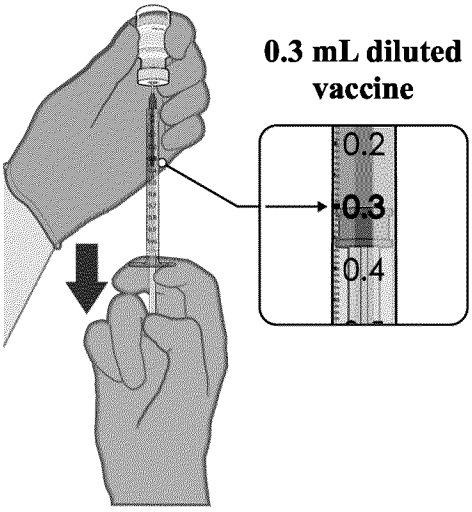
Handling instructions

TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

THAWING PRIOR TO DILUTION	
	• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use. • The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation. • Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.

	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY	
	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Discard any unused vaccine within 6 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, April 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), May 2021

65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021

68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and Nutrition disorders	Decreased appetite	39/21926 (0.2%)
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis	31/21926 (0.1%)
	Night sweats	17/21926 (0.1%)
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects >16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and Nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. Please note that the following events were not reported in the 12 through 15 years of age group in Study C4591001 (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[65]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 14-JUL-2021

Date of Superseded CDS: 19-May -2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 5

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2]

This is a multidose vial and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see Section 6.6.

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3]

Concentrate for solution for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 12 years of age and older.[4,49]

4.2. Posology and method of administration

Posology

Individuals 12 years of age and older
TRADENAME is administered intramuscularly after dilution as a series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

There are no data available on the interchangeability of TRADENAME with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population
The safety and efficacy of TRADENAME in individuals under 12 years of age have not yet been established.

Geriatric population
Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

After dilution, vials of TRADENAME contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

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.[69]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 12 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12]

Participants 16 years of age and older
In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age
In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have

been followed for at least 2 months after the second dose of TRADENAME.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older
In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥30 kg/m^2)
   - Diabetes (Type 1, Type 2, or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	**TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	**TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).

Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* 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.

a. N = number of participants in the specified group.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 Tables 10 and 11.

Table 10. 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[55]

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)
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)

Table 10. 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[55]

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]

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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)

Table 11. 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[56]

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]
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)

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11. 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[56]

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]

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3]

(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

Unopened vial

6 months at -90 °C to -60 °C.

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage[2,25]

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

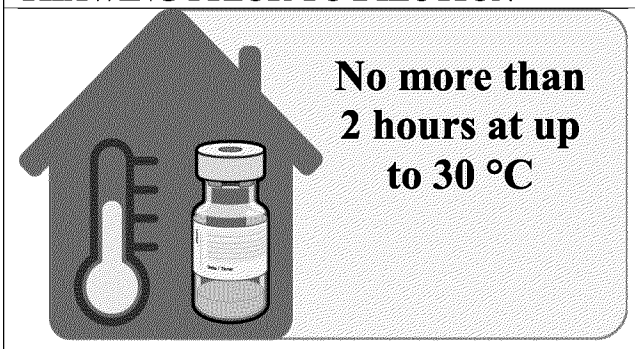
6.5. Nature and contents of container

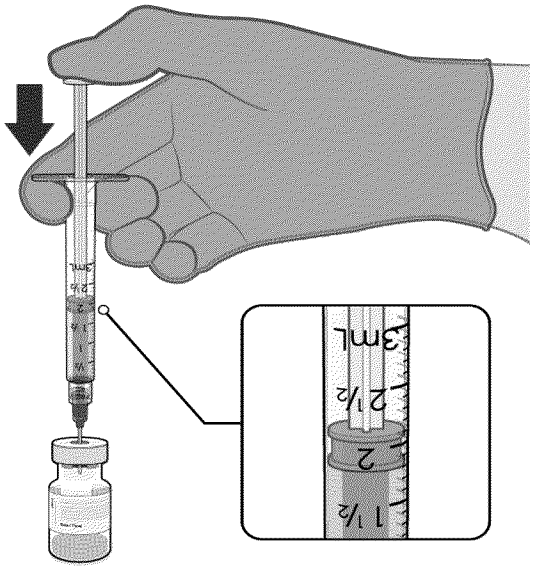
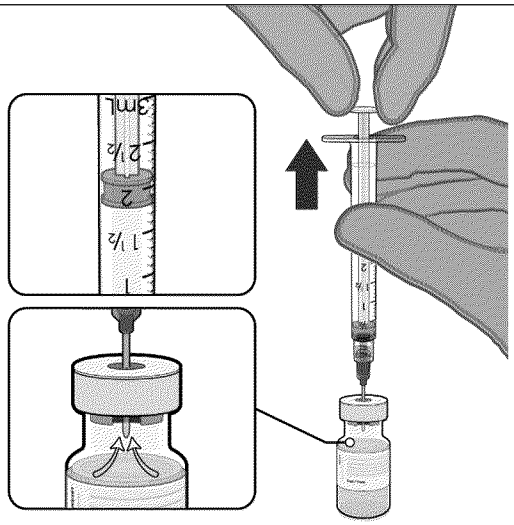
Information to be provided by local subsidiary.

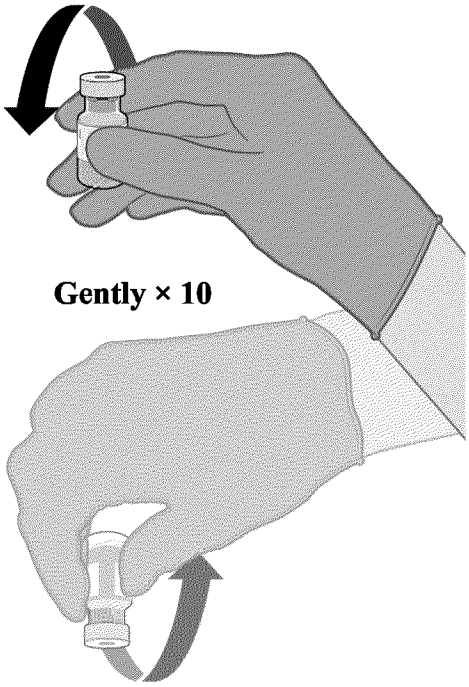
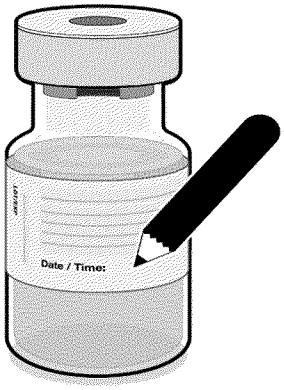
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63]

Handling instructions

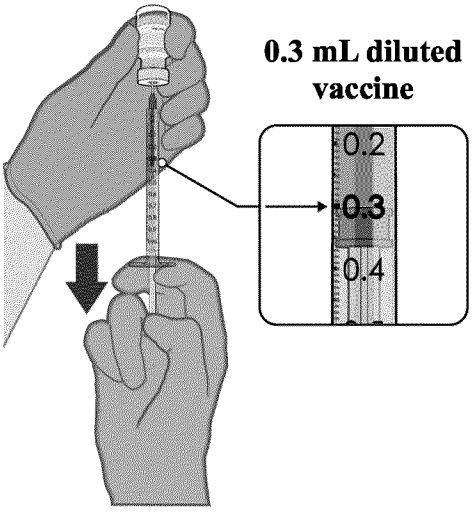
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

THAWING PRIOR TO DILUTION	
	• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use. • The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation. • Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.

	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY



- After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of TRADENAME.

  Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.

  If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, April 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), May 2021

65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021

68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants

69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and Nutrition disorders	Decreased appetite	39/21926 (0.2%)
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis	31/21926 (0.1%)
	Night sweats	17/21926 (0.1%)
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects >16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and Nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. Please note that the following events were not reported in the 12 through 15 years of age group in Study C4591001 (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[65]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 11-AUG-2021

Date of Superseded CDS: 14-Jul-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 6

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2]

This is a multidose vial and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see Section 6.6.

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3]

Concentrate for solution for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 12 years of age and older.[4,49]

4.2. Posology and method of administration

Posology

Individuals 12 years of age and older
TRADENAME is administered intramuscularly after dilution as a series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

There are no data available on the interchangeability of TRADENAME with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population
The safety and efficacy of TRADENAME in individuals under 12 years of age have not yet been established.

Geriatric population
Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

After dilution, vials of TRADENAME contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

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.[69]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 12 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12]

Participants 16 years of age and older
In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age
In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have

been followed for at least 2 months after the second dose of TRADENAME.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older
In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥30 kg/m^2)
   - Diabetes (Type 1, Type 2, or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	**TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	**TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).

Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* 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.

a. N = number of participants in the specified group.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 Tables 10 and 11.

Table 10. 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[55]

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)
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)

Table 10. 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[55]

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]

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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)

Table 11. 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[56]

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]
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)

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11. 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[56]

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]

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19

Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3]

(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

Unopened vial

9 months at -90 °C to -60 °C.[63,70]

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage[2,25]

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

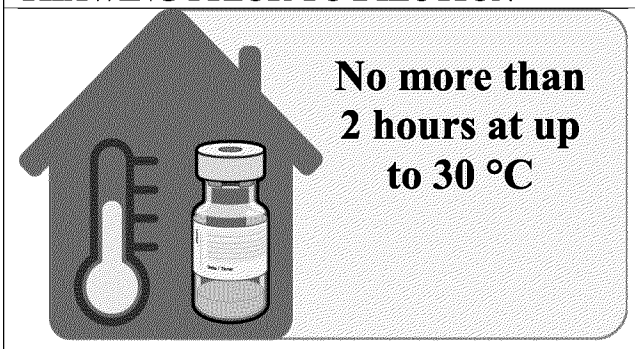
6.5. Nature and contents of container

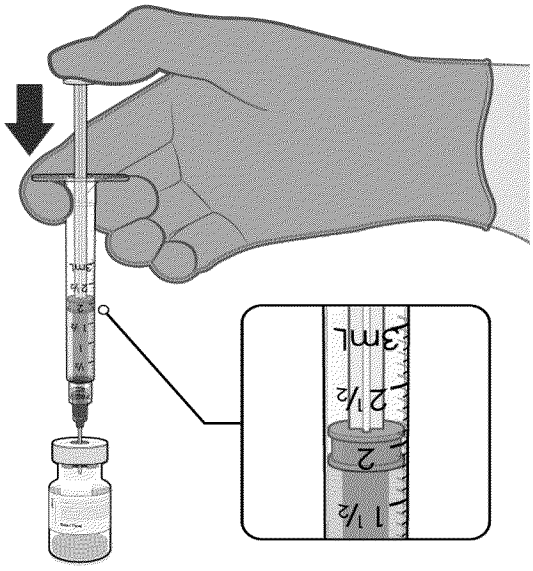
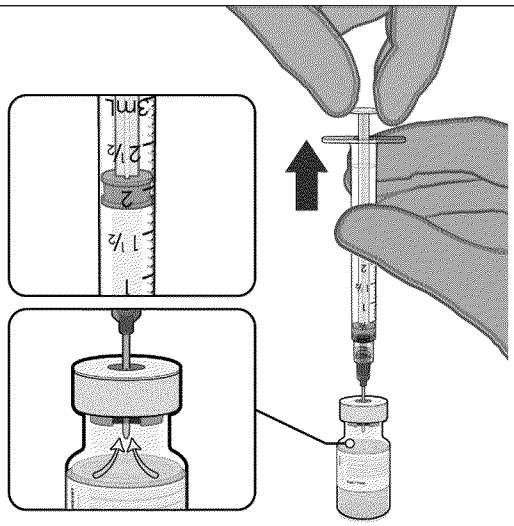
Information to be provided by local subsidiary.

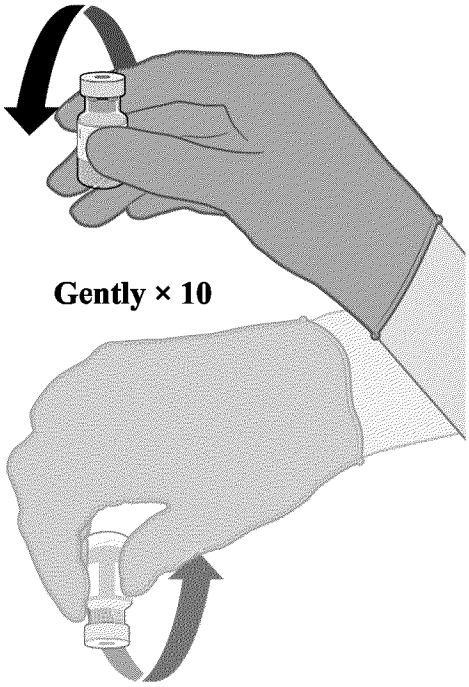
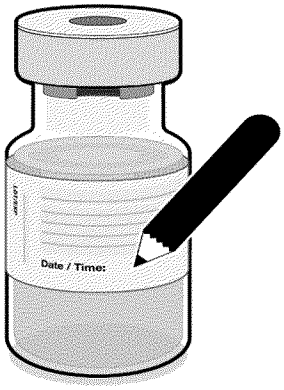
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63]

Handling instructions

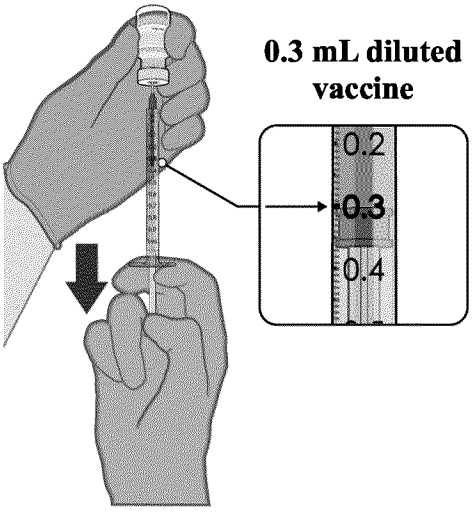
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

THAWING PRIOR TO DILUTION	
	• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use. • The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation. • Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.

	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY



- After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of TRADENAME.

  Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.

  If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), May 2021

65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and Nutrition disorders	Decreased appetite	39/21926 (0.2%)
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis	31/21926 (0.1%)
	Night sweats	17/21926 (0.1%)
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects >16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and Nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and Subcutaneous Tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. Please note that the following events were not reported in the 12 through 15 years of age group in Study C4591001 (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,65

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 08-SEP-2021

Date of Superseded CDS: 11-Aug-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 7

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2]

This is a multidose vial and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see Section 6.6.

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3]

Concentrate for solution for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 12 years of age and older.[4,49]

4.2. Posology and method of administration

Posology

Individuals 12 years of age and older
TRADENAME is administered intramuscularly after dilution as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

A booster dose (third dose) of TRADENAME may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.[71]

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series or the booster dose (third dose) has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series and for any additional doses.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population
The safety and efficacy of TRADENAME in individuals under 12 years of age have not yet been established. The safety and effectiveness of a booster dose (third dose) of TRADENAME 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.[71]

Geriatric population
Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50] The safety and effectiveness of a booster dose (third dose) of TRADENAME in individuals 65 years of age and older is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

After dilution, vials of TRADENAME contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

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.[69]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 12 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12]

Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose (third dose) of TRADENAME approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.[71]

Participants 16 years of age and older – after 2 doses
In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%),

headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age – after 2 doses
In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have been followed for at least 2 months after the second dose of TRADENAME.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Participants 18 years of age and older – after booster dose (third dose)[71]
A subset from Study 2 Phase 2/3 participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose (third dose) of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a.]
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.[71]

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older – after 2 doses
In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥30 kg/m^2)
   - Diabetes (Type 1, Type 2, or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	**TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	**TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)

* 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.

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 Tables 10 and 11.

Table 10. 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[55]

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)
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)

Table 10. 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[55]

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]

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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)

Table 11. 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[56]

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]
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)

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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11. 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[56]

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]

f. Included confirmed cases in participants 12 to 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19 - after 2 doses
Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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 – after 2 doses

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

Immunogenicity in participants 18 years of age and older – after booster dose (third dose)[71]
Effectiveness of a booster dose (third dose) of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after a booster dose (third dose). In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose (third dose) compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose (third dose), based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 14 and Table 15).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose (third dose) to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 98.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: -0.7%, 3.7%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >-10%).

Table 14: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	210	2476.4 (2210.1, 2774.9)	753.7 (658.2, 863.1)	3.29 (2.76, 3.91)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. 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.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.

e. 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.

Table 15: Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[e])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	198	197 99.5 (97.2, 100.0)	194 98.0 (94.9, 99.4)	1.5 (-0.7, 3.7)	Y

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

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 after receipt of booster dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster dose were included in the analysis.

a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.
g. 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.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3]

(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

Unopened vial

9 months at -90 °C to -60 °C.[63,70]

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 ºC to 30 ºC after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage[2,25]

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

6.5. Nature and contents of container

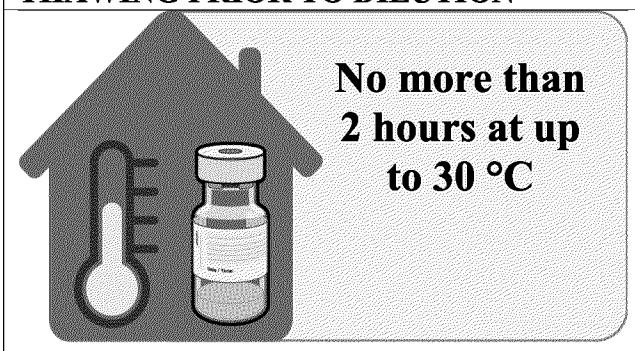
Information to be provided by local subsidiary.

6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63]

Handling instructions

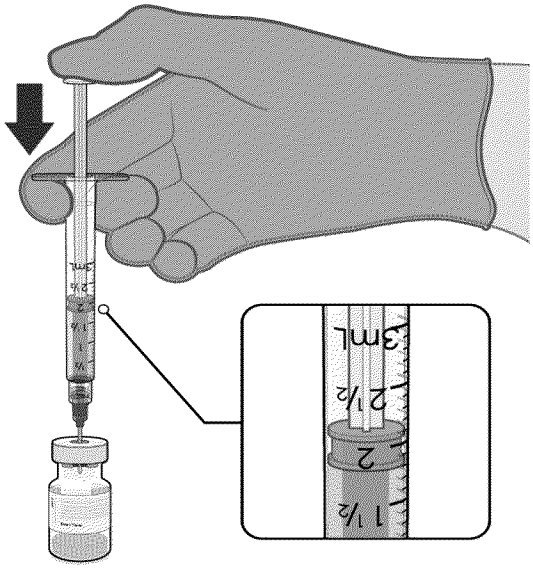
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

THAWING PRIOR TO DILUTION



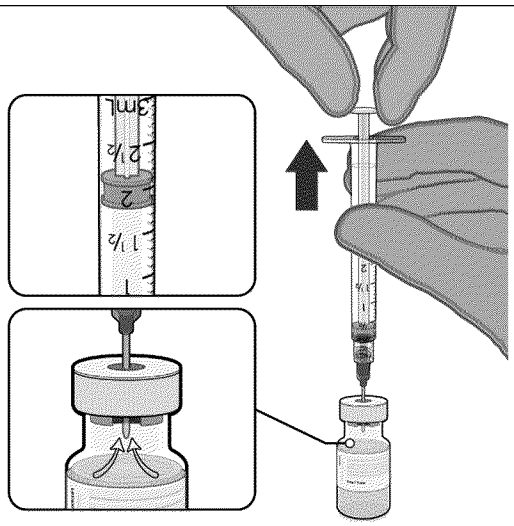
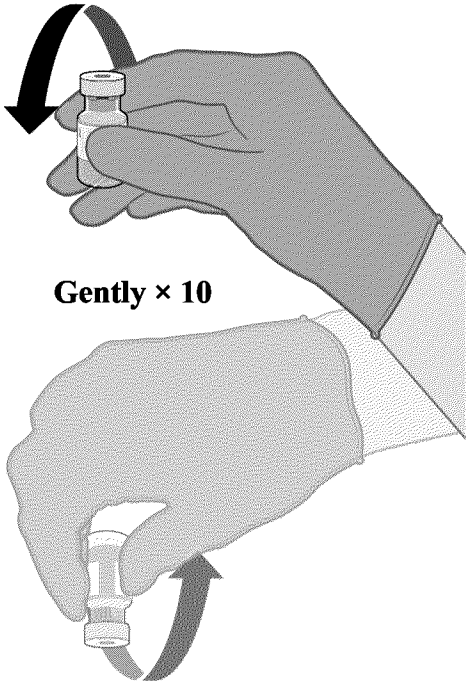
- The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
- The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.
- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

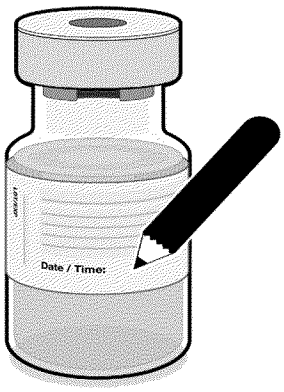
DILUTION



1.8 mL of 0.9% sodium chloride injection

- The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

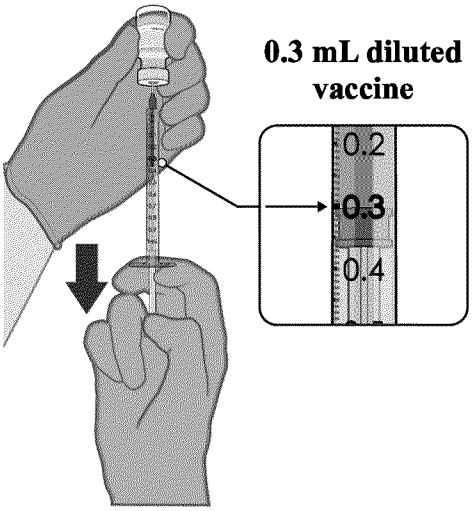
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.



Record appropriate date and time.
Use within 6 hours after dilution.

- The diluted vials should be marked with the appropriate date and time.
- After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY



- After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of TRADENAME.

  Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.

  If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), August 2021

65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021

68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants

69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021

70. Module 3.2.P.8.3 Stability Data, August 2021

71. Interim Report – BNT162b2 Booster (Dose 3): 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

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and nutrition disorders	Decreased appetite	39/21926 (0.2%)
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis	31/21926 (0.1%)
	Night sweats	17/21926 (0.1%)
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects >16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Table A.3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. A higher frequency of lymphadenopathy (5.2% vs. 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Cutoff date: 17June2021).

e. These adverse reactions were identified in the post-authorization period.

f. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age following the 2-dose series (13 March 2021 Data Cut-off Date) Table 1:angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. Please note that the following events were not reported in the 12 through 15 years of age group in Study C4591001 (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria and rash.

Table B-3. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Rash[a]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea[a] Vomiting[a]	Nausea			
Skin and subcutaneous tissue disorders						
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period.

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,65

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,66

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 19-OCT-2021

Date of Superseded CDS: 08-Sep-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 8

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine (nucleoside modified) and COMIRNATY are called TRADENAME.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2,72]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use): This is a multidose vial and must be diluted before use. One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute): This is a multidose vial. One vial (2.25 mL) contains 6 doses of 0.3 mL (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years): This is a multidose vial and must be diluted before use. One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.2 mL) contains 10 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3,72]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use): Concentrate for dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute): Dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years): Concentrate for dispersion for injection.

The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The following is a representative indication. Locally approved indications may differ.

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 5 years of age and older.[4,49,73]

4.2. Posology and method of administration

Posology

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*
Or
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

Individuals 12 years of age and older

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) are administered intramuscularly as a primary series of 2 doses (0.3 mL each) at greater than or equal to 21 days (preferably 3 weeks) apart.[5,49]

A booster dose (third dose) of TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.[71]

Doses of TRADENAME (Dilute Before Use) concentrate for dispersion for injection (30 micrograms/dose) and TRADENAME (Do Not Dilute) dispersion for injection (30 micrograms/dose) vaccine are considered interchangeable.

TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) intended for individuals ages 12 years and older cannot be used for individuals age 5 years to <12 years.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series or the booster dose (third dose) has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series and for any additional doses.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) 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.[73]

TRADENAME (for age 5 years to <12 years) cannot be used in individuals 12 years of age and older.

The interchangeability of TRADENAME with other COVID-19 vaccines to complete the primary vaccination series has not been established. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the primary vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.[6]

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 5 years of age have not yet been established. The safety and effectiveness of a booster dose (third dose) of TRADENAME 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.[71]

Geriatric population

Clinical studies of TRADENAME include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy.[7] Of the total number of TRADENAME recipients in Study 2 (N = 22,026), 16.5% (n = 3627) were 65 through 74 years of age and 4.2% (n = 925) were 75 years of age and older (see Section 5.1).[50] The safety and effectiveness of a booster dose (third dose) of TRADENAME in individuals 65 years of age and older is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

After dilution, vials of TRADENAME (Dilute Before Use) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead -volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

Vials of TRADENAME (Do Not Dilute) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

After dilution, vials of TRADENAME (for age 5 years to <12 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 5 through <12 years of age

Low dead-volume syringes and/or needles can be used to extract 10 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

For instructions on the handling, dilution, and dose preparation of the vaccine before administration, see Section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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.[9]

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.[69]

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.[9]

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.[9]

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.[67]

As with any vaccine, vaccination with TRADENAME may not protect all vaccine recipients.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Do not mix TRADENAME with other vaccines/products in the same syringe.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of TRADENAME in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see Section 5.3).[10,11] Administration of TRADENAME in pregnancy should be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

It is unknown whether TRADENAME has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see Section 5.3).[10,11]

4.7. Effects on ability to drive and use machines

TRADENAME has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through less than 12 years of age.[73]

Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose (third dose) of TRADENAME approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.[71]

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 22,021 participants 16 years of age or older received placebo.[50]

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses (in order from highest to lowest frequencies) were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.[64] A lower frequency of reactogenicity events was associated with greater age.[15]

The safety profile in 545 participants receiving TRADENAME, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.[17,28,31]

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving TRADENAME (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.[51]

Adolescents 12 through 15 years of age – after 2 doses

In an analysis of Study 2, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 through 15 years of age. Of these, 1308 adolescents (660 TRADENAME and 648 placebo) have been followed for at least 2 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).[43,44,45]

Children 5 through <12 years of age – after 2 doses[73]

In an analysis of Study 3 Phase 2/3, 2,268 participants (1,518 TRADENAME 10 mcg; 750 placebo) were 5 through <12 years of age. Of these, 2,158 (95.1%) (1,444 TRADENAME 10 mcg and 714 placebo) participants have been followed for at least 2 months after the second dose. The safety evaluation in Study 3 is ongoing.

The most frequent adverse reactions in children 5 through <12 years of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

Participants 18 years of age and older – after booster dose (third dose)[71]

A subset from Study 2 Phase 2/3 participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose (third dose) of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

Table 1. Adverse Drug Reactions[13,14,16,64]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a]
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Asthenia Malaise Fatigue Injection site pain Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.[71]

Adverse reactions from TRADENAME post-authorization experience

The following events have been identified as adverse reactions during the post-authorization use of TRADENAME.

Table 2. Adverse Drug Reactions[38]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9. Overdose

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.[18]

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological class, therapeutic class

Vaccines
Refer to the current ATC code index for the appropriate code assignment for the pharmacologic and/or therapeutic class.

Mechanism of action

The nucleoside-modified messenger RNA in TRADENAME is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.[19,20]

Efficacy

Study 2 is a multicenter, placebo-controlled efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum.[12] The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19.[12] Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1.[52] Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.[12,27]

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.[22] Table 3 presents the specific demographic characteristics in the studied population.

Table 3. Demographics (Population for the Primary Efficacy Endpoint)[a,22]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19.
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥30 kg/m^2)
   - Diabetes (Type 1, Type 2, or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the COVID-19 mRNA Vaccine and at least 2222 person-years in the placebo group.[32]

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 [e.g., asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].[23,24]

The vaccine efficacy information is presented in Table 4.

Table 4. 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*,[34]			
Subgroup	**TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
≥65 years	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)[g]
≥75 years	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)[g]

First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection[28]			
Subgroup	TRADENAME N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
≥65 years	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[g]
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)[g]
≥75 years	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)[g]

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).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* 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.

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. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

The subgroup analyses of vaccine efficacy including demographic characteristics is presented in Table 5.

Table 5. Subgroup Analyses of Vaccine Efficacy - Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 - Evaluable Efficacy Population[33]

Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Sex			
Female	5 1.090 (8536)	81 1.114 (8749)	93.7 (84.7, 98.0)
Male	3 1.124 (8875)	81 1.108 (8762)	96.4 (88.9, 99.3)
Ethnicity			
Hispanic or Latino	3 0.605 (4764)	53 0.600 (4746)	94.4 (82.7, 98.9)
Not Hispanic or Latino	5 1.596 (12,548)	109 1.608 (12,661)	95.4 (88.9, 98.5)
Race			
Black or African American	0 0.165 (1502)	7 0.164 (1486)	100.0 (31.2, 100.0)
White	7 1.889 (14,504)	146 1.903 (14,670)	95.2 (89.8, 98.1)
All others[f]	1 0.160 (1405)	9 0.155 (1355)	89.3 (22.6, 99.8)

* 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Updated efficacy analyses were performed with additional 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.

The updated vaccine efficacy information is presented in Table 6.

Table 6. 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*,[53]			
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[54]			
Subgroup	**TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* 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.

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 confidence interval (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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 7 and Table 8.

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Table 7. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[53]

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]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.

* 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.

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* 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.

Table 8. Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[54]

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]

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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 9.

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2			
At risk[f]			
Yes	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
No	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Age group (years) and at risk			
16 to 64 and not at risk	4 0.962 (7671)	69 0.964 (7701)	94.2 (84.4, 98.5)
16 to 64 and at risk	3 0.744 (5878)	74 0.746 (5917)	95.9 (87.6, 99.2)
≥65 and not at risk	0 0.227 (1701)	7 0.233 (1771)	100.0 (29.0, 100.0)
≥65 and at risk	1 0.281 (2147)	12 0.279 (2109)	91.7 (44.2, 99.8)

Table 9. 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[23]

Efficacy Endpoint Subgroup	TRADENAME N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Obese[g]			
Yes	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
No	5 1.451 (11,406)	95 1.439 (11,404)	94.8 (87.4, 98.3)
Age group (years) and obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

Abbreviations: BMI = body mass index; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) 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.

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. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated 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 10 and Table 11.

Table 10. 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[55]

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)
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 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.

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 confidence interval (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 $\geq$30 kg/m^2 or BMI $\geq$95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI $\geq$30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. 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[56]

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)

Table 11. 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[56]

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]
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)

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.

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 confidence interval (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 $\geq$30 kg/m^2 or BMI $\geq$95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI $\geq$30 kg/m^2. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19 - after 2 doses

Secondary efficacy analyses suggested benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 14 November 2020, efficacy against severe COVID-19 (as defined by the study protocol) occurring after the first dose was 88.9% (95% CI: 20.1, 99.7) (1 case in COVID-19 mRNA Vaccine group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in COVID-19 mRNA Vaccine group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.[36] Efficacy against severe COVID-19, defined by the Centers for Disease Control and Prevention as hospitalization, admission to the Intensive Care Unit, intubation or mechanical ventilation, or death occurring after the first dose, was 92.9% (95% CI: 53.2, 99.8) (1 case in COVID-19 mRNA Vaccine group and 14 cases in placebo group).[37]

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 12) 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 12. 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[57,58]			
	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[59,60]			
	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 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);

- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:[61]

- Hospitalization;
- Admission to the Intensive Care Unit;
- 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 confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all-available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention.[62]
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician.[62]
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 – after 2 doses

An analysis of Study 2 has been performed in adolescents 12 to 15 years of age up to a data cut-off date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 13.

Table 13. 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*,[46]			
	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[47]			
	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 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.

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

In Study 2 an analysis of SARS-CoV-2 neutralizing titers in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune response in participants 16 to 25 years of age (n=170), based on results for SARS-CoV-2 neutralizing titers at 1 month after Dose 2. The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.[48]

Immunogenicity in children 5 through <12 years of age – after 2 doses[73]

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicenter, multinational, randomized, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through less <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no

serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 14.

Table 14: 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[73]

		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 15.

Table 15: 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[73]

		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.

Immunogenicity in participants 18 years of age and older – after booster dose (third dose)[71]

Effectiveness of a booster dose (third dose) of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose (third dose). In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose (third dose) compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose (third dose), based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 16 and Table 17).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose (third dose) to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 98.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: -0.7%, 3.7%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >-10%).

Table 16: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	210	2476.4 (2210.1, 2774.9)	753.7 (658.2, 863.1)	3.29 (2.76, 3.91)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. 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.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.
e. 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.

Table 17: Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	198	197 99.5 (97.2, 100.0)	194 98.0 (94.9, 99.4)	1.5 (-0.7, 3.7)	Y

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.
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 after receipt of booster dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster dose were included in the analysis.
a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.
g. 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.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproduction and developmental toxicity.[10,11]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3,74]

*[Editorial Guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose.**]*

TRADENAME (Dilute Before Use)
(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose.**]*

TRADENAME (Do Not Dilute)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose.**]*

TRADENAME (for age 5 years to <12 years)

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Tromethamine
Tromethamine hydrochloride
Sucrose
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Sections 6.3 and 6.6.

6.3. Shelf life

*[Editorial Guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)

Unopened vial

9 months at -90 °C to -60 °C.[63,70]

Alternatively, unopened vials may be stored and transported at -25 °C to -15 °C for a total of 2 weeks and can be returned to -90 °C to -60 °C.[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29,63] Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Transfers of frozen vials stored at ultra-low temperature (<-60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (<-60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C[40]

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation,[30] has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for

injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute)[75]

Unopened vial

6 months when stored at -90 °C to -60 °C.

TRADENAME (Do Not Dilute) may be received frozen at -90 °C to -60 °C or at -25 °C to -15 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks within the 6-month shelf life.

Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at temperatures up to 30 °C.

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following first puncture.[77]

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 8 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)[75]

Unopened vial

6 months when stored at -90 °C to -60 °C.

TRADENAME (for age 5 years to <12 years) may be received frozen at -90 °C to -60 °C or at 25 °C to 15 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks within the 6-month shelf life.

Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at temperatures up to 30 °C.

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following dilution.[77]

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 ºC to 30 ºC, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

6.4. Special precautions for storage[2,25,75]

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3.

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Do Not Dilute)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)

TRADENAME (Do Not Dilute) and TRADENAME (for age 5 years to <12 years) can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the original expiry date (EXP). Alternatively, the vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after "EXP".

The vaccine may be received frozen at -90 °C to -60 °C or at -25 °C to -15 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt. Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

Store in the original package in order to protect from light.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

When stored frozen at -90 °C to -60 °C, the vaccine can be thawed at either 2 °C to 8 °C or at room temperature (up to 30 °C).

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

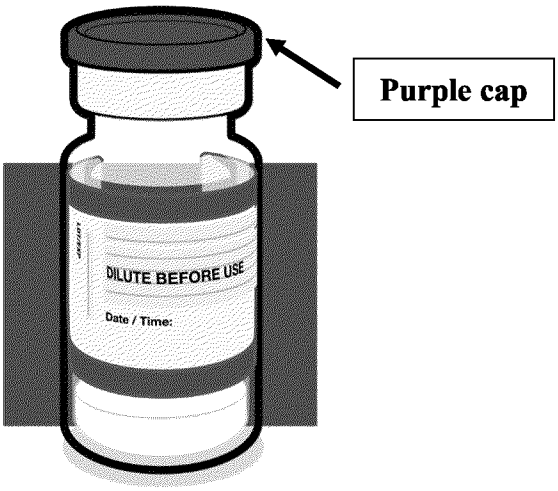
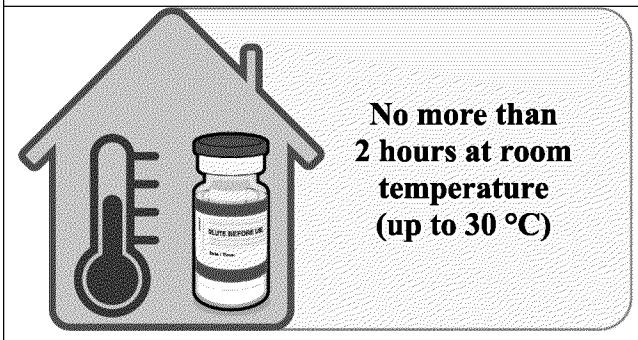
Information to be provided by local subsidiary.

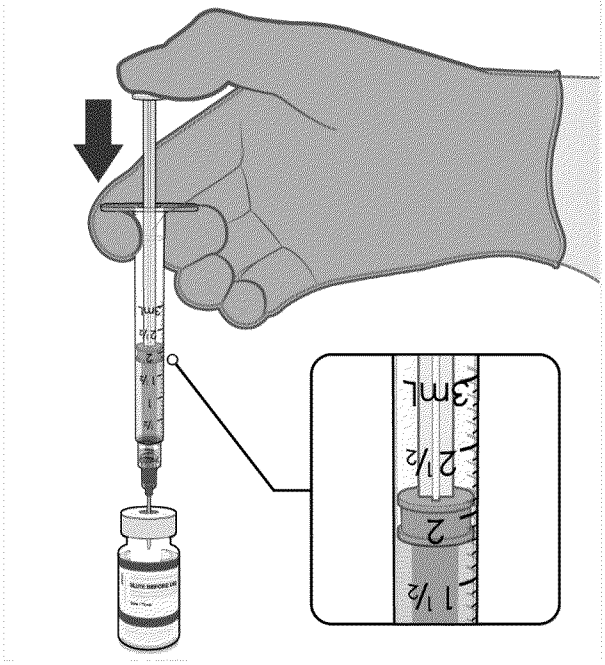
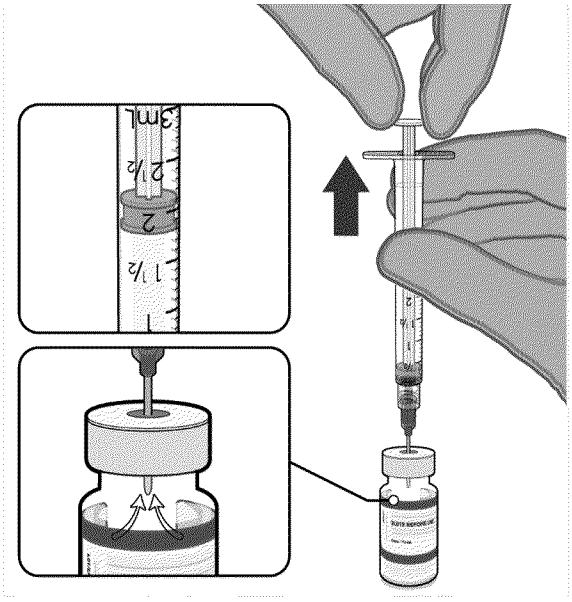
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63,75,77,78]

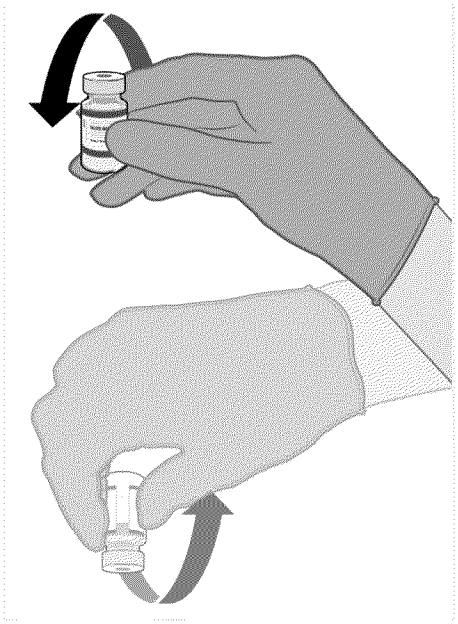
Handling instructions

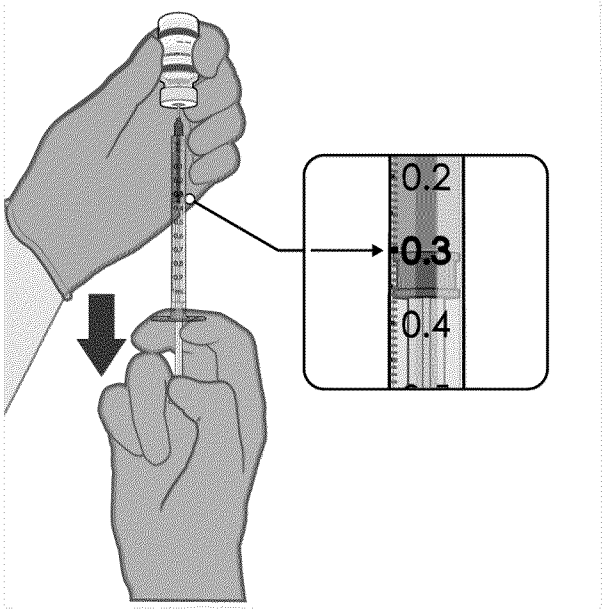
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

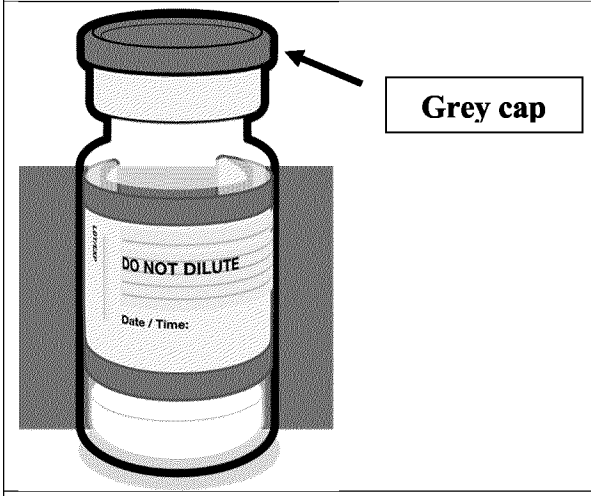
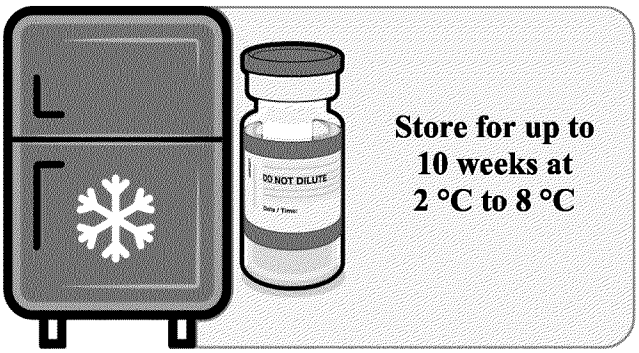
<table>
<tr><th colspan="2">TRADENAME (Dilute Before Use)</th></tr>
<tr><td colspan="2">DOSE VERIFICATION</td></tr>
<tr><td> 
</td><td>Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years).</td></tr>
<tr><td colspan="2">THAWING PRIOR TO DILUTION</td></tr>
<tr><td> 
</td><td>• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
• The unopened vial can be stored for up to 1 month at 2 °C to 8 °C. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.
• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
• Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.</td></tr>
</table>

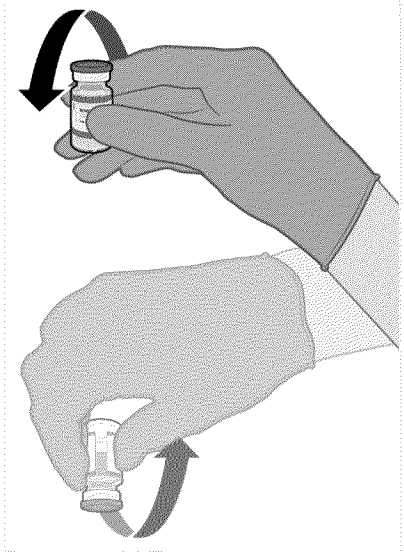
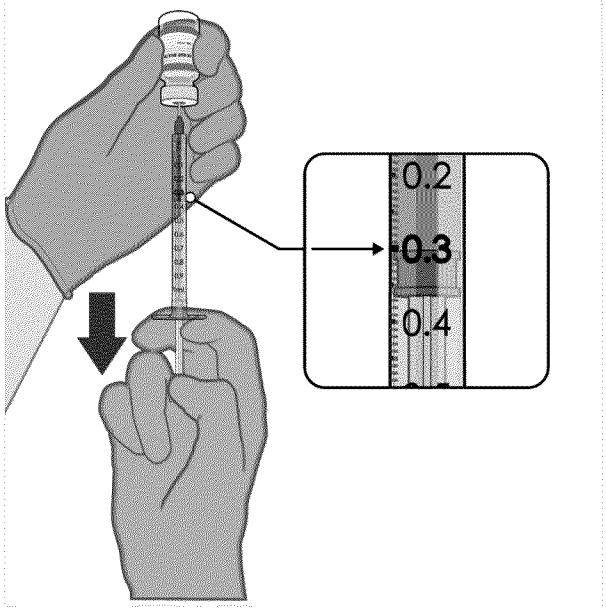
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.

TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

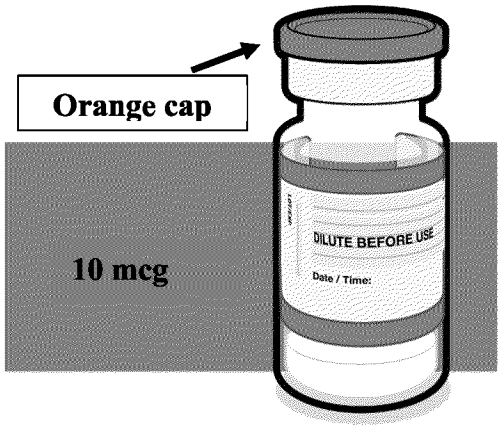
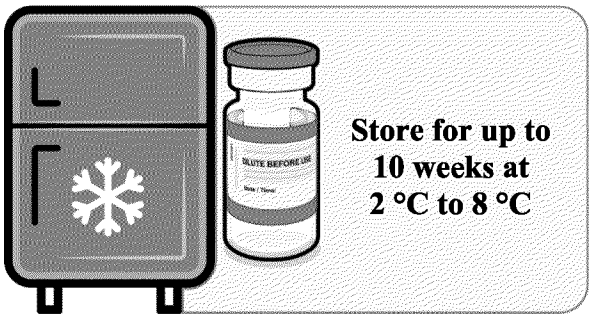
TRADENAME (Dilute Before Use)	
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL diluted vaccine**	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead-volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Discard any unused vaccine within 6 hours after dilution.

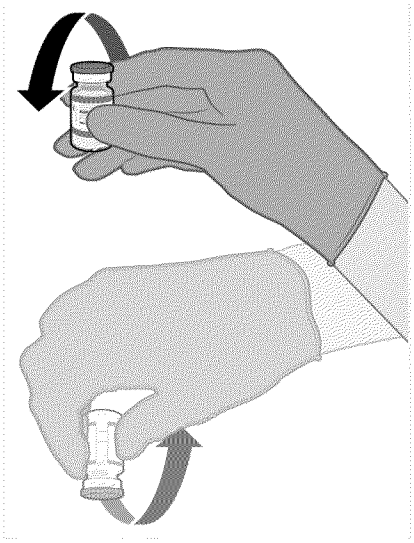
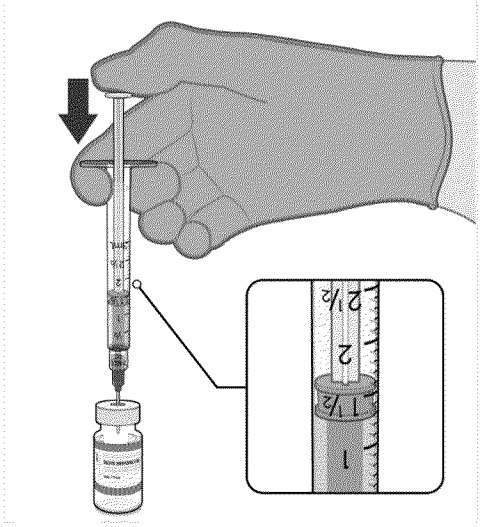
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose.**]*

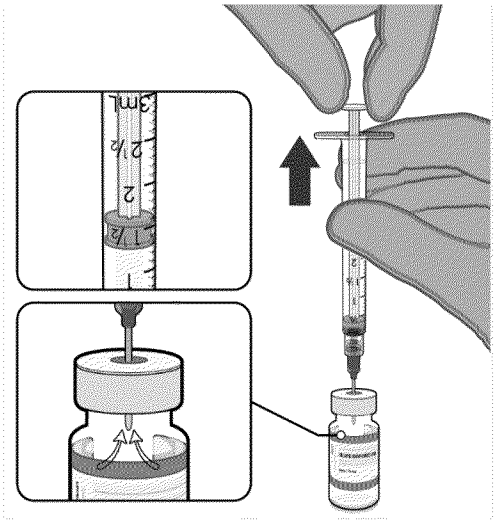
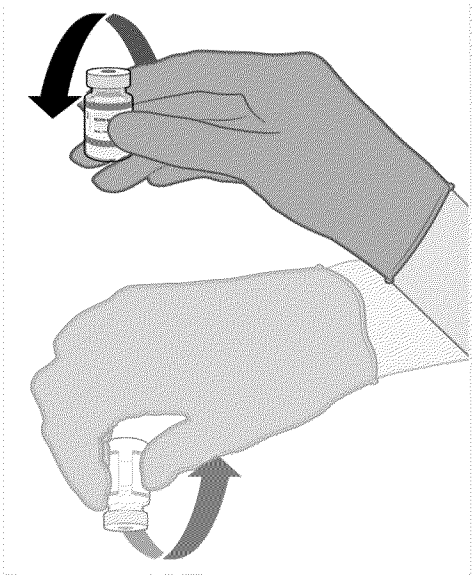
TRADENAME (Do Not Dilute)	
DOSE VERIFICATION	
	• Verify that the vial has a grey plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use. • Update the expiry date on the carton. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C. • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

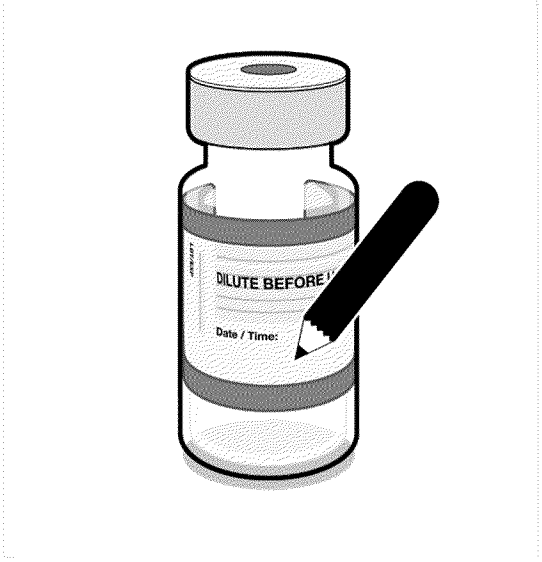
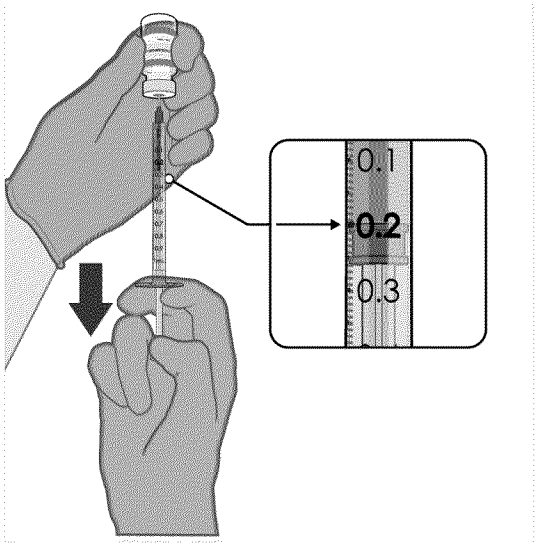
TRADENAME (Do Not Dilute)	
 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration are present.
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Discard any unused vaccine 12 hours after first puncture. Record the appropriate date/time on the vial.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)	
DOSE VERIFICATION	
	• Verify that the vial has an orange plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C. • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
DILUTION	
 **1.3 mL of 0.9% sodium chloride**	• The thawed vaccine must be diluted in its original vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 °C to 30 °C and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF TRADENAME	
 **0.2 mL diluted vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.2 mL of TRADENAME for children age 5 to 11 years. Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial. • Each dose must contain 0.2 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume. • Discard any unused vaccine within 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REFERENCES

1. BB-IND19736 Section 3.2.S.1.1
2. BB-IND19736 Section 3.2.P.2
3. BB-IND19736 Section 3.2.P.1
4. Global Emergency Use Authorization Application, Section 1.3 Intended Use
5. Global Emergency Use Authorization Application, Section 1.2 Description of Product
6. Vaccine Efficacy – First COVID-19 Occurrence ≥7 Days After Dose 2 – Subjects Without Evidence of Infection Before Vaccination, by Subgroup – Evaluable Efficacy (7 Days) Population
7. Global Emergency Use Authorization Application, Section 7.3.1 Geriatric use
8. ~~Module 5.3.5.1 Table 5: Demographic Characteristics – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population~~ Reference no longer applicable; removed in CDS version 4
9. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
10. Module 4.2.3 Study 20256434 (RN9391R58), Section 4.2.3.5 Final Report - A Combined Fertility and Developmental Study of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
11. Module 4.2.3.5 Study 20256434 (RN9391R58) Summary for BNT162b2 DART
12. Global Emergency Use Authorization Application, Section 6.2.1.2
13. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
14. Module 5.3.5.1 Study 20256434 (RN9391R58), Table Title: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population
15. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.5 Overall Conclusions
16. Module 2.5 Clinical Overview, COVID-19 Vaccine, 2021, CO for CDS (anaphylaxis & hypersensitivity)
17. Global Emergency Use Authorization, Section 6.2.4.1.1.3.1 Overview of Adverse Events
18. Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.4.5
19. Global Emergency Use Authorization Application, Section 1.2.2 RNA-Lipid Nanoparticle Formulation
20. Global Emergency Use Authorization, Section 6.2.2.1.1.3 Study BNT162-01 Immunogenicity Conclusions in Phase 1
21. Global Emergency Use Authorization, Section 6.2.1.1 Phase 1 First-in-Human BNT162-01

22. Module 5.3.5.1 Study C4591001, Table Title: Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 Evaluable Efficacy (7 Days) Population
23. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
24. Baseline Charlson Comorbidities – ~38,000 Subjects for Phase 2/3 Analysis – Safety Population
25. BB-IND19736, Section 3.2.P.8
26. BB-IND19736, Section 3.2.P.5.2
27. Global Emergency Use Authorization, Table 5: Demographic Characteristics – Phase 2 – Dose 2 Evaluable Immunogenicity Population
28. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
29. BB-IND19736, Section 3.2.P.3.5
30. BB-IND19736, Section 3.2.P.2.6
31. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status -- ~38000 Subjects for Phase 2/3 Analysis – Safety Population
32. Global Emergency Use Application, Table 35 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
33. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
34. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup - Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Dose 2 All-Available Efficacy
35. Module 3.2.P Dosage and Administration Instructions for BNT162 (PF-07302048) Vaccine, 0.5 mg/mL
36. Module 5.3.5.1 C4591001 Clinical Study Report, Section 11.1.2.3.2.1.3 Table 40
37. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Dose 1 All-Available Efficacy Population
38. Module 2.5, Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet, February 2021
39. Module 3.2.P.8.1 Stability Summary and Conclusion
40. IND Section 3.2.P.2.3 Storage Shipping and Distribution

41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. 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
47. 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
48. 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
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: 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 [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: 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 (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. 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
54. 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
55. 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
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), October 2021
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

– Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. 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 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): 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
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. 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
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021

Appendix A: Adverse Drug Reactions (ADRs) and Numeric Frequencies Listed in Order of Decreasing Frequency Within Each System Organ Class (SOC)[64]

Table A-1. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	83/21926 (0.4%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	54/21926 (0.2%)[a]
	Pruritus[d]	23/21926 (0.1%)[a]
	Urticaria[d]	15/21926 (0.1%)[a]
	Angioedema[d]	3/21926 (0.01%)[a]
Metabolism and nutrition disorders	Decreased appetite	39/21926 (0.2%)[a]
Nervous system disorders	Headache	2814/4924 (57.1%)[b]
	Lethargy	25/21926 (0.1%)[a]
Gastrointestinal disorders	Diarrhea[d]	758/4924 (15.4%)[b]
	Vomiting[d]	110/4924 (2.2%)[b]
	Nausea	274/21926 (1.2%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis	31/21926 (0.1%)[a]
	Night sweats	17/21926 (0.1%)[a]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	1980/4924 (40.2%)[b]
	Arthralgia (joint pain)	1232/4924 (25.0%)[b]
	Pain in extremity (arm)[d]	185/21926 (0.8%)[a]
General disorders and administration site conditions	Injection site pain	4153/4924 (84.3%)[c]
	Fatigue	3185/4924 (64.7%)[b]
	Chills	1707/4924 (34.7%)[b]
	Pyrexia	749/4924 (15.2%)[b]
	Injection site swelling	546/4924 (11.1%)[c]
	Injection site redness	486/4924 (9.9%)[c]
	Malaise	130/21926 (0.6%)[a]
	Asthenia	76/21926 (0.3%)[a]

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.

Table A-2. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	9/1131 (0.8%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	2/1131 (0.2%)[a]
	Urticaria[d]	2/1131 (0.2%)[a]
	Pruritus[d,e]	
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite[e]	
Nervous system disorders	Headache	854/1131 (75.5%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	141/1131 (12.5%)[b]
	Vomiting[d]	59/1131 (5.2%)[b]
	Nausea	5/1131 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	477/1131 (42.2%)[b]
	Arthralgia (joint pain) (new)	229/1131 (20.2%)[b]
	Pain in extremity (arm)[d]	1/1131 (0.1%)[a]
General disorders and administration site conditions	Injection site pain	1023/1131 (90.5%)[c]
	Fatigue	876/1131 (77.5%)[b]
	Chills	557/1131 (49.2%)[b]
	Pyrexia	275/1131 (24.3%)[b]
	Injection site swelling	104/1131 (9.2%)[c]
	Injection site redness	97/1131 (8.6%)[c]
	Malaise[e]	
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) –Safety Population (Cutoff date: 13March2021)
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
c. Source: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population (Cutoff date: 13March2021)
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in the 12 through 15 year old age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. A higher frequency of lymphadenopathy (5.2% vs. 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Cutoff date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Cutoff date: 17June2021).

e. These adverse reactions were identified in the post-authorization period.

f. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age following the 2-dose series (13 March 2021 Data Cut-off Date) Table A-1: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – 5 to <12 Years of Age – Safety Population (Cutoff date: 06Sep2021).
d. These adverse reactions were identified in the post-authorization period.
e. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see **Error! Reference source not found.**): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.

Appendix B: Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC[64]

Table B-1. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 16 Years of Age and Older (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Pruritus;[a,b] Rash[a,b]	Angioedema[a,b]		Anaphylaxis[a]
Metabolism and Nutrition disorders			Decreased appetite			
Nervous system disorders	Headache		Lethargy			
Gastrointestinal disorders	Diarrhea[a]	Vomiting;[a] Nausea				
Skin and subcutaneous Tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling	Injection site redness	Asthenia; Malaise			

a. These adverse reactions were identified in the post-authorization period.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table B-2. ADRs by SOC and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: Individuals 12 Through 15 Years of Age (13 March 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria;[a,b] Rash[a,b]			Anaphylaxis[a]
Nervous system disorders	Headache					
Gastrointestinal disorders	Diarrhea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia	Injection site swelling; Injection site redness				

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the 12 through 15 years of age group in Study C4591001 but were reported in individuals ≥16 years of age (see Table B-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria and rash.

Table B-3. ADRs by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)*,64

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Rash[a]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea[a] Vomiting[a]	Nausea			
Skin and subcutaneous tissue disorders						
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

* The booster dose (third dose) of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age 1 month after Dose 2 (Cutoff date: 13March2021) (see Table B-1): angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

Table B-4. ADRs by System Organ Class and CIOMS Frequency Category Listed in order of Decreasing Medical Seriousness within each Frequency Category and System Organ Class: Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria[a,b]; Pruritus[a,b]; Rash[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhea;[a] Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Injection site swelling; Injection site redness	Pyrexia	Malaise			

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001 (see Table B-1): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
b. The following events are categorized as hypersensitivity reactions: urticaria, pruritus, and rash

Appendix C. HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Frequency in the Safety Population Subset

Table C-1. Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[65]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
No Grade 4 solicited local reactions were reported in HIV-Positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each reaction was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[e]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)

Table C-2. Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*,[66]

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

APPENDIX 2.1.1 - Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials

BNT162B2

Reporting Period: Through 18-DEC-2021
Total Number of Cases: 44
Total Number of Adverse Events (PT): 62
MedDRA Version: v.24.1J

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	PLACEBO	COMPARATOR
Cardiac disorders	Cardiogenic shock	1			
	Supraventricular tachycardia	1			
Sub Total:		**2**			
Congenital, familial and genetic disorders	Thyroglossal cyst			1	
Sub Total:				**1**	
Endocrine disorders	Hyperthyroidism				1
	Thyroid mass				1
Sub Total:					**2**
Gastrointestinal disorders	Diverticulum intestinal haemorrhagic	1			
	Inguinal hernia	1			
	Umbilical hernia	1			
Sub Total:		**3**			
General disorders and administration site conditions	Condition aggravated		1		
	Disease progression		1		
	Pelvic mass				1
Sub Total:			**2**		**1**
Hepatobiliary disorders	Cholecystitis acute		1		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	PLACEBO	COMPARATOR
	Drug-induced liver injury		1		
Sub Total:			**2**		
Infections and infestations	COVID-19				2
	Cystitis	1			
	Pneumonia		2		
	Urinary tract infection	3			
Sub Total:		**4**	**2**		**2**
Injury, poisoning and procedural complications	Ankle fracture	1			
	Extradural haematoma		1		
	Femur fracture	1			
	Foot fracture		1		
	Humerus fracture				1
	Joint dislocation				1
	Limb traumatic amputation		1		
	Lower limb fracture		1		
	Meniscus injury		1		
	Rib fracture		1		
	Skull fracture		1		
	Subdural haematoma		1		
	VIIth nerve injury		1		
Sub Total:		**2**	**9**		**2**
Metabolism and nutrition disorders	Diabetic ketoacidosis		1		
Sub Total:			**1**		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	PLACEBO	COMPARATOR
Musculoskeletal and connective tissue disorders	Arthralgia		1		
	Osteonecrosis		1		
Sub Total:			**2**		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Intestinal adenocarcinoma		1		
	Lung carcinoma cell type unspecified stage 0		1		
	Metastases to abdominal wall		1		
	Metastases to liver		1		
	Metastases to ovary		1		
	Oesophageal carcinoma	1			
	Ovarian germ cell teratoma		1		
	Rectal cancer		1		
	Thyroid cancer				1
	Uterine leiomyoma		1		
Sub Total:		**1**	**8**		**1**
Nervous system disorders	Cerebral infarction		5		
	Diabetic neuropathy		2		
	Syncope				1
Sub Total:			**7**		**1**
Renal and urinary disorders	Nephrolithiasis		1		
	Renal hydrocele		1		
	Ureterolithiasis		1		

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	PLACEBO	COMPARATOR
Sub Total:			**3**		
Reproductive system and breast disorders	Epididymal cyst		1		
Sub Total:			**1**		
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease		1		
Sub Total:			**1**		
Surgical and medical procedures	Hip arthroplasty	1			
Sub Total:		**1**			
Vascular disorders	Hypertensive crisis	1			
Sub Total:		**1**			
Total Number of Cases:		**14**	**22**	**1**	**7**
Total Number of Events:		**14**	**38**	**1**	**9**

* Uncoded Preferred Term displayed as Verbatim Term (As Reported)
Treatment Grouping:
Study Drug: If one of the suspect products on the case is the Study Drug, the event will be displayed under Study Drug regardless of other suspect products on the case.
Blinded Therapy: If one of the suspect products on the case is Blinded Therapy and none are the Study Drug, then the event will be displayed under Blinded Therapy.
Placebo: If one of the suspect products on the case is Placebo and none are Study Drug or Blinded Therapy, the event will be displayed under Placebo.
Pre Randomization / No Study Drug: If the case does not have any designated study drug, the event will be displayed under Pre Randomization / No Study Drug.
Comparator: If the case category is different than the Study Drug, Blinded Therapy, Placebo, Pre Randomization / No Study Drug, but the case contains suspect products designated as part of the study, the events will fall under Comparator.
Other Suspects: If none of the above categories are met, the event will fall under Other Suspects. Some examples include background drugs or non study drugs deemed as suspect.

Appendix 2.3 Cumulative Summary Tabulations of Demographic Data (S6.1)
BNT162/PF-07302048
Cumulative demographic information entered into the database through 18-DEC-2021

	BNT162b1 (N=195)	BNT162b2 (N=27489)	BNT162b2 & Blinded boost (N=872)	Placebo to BNT162b2 (N=25110)
Age (years)				
<=17	0	5270 (19.2)	0	1411 (5.6)
18-30	39 (20.0)	3158 (11.5)	162 (18.6)	2932 (11.7)
31-50	48 (24.6)	7814 (28.4)	471 (54.0)	8282 (33.0)
51-64	18 (9.2)	6534 (23.8)	202 (23.2)	7387 (29.4)
65-74	81 (41.5)	3742 (13.6)	30 (3.4)	4092 (16.3)
>=75	9 (4.6)	971 (3.5)	7 (0.8)	1006 (4.0)
UNSPECIFIED	0	0	0	0
Mean	51.90	42.36	43.01	48.60
Median (range)	53.00 (19- 82)	45.00 (0- 89)	44.00 (18- 82)	50.00 (12- 91)
Race, n (%)				
WHITE	177 (90.8)	22394 (81.5)	695 (79.7)	20604 (82.1)
BLACK	6 (3.1)	2235 (8.1)	78 (8.9)	2230 (8.9)
ASIAN	12 (6.2)	1574 (5.7)	70 (8.0)	1143 (4.6)
HISPANIC	0	231 (0.8)	8 (0.9)	180 (0.7)
OTHER	0	1018 (3.7)	18 (2.1)	913 (3.6)
UNSPECIFIED	0	37 (0.1)	3 (0.3)	40 (0.2)
Gender, n (%)				
MALE	83 (42.6)	14044 (51.1)	427 (49.0)	12604 (50.2)
FEMALE	112 (57.4)	13445 (48.9)	445 (51.0)	12506 (49.8)

Study C4591015 enrolled pregnant women and their infants. Infant participants were not vaccinated with the study investigational product
Participants who are treated in more than one clinical trial are counted only once per column
Includes Protocols: C4591001,C4591005,C4591007,C4591015,C4591017,C4591020,C4591024,C4591031
PFIZER CONFIDENTIAL Date of Generation: 01FEB2022 (08:09)

Appendix 2.3 Cumulative Summary Tabulations of Demographic Data (S6.1)
BNT162/PF-07302048
Cumulative demographic information entered into the database through 18-DEC-2021

	BNT162b2SA (N=330)	Blinded Therapy (N=6469)	Placebo (N=3382)	Total (N=58656)
Age (years)				
<=17	0	4257 (65.8)	1653 (48.9)	12545 (21.4)
18-30	120 (36.4)	765 (11.8)	248 (7.3)	6932 (11.8)
31-50	177 (53.6)	947 (14.6)	614 (18.2)	16514 (28.2)
51-64	33 (10.0)	383 (5.9)	490 (14.5)	13445 (22.9)
65-74	0	88 (1.4)	296 (8.8)	7389 (12.6)
>=75	0	29 (0.4)	81 (2.4)	1831 (3.1)
UNSPECIFIED	0	0	0	0
Mean	35.76	15.51	29.53	40.51
Median (range)	36.00 (18- 55)	4.00 (0- 86)	21.00 (1- 87)	43.00 (0- 91)
Race, n (%)				
WHITE	258 (78.2)	4985 (77.1)	2634 (77.9)	47640 (81.2)
BLACK	40 (12.1)	601 (9.3)	335 (9.9)	5055 (8.6)
ASIAN	26 (7.9)	439 (6.8)	239 (7.1)	3222 (5.5)
HISPANIC	3 (0.9)	59 (0.9)	38 (1.1)	482 (0.8)
OTHER	3 (0.9)	370 (5.7)	129 (3.8)	2161 (3.7)
UNSPECIFIED	0	15 (0.2)	7 (0.2)	96 (0.2)
Gender, n (%)				
MALE	171 (51.8)	3195 (49.4)	1728 (51.1)	29688 (50.6)
FEMALE	159 (48.2)	3274 (50.6)	1654 (48.9)	28968 (49.4)

Study C4591015 enrolled pregnant women and their infants. Infant participants were not vaccinated with the study investigational product
Participants who are treated in more than one clinical trial are counted only once per column
Includes Protocols: C4591001,C4591005,C4591007,C4591015,C4591017,C4591020,C4591024,C4591031

Appendix 2.3B Cumulative Summary Tabulations of Demographic Data (BNT BNT162-01, BNT162-04, BNT162-14 and BNT612-17)
BNT162/PF-07302048

	BNT162a1 (N=30)	BNT162b1 (N=120)	BNT162b2 (N=325)	BNT162b2 (B.1.1.7+ B.1.617.2) (N=299)	BNT162b2 (B.1.1.7) (N=20)	BNT162b2 (B.1.617.2) (N=392)	BNT162b2s01 (N=44)	BNT162b3 (N=96)	BNT162c2 (N=96)	Total (N=1339)
Age [years]										
>=18 to <30 years	4 (13)	23 (19)	37 (11)	57 (19)	7 (35)	38 (10)	2 (5)	19 (20)	36 (38)	213 (16)
>=30 to <50 years	10 (33)	43 (36)	104 (32)	121 (40)	10 (50)	141 (36)	14 (32)	26 (27)	39 (41)	485 (36)
>=50 to <65 years	16 (53)	32 (27)	118 (36)	95 (32)	3 (15)	135 (34)	12 (27)	25 (26)	21 (22)	432 (32)
>=65 to <75 years	0 (0)	20 (17)	58 (18)	22 (7)	0 (0)	56 (14)	13 (30)	20 (21)	0 (0)	169 (13)
>=75 years	0 (0)	2 (2)	8 (2)	4 (1)	0 (0)	22 (6)	3 (7)	6 (6)	0 (0)	40 (3)
Race, n (%)										
Asian	0 (0)	2 (2)	3 (1)	7 (2)	1 (5)	10 (3)	1 (2)	1 (1)	2 (2)	26 (2)
Black Or African American	0 (0)	1 (1)	1 (0)	20 (7)	0 (0)	11 (3)	1 (2)	0 (0)	0 (0)	33 (2)
American Indian Or Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	2 (0)
Native Hawaiian Or Other Pacific Islander	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)
White	29 (97)	117 (98)	321 (99)	245 (82)	19 (95)	362 (92)	42 (95)	95 (99)	93 (97)	1242 (93)
Other	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	4 (0)
Multiple	0 (0)	0 (0)	0 (0)	23 (8)	0 (0)	3 (1)	0 (0)	0 (0)	1 (1)	27 (2)
Missing	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	3 (0)
Ethnic, n (%)										
Hispanic Or Latino	0 (0)	2 (2)	5 (2)	38 (13)	9 (45)	57 (15)	0 (0)	0 (0)	3 (3)	114 (9)
Not Hispanic Or Latino	30 (100)	118 (98)	320 (98)	261 (87)	11 (55)	332 (85)	44 (100)	96 (100)	93 (97)	1222 (91)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	2 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Gender, n (%)										
Female	12 (40)	63 (53)	162 (50)	148 (49)	10 (50)	177 (45)	20 (45)	54 (56)	54 (56)	659 (49)
Male	18 (60)	57 (48)	163 (50)	151 (51)	10 (50)	215 (55)	24 (55)	42 (44)	42 (44)	680 (51)

Data Cutoff Date: 18Dec2021, Data Extraction Date: 20Dec2021
Subjects are counted only once within each treatment group, if they got same treatment in parent study and extension study. Subjects are counted only once in Total group even though they have different treatment groups in parent study and extension study.
Source: S:\statpgm\dev\bnt162\pbrer\pbrer2\programs\tfl\t-bnt-demog.sas, Date/time of run: 10JAN2022: 9:27

Appendix 2.3C Cumulative Summary Tabulations of Demographic Data (Fosun BNT162-03 and BNT162-06)
BNT162/PF-07302048

	BNT162b1 10µg (N=48) n (%)	BNT162b1 30µg (N=48) n (%)	Placebo (N=48) n (%)	BNT162b2/ Placebo (N=959) n (%)	TOTAL* (N=1103) n (%)
Age [years]					
≥18 to <30 years	7 (14.6)	6 (12.5)	5 (10.4)	49 (5.1)	67 (6.1)
≥30 to <50 years	14 (29.2)	16 (33.3)	15 (31.3)	338 (35.3)	383 (34.7)
≥50 to <65 years	3 (6.3)	2 (4.2)	4 (8.3)	412 (43.0)	421 (38.2)
≥65 to <75 years	19 (39.6)	22 (45.8)	19 (39.6)	149 (15.5)	209 (18.9)
≥75 years	5 (10.4)	2 (4.2)	5 (10.4)	11 (1.2)	23 (2.1)
Mean (SD)	54 (18.1)	54 (16.0)	56 (16.0)	53 (11.9)	54.3 (ND)
Median	60	59	60	54	59.5
Min	22	24	28	18	18
Max	82	75	82	84	84
Race, n (%)					
Asian	48 (100)	48 (100)	48 (100)	959 (100)	1103 (100)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity, n (%)					
Chinese Nationality					
Han Nationality	48 (100)	48 (100)	48 (100)	959 (100)	1103 (100)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gender, n (%)					
Male	24 (50)	24 (50)	24 (50)	491 (51.2)	563 (51.0)
Female	24 (50)	24 (50)	24 (50)	468 (48.8)	540 (49.0)

*Calculated; Includes BNT162-03 (b1 study) and BNT62-06 (B2 study)

Program: Tbase_Demo_3_1_PSUR.sas
Staburo GmbH. Based on unclean SDTM data received on 21JUN2021 with cut-off 18JUN2021.

Appendix 2.3.1 Cumulative Summary Tabulation of Demographic Data (S6.1)
BNT162/PF-07302048
Cumulative demographic information entered into the database through 18-DEC-2021

	B7471026: BNT162b2/ 20vPnC (N=187)	B7471026: BNT162b2/ Placebo (N=185)	Total (N=372)
Age (years)			
<=17	0	0	0
18-30	0	0	0
31-50	0	0	0
51-64	0	0	0
65-74	149 (79.7)	131 (70.8)	280 (75.3)
>=75	38 (20.3)	54 (29.2)	92 (24.7)
UNSPECIFIED	0	0	0
Mean	71.01	71.78	71.39
Median (range)	70.00 (65- 84)	71.00 (65- 85)	71.00 (65- 85)
Race, n (%)			
WHITE	164 (87.7)	165 (89.2)	329 (88.4)
BLACK	8 (4.3)	10 (5.4)	18 (4.8)
ASIAN	10 (5.3)	9 (4.9)	19 (5.1)
HISPANIC	1 (0.5)	0	1 (0.3)
OTHER	4 (2.1)	1 (0.5)	5 (1.3)
UNSPECIFIED	0	0	0
Gender, n (%)			
MALE	98 (52.4)	108 (58.4)	206 (55.4)
FEMALE	89 (47.6)	77 (41.6)	166 (44.6)

APPENDIX 3 (REFERRED TO IN SECTION 15 – OVERVIEW OF SIGNALS)

Tabular Summary of Safety Topics and Signals Evaluated During the Reporting Period

Product name: PF-07302048 (BNT162b2)

Reporting interval: 19 June 2021 – 18 December 2021

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Ongoing Signals							
Vasculitis	22 Nov 2021	Ongoing	N/A ongoing	Enquiry from a competent authority	Lareb (Netherlands) reviewed cases of vasculitis reported to the Netherlands Pharmacovigilance Centre and suggested that the relationship between vasculitis and Comirnaty should be further investigated	Safety & Clinical database review	Ongoing
Cerebral venous sinus thrombosis	02 Dec 2021	Ongoing	N/A – ongoing	Enquiry from a competent authority	Swissmedic requested Pfizer to submit a cumulative safety report on Comirnaty and cerebral venous sinus thrombosis.	Safety & Clinical database review	Ongoing

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Signals Determined Important Risks							
Myocarditis and Pericarditis Cont'ed	15 Feb 2021 Re-opened 19 Apr 2021 Re-opened 24 May 2021 Re-opened 24 Jun 2021 Re-opened 30 Jun 2021 Re-opened 14 Oct 2021	Closed	10 Nov 2021	Enquiry from a competent authority	Signal previously reviewed in the context of ongoing discussions with a health authority (Israel MoH) and in response to a PRAC signal assessment report and several requests from other Health Authorities. The MAH has continuously monitor the emerging evidence on the association between COVID-19 mRNA vaccine Comirnaty and myocarditis and pericarditis arising from all available of sources. In October 2021, PRAC Signal procedure prompted by new data on the known risk of myocarditis, pericarditis in a preliminary report of a meta-analysis of data from Denmark, Finland, Norway and Sweden. The signal re-evaluation found that in large, controlled, pivotal study C4591001, myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis and pericarditis.	Safety & Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been confirmed. Continuous monitoring of the emerging data continues. At the request of several HAs, the events were included as adverse reactions in local product labeling and as Important 1dentified risk in risk management and pharmacovigilance plans.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Myocarditis and Pericarditis Cont'ed					The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. In aggregate, the epidemiology studies reported higher risk after Dose 2 compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination.		Most recently, in response to the Nordic observational study data, the PRAC requested that the frequency be changed from "Not known" to "very rare" in the SmPC.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					The review of the post-marketing cases of myocarditis found that although the number of cases increases as the vaccine exposure increases, the profile of cases remains largely unchanged. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration.		

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Uveitis Cont'ed	31 Aug 2021	Closed	30 Sep 2021	Scientific Literature	Published article was retrieved ("Anterior uveitis onset after BNT162b2 vaccination: is this just a coincidence?", Renisi et al.). A safety database review of cases for Comirnaty coded with the PT, Uveitis, identified 142 cases amid 1,359,989,180 doses have been administered globally as of 22-Sep-2021. Given the complexity of diagnosing uveitis, the majority (53.5%) were not medically confirmed, with only 46.5% of cases categorized as medically confirmed. Almost half of the medically confirmed cases had either history of uveitis and/or no time of onset reported and thus excluded from analysis. Only 35 cases (almost 25% of the total reported cases) were medically confirmed without a medical history of an ocular pathology and had a time to onset of 30 days or less post-vaccination.	Safety database review O/E analysis	A causal association between the vaccine and this event has not been concluded based on available information. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Uveitis					A review of these cases showed that while the majority did not resolve at the time of reporting, there were no dose-dependent sequence of occurrence. None of these cases resulted in hospitalization or was fatal. Nevertheless, 20 of these cases did not have a medical history reported, some did not have concomitant medications reported, clinical or laboratory investigations conducted to exclude causes for differential diagnosis, nor intensity assessment. This missing information further confounds a proper assessment of causality to the vaccine. Lastly, the O/E ratios for both 21-day and no risk windows were <1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.		

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Rhabdomyolysis					Observed versus expected signal detection analyses for rhabdomyolysis showed some O/E ratios > 1, however the conservative approach and multiple limitations of these analyses lead this data to be weighed less heavily than the clinical study and spontaneous case series review		

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Glomerulo nephritis and Nephrotic Syndrome Cont'ed	27 Jul 2021	Closed	18 Aug 2021	Enquiry from a competent authority	PRAC provided a signal assessment report for glomerulonephritis and nephrotic syndrome and based on this and the SMSR #7 assessment, MAH was requested to provide a cumulative review of Glomerulonephritis and Nephrotic Syndrome. Subsequent to SMSR #10, Health Canada requested an updated cumulative review for SMSR #11. No cases of Glomerulonephritis or Nephrotic syndrome were reported in the large placebo controlled clinical trial with over 20,000 participants vaccinated with BNT162b2 (Study C4591001, cutoff date of 13 March 2021). There were no literature reports of studies or case series presentations of these conditions following vaccination with this vaccine. The safety database contains a total of 89 potentially relevant cases that were retrieved with the aforementioned search strategy. Most reports contained limited details, and the majority of cases with more detail reported alternate etiologies and/or significant confounding comorbidities.	Safety & Clinical database review Literature review O/E analysis	A causal association between the vaccine and these events has not been concluded. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Glomerulo nephritis and Nephrotic Syndrome					Even when utilizing a very conservative O/E analysis, the resulting ratio is <1, including the upper limit of the 95% CI.		
Erythema Multiforme Cont'ed	27 Jul 2021	Closed	18 Aug 2021	Enquiry from a competent authority	PRAC provided a signal assessment report on Erythema multiforme and requested a cumulative review of all cases concerning Comirnaty and erythema multiforme. No occurrences of EM were reported in the pivotal clinical trial in which over 20,000 participants received BNT162b2 (Study C4591001, cutoff date of 13 March 2021). One occurrence of EM was reported in a study of BNT162b2 in healthy Japanese adults (Study C4591005). The safety database contains a total of 124 potentially relevant cases, the majority of spontaneous cases were reported in females, from the age of 31 years and greater, post Dose 1, and the majority of EM events occurred from Day 1 to Day 3 post vaccination.	Safety & Clinical database review Literature review O/E analysis	A causal association between the vaccine and EM has not been concluded, , therefore the RSI has not been amended. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available. The EU SmPC was required by EMA to be updated to include Erythema multiforme as an adverse reaction

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Erythema Multiforme					The most commonly reported outcome of EM was resolved/resolving. There were no literature reports of studies or case series presentations of EM following vaccination with this vaccine. The O/E ratios for all risk windows overall and by dose are <1.		in section 4.8 with a frequency of "Not known"

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Myasthenia gravis Cont'ed	11 Mar 2021 (non-validated signal) Re-opened as a validated signal 16 Aug 2021	Closed	25 Aug 2021	Epidemiology O/E Analysis Enquiry from a competent authority	O/E finding (upper level of 95% CI exceeding 1) Health Canada Request for an updated review and analysis of myasthenia gravis in response to a Summary Monthly Safety Report inclusion of an O/E with an upper level of the 95% confidence interval exceeding 1 for both the 21-day and no risk windows in the interval period in the overall observed versus expected (O/E) analysis. The review of the post-marketing safety database found that most spontaneous cases are confounded by a medical history reporting a pre-existing MG or other significant clinical risk factors (ongoing autoimmune disease and or cancer).	Safety & Clinical database review Literature review O/E analysis	A causal association between the vaccine and MG has not been concluded. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Myasthenia gravis					Overall, 10 subjects reported the diagnosis confirmed by EMG and/or autoantibodies of which 5 had underlying autoimmune condition and 3 had an ongoing neoplasm Clinical study results do not demonstrate an imbalance between placebo and vaccine. At the time of the review, statistical signal detection in the Pfizer safety database has not shown a signal of disproportionate reporting for Myasthenia gravis. Further, O/E analysis does not suggest an increased rate for this topic. In the literature a worsening of MG symptoms after vaccination has not been identified as a risk while is clearly reported that infections account for 40-70% of the exacerbations. In addition, if the patient is not medically optimized, could developed a cytokine storm, despite being on steroids. Moreover, up to 15% of patients may experience worsening MG symptoms and/or exacerbations upon initiation of oral prednisolone therapy.		

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Immune Thrombocytopenia *Cont'ed*	21 Jan 2021 Re-opened 25 Feb 2021 Re-opened 14 Jun 2021 Re-opened 25 Jun 2021	Closed	04 Aug 2021	Enquiry from a competent authority Evaluation for PSUR	This topic was originally opened as a signal following a fatal case of thrombocytopenia following vaccination in the US and a subsequent FDA request. The signal re-opened following PRAC assessment for SMSR (#2 requesting cumulative overview of all cases reporting Immune thrombocytopenia/ Thrombocytopenia. Signal re-opened with request of FDA Office of Biostatistics and Epidemiology that signal detection on the Center for Medicare & Medicaid Services (CMS) database showed this event as an AESIs as a signal for the Pfizer/BNT COVID-19 vaccine (any dose) with a relative risk >1. Signal re-opened for full evaluation of data for PSUR.	Safety & Clinical database review. Literature review. O/E analysis.	A causal association between the vaccine and this event has not been concluded. Routine PV monitoring will continue, and the topic will be re-opened if new relevant information becomes available.

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Immune Thrombocytopenia					Overall, the review of thrombocytopenia from clinical study data, post-authorization spontaneous reports, medical literature and observed versus expected analyses did not identify sufficient information to establish a causal relationship with the vaccine. While there are spontaneous post-vaccination reports of de-novo and worsening thrombocytopenia in patients with and without known thrombocytopenia, respectively, it is not outside of the range that would be expected without BNT162b2 vaccination. While it is acknowledged that patients with a diagnostic history of immune thrombocytopenia may be the most vulnerable to thrombocytopenia if precipitated by the vaccine, the undulating nature of the disorder calls into question the vaccine as the clear cause. A hypothesis can be made about an immune response and molecular mimicry as a mechanism for thrombocytopenia, but this would be speculative in nature.		

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

Table 1. Tabular Summary of Safety Topics and Signals Considered During the Reporting Period

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

APPENDIX 4.2 **As of: 09-Jan-2022**

Periodic Safety Update Report

Status of Ongoing SS* Clinical Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period

Report Name - BNT162::ALL

Reporting Period: 19-Jun-2021 Through 18-Dec-2021

Protocol Id: C4591015** EudraCT Number: 2020-005444-35 Phase: III Planned Enrollment: 700

Study Design Blinding: DOUBLE-BLIND Statistical Design: PARALLEL

Minimum Age: 0 YR Maximum Age: 999 YR Gender: BOTH (MALES AND FEMALES)

Protocol Title: 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

Country: BRAZIL; SOUTH AFRICA; SPAIN; UNITED KINGDOM; UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	MATERNAL IMMUNISATION	16-Feb-2021/ N/A		
	PLACEBO	PLACEBO	INTRAMUSCULAR-INJECTION VIAL-0NO UNITS				

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

Protocol Id: C4591024** EudraCT Number: 2021-001290-23 Phase: IIB Planned Enrollment: 360

Study Design Blinding: OPEN Statistical Design: SINGLE GROUP

Minimum Age: 2 YR Maximum Age: 999 YR Gender: BOTH (MALES AND FEMALES)

Protocol Title: A PHASE 2b, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF VACCINE CANDIDATE BNT162b2 IN IMMUNOCOMPROMISED PARTICIPANTS ≥2 YEARS OF AGE

Country: BRAZIL; GERMANY; UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	BNT162B2	STUDY DRUG	INTRAMUSCULAR-INJECTION VIAL-30UG	COVID-19 INFECTION	15-Oct-2021/ N/A		

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

APPENDIX 4.4 **As of: 09-Jan-2022**

Periodic Safety Update Report

Status of Ongoing SS* NIS Trials (Started, or Concluded with No Final Clinical Study Reports) During the Reporting Period

Report Name - BNT162::ALL

Reporting Period: 19-Jun-2021 through 18-Dec-2021

Protocol Id: C4591008** EudraCT Number: Phase: N/A Planned Enrollment: 20000

Study Design Blinding: NOT APPLICABLE Statistical Design: NOT APPLICABLE

Minimum Age: 18 YR Maximum Age: 120 YR Gender: BOTH (MALES AND FEMALES)

Protocol Title: HERO-Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers, their families, and their communities

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	NO DRUG	NONE		SAFETY ADVERSE EVENTS OF INTEREST	17-Dec-2020/ N/A	INTERIM	22-Jun-2021

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

Protocol Id: C4591010** EudraCT Number: Phase: N/A Planned Enrollment: 13334

Study Design Blinding: NOT APPLICABLE Statistical Design: NOT APPLICABLE

Minimum Age: 18 YR Maximum Age: 120 YR Gender: BOTH (MALES AND FEMALES)

Protocol Title: A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU

Country: GERMANY; ITALY; SPAIN

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	NO DRUG	NONE		ADVERSE EVENTS OF SPECIAL INTEREST	28-Sep-2021/ N/A		

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

Protocol Id: C4591012** EudraCT Number: Phase: N/A Planned Enrollment: 0

Study Design Blinding: NOT APPLICABLE Statistical Design: NOT APPLICABLE

Minimum Age: Maximum Age: Gender:

Protocol Title: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Country: UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	NO DRUG	NONE		SAFETY ADVERSE EVENTS OF INTEREST	11-Mar-2021/ N/A	INTERIM	23-Jun-2021

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

Protocol Id: C4591021** EudraCT Number: Phase: N/A Planned Enrollment: 0

Study Design Blinding: NOT APPLICABLE Statistical Design: NOT APPLICABLE

Minimum Age: Maximum Age: Gender: BOTH (MALES AND FEMALES)

Protocol Title: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Country: ITALY; NETHERLANDS; NORWAY; SPAIN; UNITED KINGDOM

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	NO DRUG	NONE		ADVERSE EVENTS OF SPECIAL INTEREST	03-Sep-2021/ N/A		

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

Protocol Id: C4591022** EudraCT Number: Phase: N/A Planned Enrollment: 1800

Study Design Blinding: NOT APPLICABLE Statistical Design: NOT APPLICABLE

Minimum Age: 18 YR Maximum Age: 64 YR Gender: FEMALES

Protocol Title: Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

Country: CANADA; UNITED STATES

Protocol Status	Drug	Drug Type	Route - Form - Max Daily Dose	Indication	First Subj Visit/ Last Subj Visit	Report Type	Max Interim -Final Report Date
ONGOING	NO DRUG	NONE		MAJOR CONGENITAL MALFORMATION/ POSTNATAL GROWTH RESTRICTION/PRETERM DELIVERY/SMALL FOR GESTATIONAL AGE/ SPONTANEOUS ABORTION/ STILLBIRTH	01-Oct-2021/ N/A		

*SS = Safety Studies ; **Post Authorization Safety Studies (PASS)

APPENDIX 5

LIST OF SOURCES OF INFORMATION USED TO PREPARE THE PSUR – ABSTRACTS OF LITERATURE STUDIES

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	Anaphylaxis
Cherrez-Ojeda I, Robles-Velasco K, Osorio MF et al. Pilot study of acute allergic reactions to mRNA-BNT162b2 vaccine in an ecuadorian cohort European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 483-484. Sucre-Adrianza I, Garcia-Villa H, Garcia-Zaragoza MDR et al. Hypersensitivity reactions to pfizer-biontech COVID-19 vaccine in the staff of Hospital Clinico San Carlos in Madrid, Spain: European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 650. Crespo Quiros J, Juarez Guerrero A, Rodriguez Hermida S et al. Changes in asthma control after administration of COVID-19 mRNA vaccines: European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 487-488. Lee E, Yeon-Kyeong L, Tae Eun K et al. Reports of anaphylaxis after coronavirus disease 2019 vaccination, South Korea, 26 February to 30 April 2021. Euro Surveill. 2021 Aug;26(33):2100694. Shavit R, Maoz-Segal R, Iancovici-Kidon M et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. JAMA Network Open 2021: 4(8): e2122255.	Allergic reactions to vaccines are rare, occurring at 1 per 1'000.000 to 30 per 100.000; BNT162b2 vaccine excipients include PEG/macrogol, rarely cause of allergy. Contact sensitivity to PEG is more frequent than anaphylaxis. CDC reported an estimated rate of 11.1 cases of anaphylaxis per million doses administered in patients with a history of allergies. Different studies performed confirm that the majority of patients, 94.65%, did not report any allergic symptoms after BNT162b2, similar to previous studies (98%). Anaphylaxis with COVID-19 vaccination is extremely rare (Cherrez-Ojeda I et al 2021). Similarly, he incidence of hypersensitivity reactions to Comirnaty vaccine is very low (0.07%) (Sucre-Adrianza I et al 2021). The vaccine has been found to be safe in subject with underlying asthma and specifically asthma exacerbation after mRNA vaccination is infrequent and not related to asthma severity (Crespo Quiros J et al 2021). A lower estimation incidence rate has been found in different countries, Lee E et al report the incidence rate of anaphylaxis in South Korea after mass vaccination programme (administered 3.8 million doses) of COVID-19 vaccinations between 26 February and 30 April 2021. The rates per million doses were 18.2 cases and 6.2 cases for Vaxzevria and Comirnaty, respectively (Lee E et al 2021). Shavit R et al studied the prevalence of allergic reactions after Pfizer-BioNTech COVID-19 Vaccination among adults with high allergy risk and concluded that the rate of allergic reactions to BNT162b2 vaccine, is higher among patients with allergies, particularly among a subgroup with a history of high-risk allergies.
	Myocarditis and pericarditis
Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 Dec 2;385(23):2140-2149. Witberg G, Barda N, Hoss S et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021 Dec 2;385(23):2132-2139.	Mervorach et al report a retrospective review of reports of myocarditis in Israel conducted up to 31 May 2021. The authors found that the overall risk difference between the first and second doses was 1.76 per 100,000 persons (95% CI, 1.33 to 2.19), with the largest difference among male recipients between the ages of 16 and 19 years (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46). As compared with the expected incidence based on

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Patone M, Mei XW, Handunnetthi L et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2021 Dec 14. doi: 10.1038/s41591-021-01630-0. Epub ahead of print. PMID: 34907393. Das BB, Kohli U, Ramachandran P et al. Myopericarditis after messenger RNA Coronavirus Disease 2019 Vaccination in Adolescents 12 to 18 Years of Age. J Pediatr. 2021 Nov;238:26-32.e1. Lazaros G, Anastassopoulou C, Hatziantoniou S et al. A case series of acute pericarditis following COVID-19 vaccination in the context of recent reports from Europe and the United States. Vaccine. 2021 Oct 29;39(45):6585-6590. Kim HW, Jenista ER, Wendell DC et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol. 2021 Oct 1;6(10):1196-1201. doi: 10.1001/jamacardio.2021.2828. PMID: 34185046; PMCID: PMC8243258. Snapiri O, Rosenberg Danziger C, Shirman N et al. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J. 2021 Oct 1;40(10):e360-e363. doi: 10.1097/INF.0000000000003235. PMID: 34077949; PMCID: PMC8443419.	historical data, the standardized incidence ratio was 5.34 (95% CI, 4.48 to 6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 years (13.60; 95% CI, 9.30 to 19.20). The rate ratio 30 days after the second vaccine dose in fully vaccinated recipients, as compared with unvaccinated persons, was 2.35 (95% CI, 1.10 to 5.02); the rate ratio was again highest in male recipients between the ages of 16 and 19 years (8.96; 95% CI, 4.50 to 17.83), with a ratio of 1 in 6637. Also from Israel, but from a healthcare organization, Witberg et al found that the estimated incidence per 100,000 persons who had received at least one dose of vaccine was 2.13 cases (95% CI, 1.56 to 2.70). The highest incidence of myocarditis (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46) was reported in male patients between the ages of 16 and 29 years. Most cases of myocarditis were mild or moderate in severity. Patone et al report a self-controlled and very large case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021 to investigate hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 1-28 days following adenovirus (ChAdOx1, n = 20,615,911) or messenger RNA-based (BNT162b2, n = 16,993,389; mRNA-1273, n = 1,006,191) vaccines or a SARS-CoV-2 positive test (n = 3,028,867). Authors found increased risks of myocarditis associated with the first dose of ChAdOx1 and BNT162b2 vaccines and the first and second doses of the mRNA-1273 vaccine over the 1-28 days postvaccination period, and after a SARS-CoV-2 positive test. They estimated an extra two (95% CI 0, 3), one (95% CI 0, 2) and six (95% CI 2, 8) myocarditis events per 1 million people vaccinated with ChAdOx1, BNT162b2 and mRNA-1273, respectively, in the 28 days following a first dose and an extra ten (95% CI 7, 11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273. Authors also observed increased risks of pericarditis and cardiac arrhythmias following a positive SARS-CoV-2 test. Similar associations were not observed with any of the COVID-19 vaccines, apart from an increased risk of arrhythmia following a second dose of mRNA-1273.

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	Subgroup analyses by age showed the increased risk of myocarditis associated with the two mRNA vaccines was present only in those younger than 40. Regarding myocarditis in adolescents (12 to 18 years), Das et al report a cross-sectional study of 25 children, aged 12-18 years, diagnosed with probable myopericarditis. The authors found that most (88%) cases followed the second dose of vaccine, and chest pain (100%) was the most common presenting symptom. Symptoms owing to myopericarditis after the mRNA COVID-19 vaccination tend to be mild and transient. Approximately two-thirds of patients underwent cardiac magnetic resonance imaging, which revealed evidence of myocardial inflammation despite a lack of echocardiographic abnormalities. Symptom resolution was observed within 7 days in all patients. Several other publications provided case series of myocarditis supporting that cases of myocarditis appear to be mild, respond to standard of care and resolve without sequelae, although the duration of follow up is generally limited (Lazaros et al, Kim et al, Snapiri et al).
	Immune-mediated/Autoimmune conditions
Li X, Tong X, Wan Yin Yeung W et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis. 2021 Oct 22;annrheumdis-2021-221571. Furer V, Eviatar T, Zisman D et al. Immunogenicity and safety of the BNT162B2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and general population: A multicenter study. European Congress of Rheumatology, EULAR 2021. Virtual. Publication: Annals of the Rheumatic Diseases 2021: 80(SUPPL 1): 200-201. Furer V, Eviatar T, Zisman D et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Annals of the Rheumatic Diseases 2021: 80(10): 1330-1338.	Arthritis A number of study have been performed on possible arthritis flare after COVID-19 vaccination and all of them were very reassuring (Li X et al 2021). Furer V et al performed a multicenter study to evaluate immunogenicity and safety of the BNT162B2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and general population. They concluded that vaccination with the BNTb262 vaccine resulted in an adequate immunogenic response with an acceptable safety profile in the majority of patients with AIIRD. Treatment with GC, rituximab, MMF, and abatacept may impair BNT162b2-induced immunogenicity. Postponing administration of rituximab, when clinically feasible, seems to be reasonable to improve vaccine-induced immunogenicity. Holding treatment with abatacept and MMF may be considered on an individual basis (Furer V et al 2021, Picchianti-Diamanti A et al 2021)

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Picchianti-Diamanti A, Aiello A, Laganà B et al. Immunosuppressive Therapies Differently Modulate Humoral- and T-Cell-Specific Responses to COVID-19 mRNA Vaccine in Rheumatoid Arthritis Patients. Frontiers in Immunology 2021: 12: 740249. Esquivel-Valerio JA, Skinner-Taylor CM, Moreno-Arquieta IA et al. Adverse events of six COVID-19 vaccines in patients with autoimmune rheumatic diseases: a cross-sectional study. Rheumatology International 2021: 41(12): 2105-2108. Bartels LE, Ammitzbøll C, Bøgh Andersenet J et al. Local and systemic reactogenicity of COVID-19 vaccine BNT162b2 in patients with systemic lupus erythematosus and rheumatoid arthritis. Rheumatology International 2021: 41(11): 1925-1931. Heshin-Bekenstein M, Elkayam O, Ziv A et al. Safety and immunogenicity of the BNT162B2 mRNA COVID-19 vaccine in adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases. Pediatric Rheumatology 2021: 19(SUPPL 1). Maritsi D, Dasoula F, Vartzelis G et al. Safety and tolerability of the biontech COVID-19 vaccine in adolescent patients with JIA on TNFi. Pediatric Rheumatology 2021: 19(SUPPL 1). Macedoni M, Calcaterra V, Smylie G et al. Safety and immunogenicity of the BNT162B2 MRNA vaccine for COVID-19 in adolescents and young adults with type 1 diabetes Diabetes 2021: 22(SUPPL 30): 15-16. Ali H, Alterki A, Sindhu S et al. Robust Antibody Levels in Both Diabetic and Non-Diabetic Individuals After BNT162b2 mRNA COVID-19. Front Immunol. 2021 Nov 24;12:752233.	Esquivel-Valerio JA studies the prevalence of AE presented with six different SARS-CoV-2 vaccines {ChadOX1 nCoV-19 (AZD1222), Ad5-nCoV2, Ad26.COV2.S, mRNA-1273, BNT162b2, and CoronaVac} in Mexican patients with AIIRD. Overall known reactogenicity events but no serious AE that required medical attention or hospitalization were reported. The current results support the safety of different COVID-19 vaccines in patients with AIIRD. Bartels LE et al studied local and systemic reactogenicity of COVID-19 vaccine BNT162b2 in patients with systemic lupus erythematosus and rheumatoid arthritis They reported that the majority of SLE and RA patients experienced either local (78.0%) or systemic reactions (80.1%). Nevertheless, reactogenicity was more frequent in patients, however, not more severe compared with healthy controls. Very encouraging results were also obtained in in adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases (Heshin-Bekenstein M et al 2021, Maritsi D et al 2021). The authors performed a prospective multicenter study and examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. They concluded that BNTb262 mRNA COVID-19 vaccine had an have excellent safety profile in immunocompromised adolescents with Juvenile-onset AIIRD, with mild post vaccination side effects, similar to the safety profile of the healthy controls. No post vaccination COVID-19 illness was documented. Post vaccination disease activity was mostly kept stable. Overall, the literature data suggest that COVID-19 vaccines in patients with AIIRD are safe. Diabetes A study from Macedoni M et al on subjects with underlying diabetes showed that these patients developed vaccine-induced antibody responses

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	after the BNT162b2 mRNA vaccine and that the vaccine showed a good safety profile. Hypertension and obesity did not show significant changes in antibody titers. Type-2 diabetic and non-diabetic individuals elicited strong immune responses to SARS-CoV-2 BNT162b2 mRNA vaccine; nonetheless, lower levels were seen in people with diabetes (Ali H et al 2021).
	Neurological events
Patone M, Handunnetthi L, Saatci D et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection Nat Med. 2021 Dec;27(12):2144-2153. Garcia-Grimshaw M, Michel-Chavez A, Vera-Zertuche JM et al. Guillain-Barre syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clinical Immunology 2021: 230: 108818. Shemer A, Pras E, Einan-Lifshitz A et al. Association of COVID-19 Vaccination and Facial Nerve Palsy: A Case-Control Study. JAMA Otolaryngology-- Head & Neck Surgery 2021: 147(8): 739-743. Wan EYF, Chui CSL, Lai FTT et al. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. Lancet Infect Dis. 2022 Jan;22(1):64-72. Massoud F, Ahmad SF, Hassan AM et al. Safety and tolerability of COVID-19 vaccine among Patients with Epilepsy (PWE) in a tertiary hospital in kuwait: A patient Survey Epilepsia 2021: 62(SUPPL 3): 80. Lotan I, Wilf-Yarkon A, Friedman Y et al. Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis: Early experience from a tertiary multiple sclerosis center in Israel Multiple Sclerosis Journal 2021: 27(2 SUPPL): 283-284. Lotan I, Wilf-Yarkoni A, Friedman Y et al Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis (MS): Early experience from a tertiary MS center in Israel. European Journal of Neurology 2021: 28(11): 3742-3748.	Guillain Barrè syndrome Patone M et al performed a self controlled case series study to investigate hospital admissions from neurological complications in the 28 days after a first dose of ChAdOx1nCoV-19 (n = 20,417,752) or BNT162b2 (n = 12,134,782), and after a SARS-CoV-2-positive test (n = 2,005,280). There was an increased risk of Guillain-Barre syndrome (incidence rate ratio (IRR), 2.90; 95% CI: 2.15-3.92 at 15-21 days after vaccination) and Bell's palsy (IRR, 1.29; 95% CI: 1.08-1.56 at 15-21 days) with ChAdOx1nCoV-19. There was an increased risk of hemorrhagic stroke (IRR, 1.38; 95% CI: 1.12-1.71 at 15-21 days) with BNT162b2. The study estimated 38 excess cases of Guillain-Barre syndrome per 10 million people receiving ChAdOx1nCoV-19 and 145 excess cases per 10 million people after a positive SARS-CoV-2 test. In summary, although we find an increased risk of neurological complications in those who received COVID-19 vaccines, the risk of these complications is greater following a positive SARS-CoV-2 test (Patone M et al 2021). Another study from Garcia-Grimshaw M et al confirm these results as they found that, among recipients of the BNT162b2 mRNA vaccine, GBS may occur at the expected community-based rate. Bell's Palsy No increased risk of Bell's palsy has been found after receiving after first dose of BNT162b2 COVID-19 vaccines (Patone M et al 2021, Shemer A et al 2021). Another study from Wan E.Y.F. et al performed a case series and nested case-control study done in Hong Kong, where the risk of Bell's palsy within 42 days following vaccination with BNT162b2 or CoronaVac was assessed.

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Chou S, Kaviani K, Ropero B et al. Incidence of multiple sclerosis relapses and pseudorelapses following mRNA COVID-19 vaccination. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 220-221. Millan-Pascual J, Valero-Lopez G, Lopez-Tovar IA et al Serological response to SARS-CoV-2 vaccination in multiple sclerosis patient in a real-life experience. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 767-768. Briggs FBS, Mateen FJ, Schmidt H et al COVID-19 Vaccination Reactogenicity in Persons With Multiple Sclerosis. Neurology neuroimmunology & neuroinflammation 2022: 9(1). Alonso R, Leguizamón, F; Silva BA et al Safety of COVID-19 vaccines in patients with multiple sclerosis from Latin America Multiple Sclerosis Journal 2021: 27(2 SUPPL): 695-696. Alroughani R, Al-Hashel J, Abokalawa F et al. COVID-19 vaccination in people with multiple sclerosis. The Kuwait experience: Multiple Sclerosis Journal 2021: 27(2 SUPPL): 785. Menascu S, Dreyer-Alster S, Dolev M et al. Safety and efficacy of COVID-19 Pfizer-BNT162b2 m-RNA vaccine in young MS population Multiple Sclerosis Journal 2021: 27(2 SUPPL): 255-256. Dreyer-Alster S, Dolev M, Menascu S et al. 2021 COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by May 2021. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 253-254.	The results suggest an overall increased risk of Bell's palsy only after CoronaVac vaccination. Epilepsy Studies in subject with underlying epilepsy showed that the relative risk of seizure worsening after the first, second BNT162b2, and first ChAdOx1 nCoV-19 vaccines was 1.027 (95% CI 0.891-1.183), 1.019 (95% CI 0.928-1.119) and 1.026 (95% CI 0.929-1.134) respectively indicating that the available vaccines have a good safety profile with minimal risk of seizure worsening (Massoud F et al 2021). A cross-sectional study to evaluate safety and tolerability of the novel 2019 coronavirus disease (COVID-19) vaccines among people with epilepsy (PwE) was performed by Massoud F et al. This study shows that the two vaccines under consideration (BNT162b2 and ChAdOx1nCoV-19) have a good safety profile (mostly known reactogenicity events) and a low risk of epilepsy worsening among a cohort of PwE with a relative risk of seizure worsening after the first and second doses of BNT162b2 and the first dose of ChAdOx1nCoV-19 vaccines was 1.027 (95% CI 0.891-1.183), 1.019 (95% CI 0.928-1.119), and 1.026 (95% CI 0.929-1.134) respectively. Overall, the literature data suggest that the available COVID-19 vaccines have a good safety profile with minimal risk of seizure worsening in subjects with underlying epilepsy. Multiple sclerosis A study on safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis showed that 15.1% of these subjects reported new or worsening neurological symptoms following the vaccination, the most frequent being sensory disturbances (58.3%). Most symptoms occurred within the first 24 hours after vaccination and resolved within three days. Most participants (77.8%) didn't require any medication to treat their symptoms. This study indicates an overall favorable safety profile of the BNT162b2 vaccine in people with MS (Lotan I et al 2021). Another study also supports these results as no clinical relapses occurred in association with mRNA vaccines and there was no association between a patient's disease-modifying therapy,

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	age, sex, or race and their risk of suffering from a pseudo-relapse after COVID-19 vaccination. The risk of transient neurological worsening was very low (average 5.9%) (Chou S et al 2021). Similarly, a study on the serological response to SARS-CoV-2 vaccination in multiple sclerosis patient showed that time from the last dosing was related to serological response in anti-CD-20 therapies; age, disease duration, disease phenotype, vaccine used, or lymphocyte counts did not affect humoral response to COVID-19 vaccination. Anti-CD20 therapies and Fingolimod seem to condition a lower humoral response to vaccines against SARS-CoV-2. Vaccination prior initiation of these DMTs medication administration would be recommendable whenever possible (Millan-Pascual J et al). Briggs FBS et al executed a retrospective cross-sectional study to generate real-world multiple sclerosis-specific vaccine safety information, particularly in the context of specific DMTs. SARS-CoV-2 vaccine reactogenicity profiles and the associated factors in MS patients appear similar to those reported in the general population.MS patients on specific DMTs were less likely to report vaccine reactions. Overall, the short-term vaccine reactions experienced in the study population were mostly self-limiting, including pain at the injection site, fatigue, headache, and fever. Overall studies in subjects with underlying multiple sclerosis show that COVID-19 vaccines seem to be safe for patients with Multiple sclerosis. No major safety signals were detected (Alonso R et al 2021, Alroughani R et al 2021, Chou S. et al 2021, Menascu S et al 2021) and the rate of acute relapses during the follow-up period was similar between vaccinated and non-vaccinated MS patients (4.6%) (Dreyer-Alster S et al 2021).
	Herpes zoster
Barda N, Dagan N, Ben-Shlomo Y et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. New England Journal of Medicine. 2021 Aug 25.	A large study using data from the largest health care organization in Israel to evaluate the safety of the BNT162b2 mRNA vaccine. For each potential adverse event, in a population of persons with no previous diagnosis of that event, the authors individually matched vaccinated persons to unvaccinated

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Furer V, Zisman D, Kibari A et al. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. Rheumatology. 2021 Apr 12. Furer V, Zisman D, Elkayam O. Comment on: Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series: reply. Rheumatology (Oxford, England). 23 Sep 2021.	persons according to sociodemographic and clinical variables. Risk ratios and risk differences at 42 days after vaccination were derived with the use of the Kaplan-Meier estimator. To place these results in context, the authors performed a similar analysis involving SARS-CoV-2-infected persons matched to uninfected persons. The same adverse events were studied in the vaccination and SARS-CoV-2 infection analyses. In the vaccination analysis, the vaccinated and control groups each included a mean of 884,828 persons. Vaccination was most strongly associated with a number of adverse events including herpes zoster infection (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24 (Barda N et al 2021). Furer V et al assessed the safety of the BNT162b2 mRNA vaccination in an observational study monitoring post-vaccination adverse effects in patients with AIIRD (n = 491) and controls (n = 99), conducted in two rheumatology departments in Israel. As per the results. the prevalence of HZ was 1.2% (n = 6) in patients with AIIRD compared with none in controls. Six female patients aged 49 +/- 11 years with stable AIIRD: RA (n = 4), Sjogren's syndrome (n = 1), and undifferentiated connective disease (n = 1), developed the first in a lifetime event of HZ within a short time after the first vaccine dose in five cases and after the second vaccine dose in one case. In the majority of cases, HZ infection was mild, except a case of HZ ophthalmicus, without corneal involvement, in an RA patient treated with tofacitinib. There were no cases of disseminated HZ disease or postherpetic neuralgia. All but one patient received antiviral treatment with a resolution of HZ-related symptoms up to 6 weeks. Five patients completed the second vaccine dose without other adverse effects. The authors concluded that epidemiologic studies on the safety of the mRNA-based COVID-19 vaccines in patients with AIIRD are needed to clarify the association between the BNT162b2 mRNA vaccination and reactivation of zoster. Furer V et al provided a response to the article published by the authors' group, entitled 'Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	case series'. The authors stated in the response that: "Herpes zoster is indeed a common comorbidity in patients suffering from AIIRD and therefore it is challenging to postulate the direct causality to vaccination based on the cluster of cases. Following the publication of the above article, the authors received numerous mail from all over the world with reports of post-vaccination herpes zoster occurrence in both immunocompetent and immunocompromised patients (personal communication). Furthermore, accumulating evidence has recently emerged confirming the increased incidence of herpes zoster infection following mRNA-based COVID-19 vaccination in immunocompetent subjects, as reported in case series by Psichogiou from Greece and a large-scale population-based study from Israel. In the latter, the BNT162b2 mRNA vaccinated and control groups, including a mean of 884 828 persons each, were followed for 42 days after vaccination. Vaccination was strongly associated with herpes zoster infection: risk ratio, 1.43; 95% CI: 1.20, 1.73; risk difference, 15.8 events per 100 000 persons; 95% CI: 8.2, 24.2. Interestingly, data on >240 000 SARS-CoV-2 infected persons were assessed to estimate the effects of a documented SARS-CoV-2 infection on the incidence of adverse events. SARS-CoV-2 infection was not estimated to have a meaningful effect on the incidence of herpes zoster infection. In summary, the present epidemiological data points out that herpes zoster might represent a potential adverse event of mRNA SARS-CoV-2 vaccination, with the limitation of the lack of dermatopathological assessment in most cases. In the authors' opinion, reactivation of herpes zoster following SARS-CoV-2 vaccination should be considered by the medical community and vaccination for herpes zoster should be offered when appropriate.
	Mortality
Xu S, Huang R, Sy LS, Glenn SC, Ryan DS, Morrissette K, Shay DK, Vazquez-Benitez G, Glanz JM, Klein NP, McClure D, Liles EG, Weintraub ES, Tseng HF, Qian L. COVID-19 Vaccination and Non-COVID-19 Mortality Risk - Seven Integrated Health Care Organizations, United States, December 14, 2020-July 31, 2021. MMWR Morb Mortal Wkly Rep. 2021	Xu et al report an analysis of Vaccine Safety Datalink of approx. 11 million persons enrolled by July 2021. This study found that COVID-19 vaccine recipients had lower non-COVID-19 mortality than did unvaccinated persons. After adjusting for demographic characteristics and VSD site, this study found that adjusted relative risk (aRR) of non-COVID-19 mortality

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Oct 29;70(43):1520-1524. doi: 10.15585/mmwr.mm7043e2. PMID: 34710075; PMCID: PMC8553028.	for the Pfizer-BioNTech vaccine was 0.41 (95% CI = 0.38-0.44) after dose 1 and 0.34 (95% CI = 0.33-0.36) after dose 2 and thus, there is no increased risk for mortality among COVID-19 vaccine recipients.
	Booster dose
Shapiro Ben David S, Shamir-Stein N, Baruch Gez S et al. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. Clinical Immunology 2021: 232: 108860. Bar-On Y M, Goldberg Y, Mandel M et al. Protection of BNT162B2 vaccine booster against covid-19 in Israel. New England Journal of Medicine 2021: 385(15): 1393-1400. Bensouna I, Caudwell V, Kubab S et al. SARS-CoV-2 Antibody Response After a Third Dose of the BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. Am J Kidney Dis. 2021 Sep 8;S0272-6386(21)00833-7.	Data on administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (in Israel for persons who were 60 years of age or older and who had received a second dose of vaccine at least 5 months earlier were studied (from July 30 through August 31, 2021). The study shows that in participants who were 60 years of age or older and had received two doses of the BNT162b2 vaccine at least 5 months earlier, had rates of confirmed Covid-19 and severe illness substantially lower among those who received a booster (third) dose of the BNT162b2 vaccine. Another study from Israel describes a retrospective cohort, using electronic surveys sent to booster vaccine recipients, during July 20-August 10, 2021. Overall 17,820 participated in the survey, with a response rate of 30.2% among which 3195 (17.9%) were immunocompromised. Fatigue, myalgia and fever were the most frequent systemic side effects reported (19.6%, 9.2% and 8.1% respectively among immunocompromised; 21.3%, 9.9% and 9.2% respectively among seniors). A total of 67.3% of immunocompromised and 62% of seniors reported experiencing a better or a similar response to the third dose, compared to the second. The data overall show that local and systemic reactions after third BNT162b2 vaccine, reported by immunocompromised and seniors, were similar to those observed following previous vaccines and mostly self-resolved. Bensouna I et al reported also the data of a third dose of the BNT162b2 vaccine is patients with dyalisis. The study shows that the booster dose substantially increased antibody levels in patients receiving maintenance dialysis and appeared to be as well tolerated as a second dose.
	Heterologous vaccination
Borobia AM, Carcas AJ, Perez-Olmeda M et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants	Borobia AM et al assessed the immunogenicity and reactogenicity of BNT162b2 administered as second dose in participants primed with ChAdOx1-S trough a phase 2, open-label, randomised, controlled trial on

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
(CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet 2021: 398(10295): 121-130.	adults aged 18-60 years, vaccinated with a single dose of ChAdOx1-S 8-12 weeks before screening, and no history of SARS-CoV-2 infection. A 14-day immunogenicity and safety outcome as 7-day reactogenicity were evaluated. Between April 24 and 30, 2021, 676 individuals were enrolled. In the intervention group. Geometric mean titres of RBD antibodies and IgG against trimeric spike protein highly increased. Reactions were mild (n=1210 [68%]) or moderate (n=530 [30%]), with injection site pain, headache and myalgia being the most commonly reported adverse events. No serious adverse events were reported. Overall the data suggest that BNT162b2 given as a second dose in individuals prime vaccinated with ChAdOx1-S induced a robust immune response, with an acceptable and manageable reactogenicity profile.
	Safety in special populations
Longlune N, Nogier MB, Miedougé M et al. High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrology Dialysis Transplantation 2021: 36(9): 1704-1709. Russo G, Lai Q, Poli L et al SARS-COV-2 vaccination with BNT162B2 in renal transplant patients: Risk factors for impaired response and immunological implications. Clin Transplant. 2021 Sep 26;e14495. Grupper A, Rabinowich L, Schwartz D et al Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. American Journal of Transplantation 2021: 21(8): 2719-2726. Yeshurun M, Pasvolsky O, Shargian L et al. Humoral serological response to the BNT162b2 vaccine after allogeneic haematopoietic cell transplantation. Clin Microbiol Infect. 2021 Oct 29;S1198-743X(21)00606-6. Ram R, Hagin D, Freund T et al. Safety and efficacy of the BNT162B2 MRNA Covid-19 vaccine in patients after allogeneic HCT and CD19-based CAR-T therapy - A single center prospective cohort study. 26th Congress of the European Hematology Association, EHA 2021. Virtual. Publication: HemaSphere 2021: 5(SUPPL 2): 101.	Safety profile in individuals with a history of COVID-19 infection A total of 3 relevant articles presented information regarding safety of BNT162b2 administration in individuals with a history of COVID-19 infection. Studies generally showed that compared with individuals without a history of COVID-19 infection, the individuals with a positive history have a higher risk (up to 3-fold) of adverse events following the first dose, but notably lower risk of side effects after the second dose. Safety profile in patients with underlying comorbidities – Cancers Several studies concerned BNT162b2 administration in patients with cancers, including patients receiving chemotherapy and/or immunotherapy at the time of vaccination. The largest cohorts were presented by Brunello et al consisting of 5297 patients with solid and/or onco-hematologic malignancies from an Italian oncology center, and Subbiah et al of a real-world observational cohort of 6388 patients. Generally, the safety profile of BNT162b2 administration in patients with malignancies was similar to the known safety profile of BNT162b2. No new safety concerns were identified based on the review of vaccination safety in patients with malignancies. Safety profile in patients with underlying comorbidities – Transplant

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
Ali H, Ngo D, Aribi A et al. Safety and Tolerability of SARS-CoV2 Emergency-Use Authorized Vaccines for Allogeneic Hematopoietic Stem Cell Transplant Recipients. Transplantation and Cellular Therapy 2021: 27(11): 938.e1-938.e6. Ram R, Hagin D, Kikozashvilli N et al. Safety and Immunogenicity of the BNT162b2 mRNA COVID-19 Vaccine in Patients after Allogeneic HCT or CD19-based CART therapy-A Single-Center Prospective Cohort Study Transplantation and Cellular Therapy 2021: 27(9): 788-794. Davidov-Derevyanko Y, Tsaraf K, Ezra OC et al. Safety and efficacy of bnt162b2 mrna vaccine among liver transplant recipients Hepatology 2021: 74(SUPPL 1): 336A-337A. Rabinowich L, Grupper A, Baruch R et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. Journal of Hepatology 2021: 75(2): 435-438. Ou MT, Boyarsky, Moter JD et al. Safety and Reactogenicity of 2 Doses of SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients. Transplantation 2021: 105(10): 2170-2174. Peled I, Ram E, Lavee J et al. BNT162b2 vaccination in heart transplant recipients: Clinical experience and antibody response. Journal of Heart & Lung Transplantation 2021: 40(8): 759-762.	Patients with chronic kidney disease, dialysis patients and kidney transplant patients are at high risk of developing severe coronavirus disease 2019. A study from Longlune L et al has been conducted and show that the seroconversion rate was 88.7% among SARS-CoV-2 seronegative patients at the initiation of vaccination. Receiving immunosuppressive therapy was an independent predictive factor for non-response to vaccination. A third dose can be required in non-responders to two doses. When possible, patients waiting for a kidney transplantation should be offered the vaccine before transplantation. Studies on renal transplant patients to assess safety and efficacy of a two-dose vaccination cycle with mRNA-based COVID-19 vaccine were performed and after a median of 43 post-vaccine days, a SARS-CoV-2 anti-Spike seroprevalence of 52.4% was observed but among younger patients not taking anti-metabolites, the seroconversion rate was high (92.9%) (Russo G et al 2021). Similar results were also presented by Grupper A et al: Mean IgG anti-spike level was higher in the controls. Variables associated with null humoral response were older age, high-dose corticosteroids in the last 12 months, maintenance with triple immunosuppression, and regimen that includes mycophenolate. There was a similar rate of side effects between controls and recipients, and no correlation was found between the presence of symptoms and seroconversion. In addition, a study on humoral serological response to the BNT162b2 vaccine after allogeneic HCT showed that a significant proportion of allogeneic HCT recipients receiving immunosuppression demonstrated an inadequate humoral response to the BNT162b2 vaccine, while recipients who were off immunosuppression had a humoral response that was comparable to that of the general population (Yeshurun M et al 2021). Ali H et al. performed a study to identify the incidence of adverse events following SARS-CoV2 EUA vaccines, the incidence of new-onset GVHD or worsening of existing GVHD after EUA vaccine administration, and the incidence SARS-CoV2 positivity in vaccinated HCT patients. Most patients

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	presented with myalgias/arthralgias (first dose, 7.7%; second dose, 14.6%), fatigue (first dose, 15.4%; second dose, 29.2%), and injection site pain (first dose, 40.4%; second dose, 43.8%). Other side-effects experienced by patients included nausea, vomiting, diarrhea, headache, and injection-site rash and swelling. Liver function abnormalities occurred in 18.6% of patients. Neutropenia, thrombocytopenia, and lymphopenia occurred in 13.3%, 11.5%, and 8.8% of patients, respectively. Forty percent of patients had active chronic GVHD at the time of vaccination and worsening chronic GVHD occurred in 3.5% of the patients. New chronic GVHD developed in 9.7% of patients after vaccination. The SARS-CoV2 EUA vaccines were well tolerated in allogeneic HCT recipients. A single center prospective cohort study was performed by Ram R et al to evaluate the safety and efficacy of the BNT162B2 MRNA COVID-19 vaccine in patients after allogeneic HCT and CD19-based CAR-T therapy. Overall, the 2 vaccine doses were well tolerated. Adverse events were reported in 39% of allogeneic HCT recipients (4.6% grade >=3) and 32% of CAR-T recipients (7% grade >=3). All events resolved within few days, with the exception of 1 secondary graft rejection which is still under investigation. Overall humoral response to the BNT162b2 mRNA COVID-19 vaccine in CAR-T patients with B cell aplasia is significantly impaired, while overall response in patients after allogeneic HCT is encouraging. Patients on concomitant high intensity IST had impaired humoral response to BNT162b2. A study to determine safety and efficacy of BNT162b2 mRNA vaccine among liver transplant recipients showed that overall most self-reported side effects that were detected in LT recipients were mild and that the immune response did not correlate with more severe side effects. Nevertheless, compared with immunocompetent subjects, liver transplant recipients had reduced immune response. Factors affecting serological antibodies response include renal function and type of immunosuppression used (Davidov-Derevyanko Y 2021). Similar results were also reported by Rabinowich L et al for liver transplant patients. No serious adverse events were reported but

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
	liver transplant recipients developed substantially lower immunological response to the Pfizer-BioNTech SARS-CoV-2 mRNA-based vaccine. Factors influencing serological antibody responses include age, renal function and immunosuppressive medications. OU MT et al studied safety and reactogenicity SARS-CoV-2 mRNA vaccines in solid transplant recipients. Although local site reactions decreased after Dose 2, systemic reactions increased. Younger participants were more likely to develop systemic symptoms after Dose 1 and Dose 2. Participants who experienced pain or redness were more likely to develop an antibody response to Dose 1 of mRNA vaccines. No anaphylaxis, neurologic diagnoses, or SARS-CoV-2 diagnoses were reported. Infections were minimal. One patient reported incident acute rejection post-D2. Overall, the authors concluded that for solid organ transplant recipients undergoing mRNA vaccination, reactogenicity was similar to that reported in the original trials and severe reactions were rare. Peled Y et al report their Clinical experience and antibody response after BNT162b2 vaccination in heart transplant recipients. They concluded that: BNT162b2 vaccination was associated with a low rate of adverse events, characterized mostly by pain at the injection site. By a mean 41 days post second dose there were no clinical episodes of rejection, as suggested by a troponin leak or allograft dysfunction.
	Safety profile in patients with underlying comorbidities- HIV and immunocompromised individuals
Ferrari L, Caldara F, Teti E et al. Systematic evaluation of the tolerability of two doses of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in a diverse cohort of people with HIV (PWH). HIV Medicine 2021: 22(SUPPL 3): 221-222. De Vito A, Coradduzza D, Colpani A et al. Development of SARS-CoV- 2 IgG after first dose of mRNA vaccine in people living with HIV HIV Medicine 2021: 22(SUPPL 3): 210-211. Bergman P, Blennow O, Hansson L et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of	Systematic evaluation of the tolerability of two doses of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in a diverse cohort of people with HIV showed that the vaccine was well tolerated. Injection site swelling, fatigue, muscle/joint aches and fever increased in incidence after dose-2. Side effects were similar to those reported in general trial populations (Ferrari L et al). Furthermore after 21 days from first SARS-CoV- 2 vaccine administration, >90% of patients developed antibodies. However, patients with a CD4 nadir <200 copies/ mL had achieved a lower response (De Vito A et al 2021).

Table 1. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

References	Topic
immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine. 2021 Dec;74:10370.	A safety and efficacy of the mRNA BNT162B2 COVID-19 vaccine was performed in a prospective open label clinical trial in patients with either primary, or secondary immunodeficiency disorders due to human immunodeficiency virus infection, allogeneic HCT/CAR-T cell therapy, solid organ transplantation (SOT), or CLL. The results showed that the mRNA BNT162b2 vaccine was safe in immunocompromised patients. Rate of seroconversion was substantially lower than in healthy controls. This clinical trial highlights the need for additional vaccine doses in certain immunocompromised patient groups to improve immunity (Bergman P et al 2021).

1. *Cherrez-Ojeda I, Robles-Velasco K, Osorio MF et al. Pilot study of acute allergic reactions to mRNA-BNT162b2 vaccine in an ecuadorian cohort European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 483-484.*

Background:
Allergic reactions to vaccines are rare, occurring at 1 per 1'000.000 to 30 per 100.000; BNT162b2 vaccine excipients include polyethylene glycol/macrogol (PEG), rarely cause of allergy. Contact sensitivity to PEG is more frequent than anaphylaxis. CDC reported an estimated rate of 11.1 cases of anaphylaxis per million doses administered in patients with a history of allergies.
Method:
We prospectively assessed the early allergic reactions of Phase 0 COVID-19 vaccination plan in Guayaquil, Ecuador. Participants received two 30-μg doses, administered intramuscularly 21 days apart. Phase 0 included first line health care workers who were healthy or had stable chronic medical conditions. Participants were observed for 30 minutes after vaccination for any acute reactions;we used Brighton scale for anaphylaxis definition criteria. The primary endpoint was to measure any allergic reaction, anaphylaxis and use of medication within 14 days after the receipt of each dose of vaccine;day 1 referred to the vaccination day. Participants reported their symptoms on weekly telephonic follow-up made by the pollsters team.
Results:
187 subjects were enrolled, the mean age was 41.11 ± 17.78, 61% were female and 27.3% patients presented with an allergic past history, 15% had allergic rhinitis (Table 1). Allergic symptom onset was 2.2 ± 3.63 minutes compared to 30 minutes of another study. We did not report any anaphylaxis case. On the first day, 5.35% presented an allergic reaction including generalized rash, injection site rash and petechiae. On second dose, 3.7% presented injection site rash, generalized pruritus and petechiae (Figure 1).
Conclusion:
Our study found a similar prevalence of allergic reaction according to previous reports. The majority of patients, 94.65%, did not report any allergic symptoms after BNT162b2, similar to previous studies (98%). Anaphylaxis with COVID-19 vaccination is extremely rare, we did not find any case similarly to other reports (0.027%). To our knowledge, this is the first study to report acute allergic reactions in South America. Further studies are needed in order to prove the allergic reactions differences with other populations. (Table Presented).

2. *Sucre-Adrianza I, Garcia-Villa H, Garcia-Zaragoza MDR et al. Hypersensitivity reactions to pfizer-biontech COVID-19 vaccine in the staff of Hospital Clinico San Carlos in Madrid, Spain: European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 650.*

Background:
The purpose of the study is to analyze the type of hypersensitivity reactions (HR) with Pfizer-BioNTech COVID-19 Vaccine (Comirnaty®) referred to our Allergy Department (AD), in order to asses vaccination with second dose safely.
Method:
Subjects with suspicion of HR after administration of first dose of Comirnaty® were referred to our AD from the Prevention and Occupational Risk Department responsible for the vaccination of hospital staff. Clinical history with special attention to atopic comorbidities and a detailed description of the HR after first dose of Comirnaty® was recorded. After providing signed informed consent, subjects underwent an allergy workup consisting of skin prick tests and intradermal tests (immediate and delayed readings) with polyethylene glycol (PEG) 4000 (1, 10 and 100 mg/ml), Polysorbate 80 (0.004 and 0.04 mg/dl), and

Comirnaty® vaccine (as is). If skin tests proved negative, the second dose of Comirnaty® was administered under close supervision at our AD with an observation period of 60 minutes.
Results:
As of March 10, 2021, 6907 subjects had received the first dose of Comirnaty® and 5 were referred to our AD for evaluation. Mean age was 35 years, 4 were female and 1 male.
Four patients had previous allergic history consisting of seasonal allergic rhinitis, contact dermatitis to nickel and thimerosal, and allergy to metamizole and mesalazine. After vaccination, two subjects had non-immediate reactions (NIR) that were generalized erythema within the first 48-96 h. Two subjects had immediate reactions (IR) 15 min after vaccination, consisting of generalized urticaria and erythema, and one was referred with a suspicion of immediate anaphylaxis but the reaction did not meet Brighton Anaphylaxis criteria. All subjects had negative skin tests with PEG-4000, Polysorbate 80 and Comirnaty®. The patient with the "suspicion of anaphylaxis" refused to receive the second dose. The remaining 4 subjects received the second dose of Comirnaty® with no reaction.
Conclusion:
The incidence of suggestive hypersensitivity reactions to Comirnaty® vaccine in our hospital staff was very low (0.07%). The administration of the second dose after a negative allergy workup seems safe, although the number of subjects treated is small.

3. *Crespo Quiros J, Juarez Guerrero A, Rodriguez Hermida S et al. Changes in asthma control after administration of COVID-19 mRNA vaccines: European Journal of Allergy and Clinical Immunology 2021: 76(SUPPL 110): 487-488.*

Background:
Rapid development of vaccines to prevent coronavirus disease 2019 (COVID-19) has become a global imperative. Two mRNA vaccines have been recently approved by European Medicines Agency BNT162b2 and mRNA-1273 COVID-19 vaccine. They have demonstrated safety in 1-3 phase clinical trials but data in asthmatics vaccinated in real-life is scarce. We sought to assess the change in asthma control before and 4 weeks after the administration of mRNA vaccine against COVID-19 in adults diagnosed with mild to severe asthma.
Method:
We performed an observational descriptive study of asthmatic healthcare workers who were vaccinated in our Allergy Department. Asthma severity were measured following Spanish Guideline on the Management of Asthma (GEMA) criteria. Asthma control was evaluated prior to vaccination and 4 weeks after vaccination using Asthma Control Test (ACT) questionnaire. The mRNA vaccines were administered under medical supervision and 30 minutes observation.
Results:
We recorded a total of 52 asthmatic healthcare workers who receive COVID-19 vaccination in our Allergy Department. The mean age was 52.3 years (range 21-66) and 46 (88.5%) were female. Ten (19.2%) and 42 (80.8%) subjects received BNT162b2 and mRNA-1273 COVID-19 vaccine, respectively. Twenty patients (38.5%) had intermittent asthma, 8 (15.4%) mild, 18 (34.6%) moderate, and 6 (11.5%) severe asthma. One patient was receiving oral corticosteroids and one biologic treatment. Coexisting allergic diseases were common 26 (50%) had allergic rhinitis, 5 (9.6%) atopic dermatitis, 18 (34.6%) food allergy, 19 (36.5%) drug allergy. Other comorbidities were cardiovascular disease (23.1%), obesity (21.2%), autoimmunity (19.2%) and nasal polyposis (5.8%). The ACT before vaccination was 24.2 (range 21-25, SD 1.4). We detected 2 (3.8%) patients with ACT<20 who were vaccinated once ACT was ≥20. Four weeks after the first and second dose of mRNA vaccine, ACT was 23.4 (range 10-25, SD 2.6) and 23.8 (range 12-25, SD

2.5), respectively. We found no statistical significant differences in ACT changes among intermittent, mild, moderate, and severe asthma.
Conclusion:
In our experience, asthma exacerbation after mRNA vaccination is infrequent and not related to asthma severity. Asthmatic population can safely receive mRNA vaccines against COVID-19.

4. *Lee E, Yeon-Kyeong L, Tae Eun K et al. Reports of anaphylaxis after coronavirus disease 2019 vaccination, South Korea, 26 February to 30 April 2021. Euro Surveill. 2021 Aug;26(33):2100694.*

The South Korea mass vaccination programme administered 3.8 million doses of COVID-19 vaccinations between 26 February and 30 April 2021. After 173 suspected anaphylaxis reports to the nationwide monitoring system for adverse events following immunisation, 44 anaphylaxis cases were confirmed using Brighton Collaboration case definitions. The rates per million doses were 18.2 cases and 6.2 cases for Vaxzevria and Comirnaty, respectively. Median time of onset was 14 min after vaccination and most cases had recovered at the time of review.

5. *Shavit R, Maoz-Segal R, Iancovici-Kidon M et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. JAMA Network Open 2021: 4(8): e2122255.*

Importance: Allergic reactions among some individuals who received the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine discourage patients with allergic conditions from receiving this vaccine and physicians from recommending the vaccine.
Objective: To describe the assessment and immunization of highly allergic individuals with the BNT162b2 vaccine.
Design, setting, and participants: In a prospective cohort study from December 27, 2020, to February 22, 2021, 8102 patients with allergies who applied to the COVID 19 vaccine referral center at the Sheba Medical Center underwent risk assessment using an algorithm that included a detailed questionnaire. High-risk patients (n = 429) were considered "highly allergic" and were immunized under medical supervision.
Exposures: Pfizer-BioNTech (BNT162b2) COVID-19 vaccine.
Main outcomes and measures: Allergic and anaphylactic reactions after the first and second doses of BNT162b2 vaccine among highly allergic patients.
Results: Of the 429 individuals who applied to the COVID-19 referral center and were defined as highly allergic, 304 (70.9%) were women and the mean (SD) age was 52 (16) years. This highly allergic group was referred to receive immunization under medical supervision. After the first dose of the BNT162b2 vaccine, 420 patients (97.9%) had no immediate allergic event, 6 (1.4%) developed minor allergic responses, and 3 (0.7%) had anaphylactic reactions. During the study period, 218 highly allergic patients (50.8%) received the second BNT162b2 vaccine dose, of which 214 (98.2%) had no allergic reactions and 4 patients (1.8%) had minor allergic reactions. Other immediate and late reactions were comparable with those seen in the general population, except for delayed itch and skin eruption, which were more common among allergic patients.
Conclusions and relevance: The rate of allergic reactions to BNT162b2 vaccine, is higher among patients with allergies, particularly among a subgroup with a history of high-risk allergies. This study suggests that most patients with a history of allergic diseases and, particularly, highly allergic patients can be safely immunized by using an algorithm that can be implemented in different medical facilities and includes a referral center, a risk assessment questionnaire, and a setting for immunization under medical supervision of highly allergic

patients. Further studies are required to define more specific risk factors for allergic reactions to the BNT162b2 vaccine.

6. *Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 Dec 2;385(23):2140-2149.*

BACKGROUND
Approximately 5.1 million Israelis had been fully immunized against coronavirus disease 2019 (Covid-19) after receiving two doses of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) by May 31, 2021. After early reports of myocarditis during adverse events monitoring, the Israeli Ministry of Health initiated active surveillance.
METHODS
We retrospectively reviewed data obtained from December 20, 2020, to May 31, 2021, regarding all cases of myocarditis and categorized the information using the Brighton Collaboration definition. We analyzed the occurrence of myocarditis by computing the risk difference for the comparison of the incidence after the first and second vaccine doses (21 days apart); by calculating the standardized incidence ratio of the observed-to-expected incidence within 21 days after the first dose and 30 days after the second dose, independent of certainty of diagnosis; and by calculating the rate ratio 30 days after the second dose as compared with unvaccinated persons.
RESULTS
Among 304 persons with symptoms of myocarditis, 21 had received an alternative diagnosis. Of the remaining 283 cases, 142 occurred after receipt of the BNT162b2 vaccine; of these cases, 136 diagnoses were definitive or probable. The clinical presentation was judged to be mild in 129 recipients (95%); one fulminant case was fatal. The overall risk difference between the first and second doses was 1.76 per 100,000 persons (95% confidence interval [CI], 1.33 to 2.19), with the largest difference among male recipients between the ages of 16 and 19 years (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46). As compared with the expected incidence based on historical data, the standardized incidence ratio was 5.34 (95% CI, 4.48 to 6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 years (13.60; 95% CI, 9.30 to 19.20). The rate ratio 30 days after the second vaccine dose in fully vaccinated recipients, as compared with unvaccinated persons, was 2.35 (95% CI, 1.10 to 5.02); the rate ratio was again highest in male recipients between the ages of 16 and 19 years (8.96; 95% CI, 4.50 to 17.83), with a ratio of 1 in 6637.
CONCLUSIONS
The incidence of myocarditis, although low, increased after the receipt of the BNT162b2 vaccine, particularly after the second dose among young male recipients. The clinical presentation of myocarditis after vaccination was usually mild.

7. *Witberg G, Barda N, Hoss S et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021 Dec 2;385(23):2132-2139.*

BACKGROUND
Reports have suggested an association between the development of myocarditis and the receipt of messenger RNA (mRNA) vaccines against coronavirus disease 2019 (Covid-19), but the frequency and severity of myocarditis after vaccination have not been extensively explored.
METHODS
We searched the database of Clalit Health Services, the largest health care organization (HCO) in Israel, for diagnoses of myocarditis in patients who had received at least one dose of the BNT162b2 mRNA vaccine (Pfizer–BioNTech). The diagnosis of myocarditis was adjudicated by cardiologists using the case definition used by the Centers for Disease Control and

Prevention. We abstracted the presentation, clinical course, and outcome from the patient's electronic health record. We performed a Kaplan–Meier analysis of the incidence of myocarditis up to 42 days after the first vaccine dose.

RESULTS

Among more than 2.5 million vaccinated HCO members who were 16 years of age or older, 54 cases met the criteria for myocarditis. The estimated incidence per 100,000 persons who had received at least one dose of vaccine was 2.13 cases (95% confidence interval [CI], 1.56 to 2.70). The highest incidence of myocarditis (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46) was reported in male patients between the ages of 16 and 29 years. A total of 76% of cases of myocarditis were described as mild and 22% as intermediate; 1 case was associated with cardiogenic shock. After a median follow-up of 83 days after the onset of myocarditis, 1 patient had been readmitted to the hospital, and 1 had died of an unknown cause after discharge. Of 14 patients who had left ventricular dysfunction on echocardiography during admission, 10 still had such dysfunction at the time of hospital discharge. Of these patients, 5 underwent subsequent testing that revealed normal heart function.

CONCLUSIONS

Among patients in a large Israeli health care system who had received at least one dose of the BNT162b2 mRNA vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among male patients between the ages of 16 and 29 years. Most cases of myocarditis were mild or moderate in severity. (Funded by the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute.)

8. *Patone M, Mei XW, Handunnetthi L et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2021 Dec 14. doi: 10.1038/s41591-021-01630-0. Epub ahead of print. PMID: 34907393.*

Although myocarditis and pericarditis were not observed as adverse events in coronavirus disease 2019 (COVID-19) vaccine trials, there have been numerous reports of suspected cases following vaccination in the general population. We undertook a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021 to investigate hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 1–28 days following adenovirus (ChAdOx1, $n = 20{,}615{,}911$) or messenger RNA-based (BNT162b2, $n = 16{,}993{,}389$; mRNA-1273, $n = 1{,}006{,}191$) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test ($n = 3{,}028{,}867$). We found increased risks of myocarditis associated with the first dose of ChAdOx1 and BNT162b2 vaccines and the first and second doses of the mRNA-1273 vaccine over the 1–28 days postvaccination period, and after a SARS-CoV-2 positive test. We estimated an extra two (95% confidence interval (CI) 0, 3), one (95% CI 0, 2) and six (95% CI 2, 8) myocarditis events per 1 million people vaccinated with ChAdOx1, BNT162b2 and mRNA-1273, respectively, in the 28 days following a first dose and an extra ten (95% CI 7, 11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273. This compares with an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test. We also observed increased risks of pericarditis and cardiac arrhythmias following a positive SARS-CoV-2 test. Similar associations were not observed with any of the COVID-19 vaccines, apart from an increased risk of arrhythmia following a second dose of mRNA-1273. Subgroup analyses by age showed the increased risk of myocarditis associated with the two mRNA vaccines was present only in those younger than 40.

9. *Das BB, Kohli U, Ramachandran P et al. Myopericarditis after messenger RNA Coronavirus Disease 2019 Vaccination in Adolescents 12 to 18 Years of Age. J Pediatr. 2021 Nov;238:26-32.e1.*

Objectives: To characterize the clinical course and outcomes of children 12-18 years of age who developed probable myopericarditis after vaccination with the Pfizer-BioNTech (BNT162b2) coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine.
Study design: A cross-sectional study of 25 children, aged 12-18 years, diagnosed with probable myopericarditis after COVID-19 mRNA vaccination as per the Centers for Disease Control and Prevention criteria for myopericarditis at 8 US centers between May 10, 2021, and June 20, 2021. We retrospectively collected the following data: demographics, severe acute respiratory syndrome coronavirus 2 virus detection or serologic testing, clinical manifestations, laboratory test results, imaging study results, treatment, and time to resolutions of symptoms.
Results: Most (88%) cases followed the second dose of vaccine, and chest pain (100%) was the most common presenting symptom. Patients came to medical attention a median of 2 days (range, <1-20 days) after receipt of Pfizer mRNA COVID-19 vaccination. All adolescents had an elevated plasma troponin concentration. Echocardiographic abnormalities were infrequent, and 92% showed normal cardiac function at presentation. However, cardiac magnetic resonance imaging, obtained in 16 patients (64%), revealed that 15 (94%) had late gadolinium enhancement consistent with myopericarditis. Most were treated with ibuprofen or an equivalent nonsteroidal anti-inflammatory drug for symptomatic relief. One patient was given a corticosteroid orally after the initial administration of ibuprofen or an nonsteroidal anti-inflammatory drug; 2 patients also received intravenous immune globulin. Symptom resolution was observed within 7 days in all patients.
Conclusions: Our data suggest that symptoms owing to myopericarditis after the mRNA COVID-19 vaccination tend to be mild and transient. Approximately two-thirds of patients underwent cardiac magnetic resonance imaging, which revealed evidence of myocardial inflammation despite a lack of echocardiographic abnormalities.

10. *Lazaros G, Anastassopoulou C, Hatziantoniou S et al. A case series of acute pericarditis following COVID-19 vaccination in the context of recent reports from Europe and the United States. Vaccine. 2021 Oct 29;39(45):6585-6590.*

Background
COVID-19 vaccines were efficacious and safe in clinical trials. We report nine events of acute pericarditis (AP) in eight patients following COVID-19 vaccination with BNT162b2 (6/9), AZD1222 (2/9) and mRNA-1273 (1/9).
Methods
All patients were referred for AP temporally linked with COVID-19 vaccination. Chest pain was the most common clinical manifestation. Alternative etiologies were excluded upon thorough diagnostic work up. AP diagnosis was established according to ESC guidelines.
Findings
Five events occurred after the first vaccine dose and four after the second. The mean age in this cohort was 65.8 ± 10.2 years and the men/women ratio 3/5. All events resolved without sequelae; two events were complicated by cardiac tamponade requiring emergent pericardial decompression. Hospitalization was required in four cases.
Interpretation
Although causality cannot be firmly established, AP has emerged as a possible complication following COVID-19 vaccination. Further investigation is indispensable to fully characterize this new entity.

11. Kim HW, Jenista ER, Wendell DC et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol. 2021 Oct 1;6(10):1196-1201. doi: 10.1001/jamacardio.2021.2828. PMID: 34185046; PMCID: PMC8243258.

Importance: Vaccine-associated myocarditis is an unusual entity that has been described for the smallpox vaccine, but only anecdotal case reports have been described for other vaccines. Whether COVID-19 vaccination may be linked to the occurrence of myocarditis is unknown.
Objective: To describe a group of 7 patients with acute myocarditis over 3 months, 4 of whom had recent messenger RNA (mRNA) COVID-19 vaccination.
Design, setting, and participants: All patients referred for cardiovascular magnetic resonance imaging at Duke University Medical Center were asked to participate in a prospective outcomes registry. Two searches of the registry database were performed: first, to identify patients with acute myocarditis for the 3-month period between February 1 and April 30 for 2017 through 2021, and second, to identify all patients with possible vaccine-associated myocarditis for the past 20 years. Once patients with possible vaccine-associated myocarditis were identified, data available in the registry were supplemented by additional data collection from the electronic health record and a telephone interview.
Exposures: mRNA COVID-19 vaccine.
Main outcomes and measures: Occurrence of acute myocarditis by cardiovascular magnetic resonance imaging.
Results: In the 3-month period between February 1 and April 30, 2021, 7 patients with acute myocarditis were identified, of which 4 occurred within 5 days of COVID-19 vaccination. Three were younger male individuals (age, 23-36 years) and 1 was a 70-year-old female individual. All 4 had received the second dose of an mRNA vaccine (2 received mRNA-1273 [Moderna], and 2 received BNT162b2 [Pfizer]). All presented with severe chest pain, had biomarker evidence of myocardial injury, and were hospitalized. Coincident testing for COVID-19 and respiratory viruses provided no alternative explanation. Cardiac magnetic resonance imaging findings were typical for myocarditis, including regional dysfunction, late gadolinium enhancement, and elevated native T1 and T2.
Conclusions and relevance: In this study, magnetic resonance imaging findings were found to be consistent with acute myocarditis in 7 patients; 4 of whom had preceding COVID-19 vaccination. Further investigation is needed to determine associations of COVID-19 vaccination and myocarditis.

12. Snapiri O, Rosenberg Danziger C, Shirman N et al. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J. 2021 Oct 1;40(10):e360-e363. doi: 10.1097/INF.0000000000003235. PMID: 34077949; PMCID: PMC8443419.

Background: Vaccines are paramount in the effort to end the coronavirus disease 2019 global epidemic. BNT162b2 is approved for the vaccination of adolescents over 16 years of age. Systemic adverse events were scarce though the pretested cohort of this age group was relatively small. The aim of the current study is to raise awareness for potential adverse reactions.
Methods: This is a case series of patients diagnosed with perimyocarditis following vaccination. Patients were compiled from 3 pediatric medical centers in Israel through a network of pediatricians and data regarding those cases was collected. In addition, incidence of perimyocarditis during the vaccination period was compared with previous years.
Results: All patients were males 16-18 years old, of Jewish descent, who presented with chest pain that began 1-3 days following vaccination (mean, 2.1 days). In 6 of the 7 patients, symptoms began following the 2nd dose and in 1 patient following the 1st dose. All cases were

mild and none required cardiovascular or respiratory support. The incidence of perimyocarditis during the vaccination period was elevated in comparison to previous years.
Conclusions: This case series describes a time association between coronavirus disease 2019 vaccine and perimyocarditis in adolescents. All cases were mild, although only long-term follow-up can reveal the true impact of this cardiac injury. While it seems that the incidence of perimyocarditis during the vaccination campaign period is increased, a more comprehensive data collection on a wider scale should be done. We hope this report will serve as a reminder to report events and allow for analysis of potential adverse reactions.

13. *Li X, Tong X, Wan Yin Yeung W et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis. 2021 Oct 22;annrheumdis-2021-221571.*

Objectives: To investigate the relationship between COVID-19 full vaccination (two completed doses) and possible arthritis flare.
Methods: Patients with rheumatoid arthritis (RA) were identified from population-based electronic medical records with vaccination linkage and categorised into BNT162b2 (mRNA vaccine), CoronaVac (inactive virus vaccine) and non-vaccinated groups. The risk of possible arthritis flare after vaccination was compared using a propensity-weighted cohort study design. We defined possible arthritis flare as hospitalisation and outpatient consultation related to RA or reactive arthritis, based on diagnosis records during the episode. Weekly prescriptions of rheumatic drugs since the launch of COVID-19 vaccination programme were compared to complement the findings from a diagnosis-based analysis.
Results: Among 5493 patients with RA (BNT162b2: 653; CoronaVac: 671; non-vaccinated: 4169), propensity-scored weighted Poisson regression showed no significant association between arthritis flare and COVID-19 vaccination ((BNT162b2: adjusted incidence rate ratio 0.86, 95% Confidence Interval 0.73 to 1.01); CoronaVac: 0.87 (0.74 to 1.02)). The distribution of weekly rheumatic drug prescriptions showed no significant differences among the three groups since the launch of the mass vaccination programme (all p values >0.1 from Kruskal-Wallis test).
Conclusions: Current evidence does not support that full vaccination of mRNA or inactivated virus COVID-19 vaccines is associated with possible arthritis flare.

14. *Furer V, Eviatar T, Zisman D et al. Immunogenicity and safety of the BNT162B2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and general population: A multicenter study. European Congress of Rheumatology, EULAR 2021. Virtual. Publication: Annals of the Rheumatic Diseases 2021: 80(SUPPL 1): 200-201.*

Introduction Vaccination represents a cornerstone in mastering the COVID-19 pandemic. Data on immunogenicity and safety of messenger RNA (mRNA) vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) are limited.
Methods A multicentre observational study evaluated the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine in adult patients with AIIRD (n=686) compared with the general population (n=121). Serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured 2–6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/mL. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the second vaccine dose.
Results Following vaccination, the seropositivity rate and S1/S2 IgG levels were significantly lower among patients with AIIRD versus controls (86% (n=590) vs 100%, p<0.0001 and 132.9±91.7 vs 218.6±82.06 BAU/mL, p<0.0001, respectively). Risk factors for reduced immunogenicity included older age and treatment with glucocorticoids, rituximab, mycophenolate mofetil (MMF), and abatacept. Rituximab was the main cause of a seronegative

response (39% seropositivity). There were no postvaccination symptomatic cases of COVID-19 among patients with AIIRD and one mild case in the control group. Major adverse events in patients with AIIRD included death (n=2) several weeks after the second vaccine dose, non-disseminated herpes zoster (n=6), uveitis (n=2), and pericarditis (n=1). Postvaccination disease activity remained stable in the majority of patients.
Conclusion mRNA BNTb262 vaccine was immunogenic in the majority of patients with AIIRD, with an acceptable safety profile. Treatment with glucocorticoids, rituximab, MMF, and abatacept was associated with a significantly reduced BNT162b2-induced immunogenicity.

15. *Furer V, Eviatar T, Zisman D et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Annals of the Rheumatic Diseases 2021: 80(10): 1330-1338.*

Introduction: Vaccination represents a cornerstone in mastering the COVID-19 pandemic. Data on immunogenicity and safety of messenger RNA (mRNA) vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) are limited.
Methods: A multicentre observational study evaluated the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine in adult patients with AIIRD (n=686) compared with the general population (n=121). Serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured 2-6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/mL. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the second vaccine dose.
Results: Following vaccination, the seropositivity rate and S1/S2 IgG levels were significantly lower among patients with AIIRD versus controls (86% (n=590) vs 100%, p<0.0001 and 132.9±91.7 vs 218.6±82.06 BAU/mL, p<0.0001, respectively). Risk factors for reduced immunogenicity included older age and treatment with glucocorticoids, rituximab, mycophenolate mofetil (MMF), and abatacept. Rituximab was the main cause of a seronegative response (39% seropositivity). There were no postvaccination symptomatic cases of COVID-19 among patients with AIIRD and one mild case in the control group. Major adverse events in patients with AIIRD included death (n=2) several weeks after the second vaccine dose, non-disseminated herpes zoster (n=6), uveitis (n=2), and pericarditis (n=1). Postvaccination disease activity remained stable in the majority of patients.
Conclusion: mRNA BNTb262 vaccine was immunogenic in the majority of patients with AIIRD, with an acceptable safety profile. Treatment with glucocorticoids, rituximab, MMF, and abatacept was associated with a significantly reduced BNT162b2-induced immunogenicity.

16. *Picchianti-Diamanti A, Aiello A, Laganà B et al. Immunosuppressive Therapies Differently Modulate Humoral- and T-Cell-Specific Responses to COVID-19 mRNA Vaccine in Rheumatoid Arthritis Patients. Frontiers in Immunology 2021: 12: 740249.*

Objective: To assess in rheumatoid arthritis (RA) patients, treated with different immunosuppressive therapies, the induction of SARS-CoV-2-specific immune response after vaccination in terms of anti-region-binding-domain (RBD)-antibody- and T-cell-specific responses against spike, and the vaccine safety in terms of clinical impact on disease activity.
Methods: Health care workers (HCWs) and RA patients, having completed the BNT162b2-mRNA vaccination in the last 2 weeks, were enrolled. Serological response was evaluated by quantifying anti-RBD antibodies, while the cell-mediated response was evaluated by a whole-blood test quantifying the interferon (IFN)-γ-response to spike peptides. FACS analysis was performed to identify the cells responding to spike stimulation. RA disease activity was evaluated by clinical examination through the DAS28crp, and local and/or systemic clinical

adverse events were registered. In RA patients, the ongoing therapeutic regimen was modified during the vaccination period according to the American College of Rheumatology indications.
Results: We prospectively enrolled 167 HCWs and 35 RA patients. Anti-RBD-antibodies were detected in almost all patients (34/35, 97%), although the titer was significantly reduced in patients under CTLA-4-inhibitors (median: 465 BAU/mL, IQR: 103-1189, p<0.001) or IL-6-inhibitors (median: 492 BAU/mL, IQR: 161-1007, p<0.001) compared to HCWs (median: 2351 BAU/mL, IQR: 1389-3748). T-cell-specific response scored positive in most of RA patients [24/35, (69%)] with significantly lower IFN-γ levels in patients under biological therapy such as IL-6-inhibitors (median: 33.2 pg/mL, IQR: 6.1-73.9, p<0.001), CTLA-4-inhibitors (median: 10.9 pg/mL, IQR: 3.7-36.7, p<0.001), and TNF-α-inhibitors (median: 89.6 pg/mL, IQR: 17.8-224, p=0.002) compared to HCWs (median: 343 pg/mL, IQR: 188-756). A significant correlation between the anti-RBD-antibody titer and spike-IFN-γ-specific T-cell response was found in RA patients (rho=0.432, p=0.009). IFN-γ T-cell response was mediated by $CD4^+$ and $CD8^+$ T cells. Finally, no significant increase in disease activity was found in RA patients following vaccination.
Conclusion: This study showed for the first time that antibody-specific and whole-blood spike-specific T-cell responses induced by the COVID-19 mRNA-vaccine were present in the majority of RA patients, who underwent a strategy of temporary suspension of immunosuppressive treatment during vaccine administration. However, the magnitude of specific responses was dependent on the immunosuppressive therapy administered. In RA patients, BNT162b2 vaccine was safe and disease activity remained stable.

17. *Esquivel-Valerio JA, Skinner-Taylor CM, Moreno-Arquieta IA et al. Adverse events of six COVID-19 vaccines in patients with autoimmune rheumatic diseases: a cross-sectional study. Rheumatology International 2021: 41(12): 2105-2108.*

Data regarding COVID-19 vaccine efficacy and adverse events (AE) in patients with autoimmune and inflammatory rheumatic diseases (AIIRD) have been published recently although these mostly include the mRNA vaccines (Pfizer-BioNTech and Moderna) and the ChAdOx1 nCoV-19/AZD1222 (Oxford-AstraZeneca). This research aimed to study the prevalence of AE presented with six different SARS-CoV-2 vaccines {ChadOX1 nCoV-19 (AZD1222), Ad5-nCoV2, Ad26.COV2.S, mRNA-1273, BNT162b2, and CoronaVac} in Mexican patients with AIIRD. We performed a cross-sectional study about vaccine history. Two hundred and twenty five consecutive patients were recruited, mean age was 50.7 years and the majority (n = 213; 94.6%) were females. One hundred and seven (47.5%) received BNT162b2 mRNA, 34 (15.1%) Ad5-nCoV, 29 (12.8%) mRNA-1273, 28 (12.4%) ChAdOX1 nCoV-19 (AZD1222), 22 (9.7%) CoronaVac and 5 (2.2%) Ad26.COV2.S. The vaccines that had the most AE proportionally to the number of patients vaccinated were Janssen (5; 100%) followed by Pfizer-BioNTEch (86; 80%) and CanSinoBIO (27; 79.4%). Localized pain was the most frequent (158; 70.2%) AE. Fatigue (78; 34.7%), headache (69; 30.6%) and muscle ache (66; 29.3%) were the most common systemic symptoms. No serious AE that required medical attention or hospitalization were reported. The current results support the safety of different COVID-19 vaccines in patients with AIIRD. This information can help fight vaccine hesitancy in this population.

18. *Bartels LE, Ammitzbøll C, Bøgh Andersenet J et al. Local and systemic reactogenicity of COVID-19 vaccine BNT162b2 in patients with systemic lupus erythematosus and rheumatoid arthritis. Rheumatology International 2021: 41(11): 1925-1931.*

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were launched in December 2020. Vaccination of patients with rheumatic diseases is recommended, as they are

considered at higher risk of severe COVID-19 than the general population. Patients with rheumatic disease have largely been excluded from vaccine phase 3 trials. This study explores the safety and reactogenicity of BNT162b2 among patients with rheumatic diseases. Patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), median age 58.8 years, 285 subjects in total, were vaccinated twice with the BNT162b2 (Pfizer/BioNTech). Questionnaires on reactogenicity matching the original phase 3 study were answered seven days after completed vaccination. The majority of SLE and RA patients experienced either local (78.0%) or systemic reactions (80.1%). Only 1.8% experienced a grade-4 reaction. Compared to the original study, we found more frequent fatigue [Odds ratio (OR) 2.2 (1.7-2.8)], headache [OR 1.7 (1.3-2.2)], muscle pain [OR 1.8 (1.4-2.3)], and joint pain [OR 2.3 (1.7-3.0)] in patients. In contrast, the use of antipyretics was less frequent [OR 0.5 (0.3-0.6)]. Patients with SLE and RA experience reactogenicity to the Pfizer-BioNTech BNT162b2 COVID-19 vaccine. Reactogenicity was more frequent in patients, however, not more severe compared with healthy controls.

19. Heshin-Bekenstein M, Elkayam O, Ziv A et al. Safety and immunogenicity of the BNT162B2 mRNA COVID-19 vaccine in adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases. Pediatric Rheumatology 2021: 19(SUPPL 1).

Introduction: The safety, efficacy, and immunogenicity data of the vaccine against COVID-19 for adolescents with Juvenile-onset Auto-immune Inflammatory Rheumatic diseases (AIIRD) is currently limited. Vaccinating the immunocompromised adolescents for COVID-19 is particularly valuable to protect this vulnerable population.
Objectives: To evaluate the safety and immunogenicity of the BNT162b2 mRNA vaccine in adolescents with AIRD treated with immunosuppressive medications compared with healthy adolescents.
Methods: This prospective multicenter study examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. Patients were evaluated 2-10 weeks after the second dose of the vaccine. Safety and post-vaccination COVID-19 infection were evaluated, as well as disease activity prior and following the vaccine. Post vaccination serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured. Seropositivity was defined as IgG ≥15 binding antibody units (AU/ml). Anti-Nuclear (N) IgG antibodies were measured for evidence of past COVID-19 infection (level above 1.4RLU was considered positive).
Results: 71 adolescents with AIIRD patients and 28 controls from 2 countries, 4 centers, participated in the study. The most common diagnosis in the AIIRD cohort was JIA (N=27), followed by SLE (N=14). The mean disease duration was 5.1±4.48 years (N=70). A total 84.5% (N=60) of the patients were treated with immunomodulatory medications. Post vaccination disease activity remained stable in 96.88% of the adolescents with AIIRD, and post vaccination treatment change was made in the minority of the patients (N=3, 4.84%). Both patients and controls have tolerated the vaccine well, with minimal side effects. There were no severe adverse events in both groups. No post vaccination infection with COVID-19 was documented in both groups. Seropositivity rate was 90.32% in adolescents with AIIRD and 100% in the healthy controls (N=28/31 vs. N=14/14; p=0.54). The level of the S1/S2 antibodies was significantly reduced in adolescents with AIIRD compared to controls (mean± SD 218.97±150.9 vs 380.78± 71.89, P <0.0001). The N Index was negative in both adolescents with AIIRD (0.09±0.09, [N=15]) and healthy controls (0.054±0.036 [N=11]), indicating that none of these participants suffered from past COVID-19 infection.

Conclusion: In our cohort, the BNTb262 mRNA COVID-19 vaccine was shown to have excellent safety profile in immunocompromised adolescents with Juvenile-onset AIIRD, with mild post vaccination side effects, similar to the safety profile of the healthy controls. No post vaccination COVID-19 illness was documented. Post vaccination disease activity was mostly kept stable. Immunogenicity was very good in both groups, with significantly higher S antibody titers in the healthy controls.

20. *Maritsi D, Dasoula F, Vartzelis G et al. Safety and tolerability of the biontech COVID-19 vaccine in adolescent patients with JIA on TNFi. Pediatric Rheumatology 2021: 19(SUPPL 1).*

Introduction: The post-authorization safety reports of the novel mRNA vaccines against COVID-19 are generally reassuring; nonetheless their safely profile has not been evaluated in adolescents with MRDs on immune-modulating treatment.
Objectives: To evaluate the safety and tolerability of the BNT162b2(Pfizer-BioNTech) COVID-19 vaccine in adolescent and young adult patients with juvenile idiopathic arthritis (JIA) on TNFi treatment.
Methods: Study population: The study involved 21 subjects aged 16- 21 years (median 17 years) with stable JIA who have been diagnosed and treated for at least 1 year with TNFi. In particular, 10 were receiving adalimumab at two weekly intervals, eleven were given etanercept once a week, whereas 15 patients were on concomitant weekly subcutaneous methotrexate. Eight patients had poly-articular JIA, 7 psoriatic JIA and 6 ERA. Written informed consent was obtained at enrolment. Study procedures: The patients received two doses of the COVID-19 vaccine (Pfizer-BioNTech) intramuscularly at 0 and 3 weeks. In addition to the visits for vaccine administration, further visits were planned at 2, 6 and 12 months after enrolment. A blood sample for the evaluation of vaccine immunogenicity is planned to be taken from all of the subjects at the time of enrolment, after 2, 6 and 12 months after the last vaccine dose. All participants were observed for 30 min after the injection in order to assess vaccine safety and tolerability. All patients were given a diary card to record the occurrence of local symptoms or systemic symptoms for the following 14 days. The symptoms were classified as mild or severe (requiring medical attention). Adverse reactions were defined as any reaction that lasted for more than 7 days after the vaccination and serious adverse reactions as any reaction that required medical attention or hospitalization during the study period. Disease activity was evaluated by using the JADAS-27 score at all planned assessments performed so far. The ESR and CRP levels were measured simultaneously. Data were analysed using SPSS 18.0.
Results: All subjects were seronegative at baseline. All participants tolerated both doses of the vaccine well. Local reactions were frequent (74%) in the majority of participants, no difference was noted between patients on etanercept (71%) versus adalimumab (75%) (p=0.09). Localized erythema (73%), pain (72%) and swelling (68%) were among common side effects. There were no differences noted in patients with different JIA types. In addition, systemic reactions [headache (34%), myalgias (23%), tiredness (12%), transient arthralgia (11%)] were relatively infrequent (18%). The type of JIA or medication received did not reveal any differences in the rates of systemic reactions. Most localized and systemic reactions were noted after the second dose of the vaccine (p= 0.02). One patient developed an allergic reaction (hives) after the second dose, which was alleviated with anti-histamines. Finally, there were no significant changes in 27-JADAS or laboratory tests as noted at 2 the months' follow-up.
Conclusion: The mRNA vaccine seemed safe and well tolerated in adolescents with JIA on TNFi. Although our sample size was small and a restricted number of patients were included within each JIA type and treatment groups, it can be concluded that the vaccine assures an adequate safety and tolerability profile and not provoking disease flare. Further studies are needed to evaluate the immune response of patients receiving biological agents in more detail,

analyse the immunogenicity of the two-dose schedule, and determine the real duration of immune protection as well as the potential use of a booster dose.

21. *Macedoni M, Calcaterra V, Smylie G et al. Safety and immunogenicity of the BNT162B2 mRNA vaccine for COVID-19 in adolescents and young adults with type 1 diabetes. Pediatric Diabetes 2021: 22(SUPPL 30): 15-16.*

Introduction: No data are available on immunogenity and safety of mRNA vaccines for COVID-19 in patients with type 1 diabetes (T1D). <ovid:br/>Objective(s): To evaluate antibody responses to the BNT162b2 mRNA vaccine in adolescents and young adults with T1D. <ovid:br/>Method(s): BNT162b2 mRNA vaccine (Pfizer-Biontech) was offered to patients with T1D aged 16-22 ys according to national vaccination campaign following a 2-dose schedule, separated by 21 days. Sars- Cov-2 IgG levels (Spike protein subunit S1) were measured at the time of the 1st dose (T0), at the time of the 2nd dose (T1) and after 1 month from the second dose (T2). The test was performed with PerkinElmer GSP/DELFIA Anti-SARS-CoV-2 IgG kit using GSP Instrument. The Anti-SARS-CoV-2 IgG assay is based on a solid phase fluoroimmunoassay based on the DELFIA sandwich technique. The assay is qualitative measuring the ratio between sample counts and calibrator counts. The positive cut-off of at least 1.2 arbitrary units was adopted. <ovid:br/>Result(s): 25 patients were included,5 (20%) refused the vaccination. We enrolled 20 patients (10 males) mean age 18.8 +/- 2.59 ys, with mean disease duration of 7.53 +/- 3.69 ys, BMI 23.12 +/- 2.82 kg/m2, Hba1c 7.12 +/- 1.19%. At T0 Sars-Cov-2 IgG were 0.30 +/- 0.16. At T1 100% of patients had an antibody titer >1.2 with a mean value of 11.02 +/- 11.20 (range 2.1-53.8). At T1 the average value of Sars- COV-2 IgG was 32.14 +/- 18.01 (range 8.9-64.5). At T2 the antibody titer was neither significantly different in females compared to males (p = 0.72), nor related to age (p = 0.39), disease duration (p = 0.78), BMI (p = 0.8) or HbA1C (p = 0.21). The most common adverse events were localized injection-site symptoms. Pain was the most frequent symptom reported after the 1degreedose (90% vs 75% after the 2degree one). Fever was reported more frequently after the 2degreedose (30%) than after the 1degree one (5%). No serious adverse events nor hospitalization occurred. <ovid:br/>Conclusion(s): T1D patients developed vaccine-induced antibody responses after the BNT162b2 mRNA vaccine. The vaccine showed a good safety profile.

22. *Ali H, Alterki A, Sindhu S et al. Robust Antibody Levels in Both Diabetic and Non-Diabetic Individuals After BNT162b2 mRNA COVID-19. Front Immunol. 2021 Nov 24;12:752233.*

The emergence of effective vaccines for COVID-19 has been welcomed by the world with great optimism. Given their increased susceptibility to COVID-19, the question arises whether individuals with type-2 diabetes mellitus (T2DM) and other metabolic conditions can respond effectively to the mRNA-based vaccine. We aimed to evaluate the levels of anti-SARS-CoV-2 IgG and neutralizing antibodies in people with T2DM and/or other metabolic risk factors (hypertension and obesity) compared to those without. This study included 262 people (81 diabetic and 181 non-diabetic persons) that took two doses of BNT162b2 (Pfizer–BioNTech) mRNA vaccine. Both T2DM and non-diabetic individuals had a robust response to vaccination as demonstrated by their high antibody titers. However, both SARS-CoV-2 IgG and neutralizing antibodies titers were lower in people with T2DM. The mean (± 1 standard deviation) levels were 154 ± 49.1 *vs.* 138 ± 59.4 BAU/ml for IgG and 87.1 ± 11.6 *vs.* 79.7 ± 19.5% for neutralizing antibodies in individuals without diabetes compared to those with T2DM, respectively. In a multiple linear regression adjusted for individual characteristics, comorbidities, previous COVID-19 infection, and duration since second vaccine dose, diabetics had 13.86 BAU/ml (95% CI: 27.08 to 0.64 BAU/ml, p=0.041) less IgG antibodies and 4.42% (95% CI: 8.53 to 0.32%, p=0.036) fewer neutralizing antibodies than non-diabetics. Hypertension and

obesity did not show significant changes in antibody titers. Taken together, both type-2 diabetic and non-diabetic individuals elicited strong immune responses to SARS-CoV-2 BNT162b2 mRNA vaccine; nonetheless, lower levels were seen in people with diabetes. Continuous monitoring of the antibody levels might be a good indicator to guide personalized needs for further booster shots to maintain adaptive immunity. Nonetheless, it is important that people get their COVID-19 vaccination especially people with diabetes.

23. *Patone M, Handunnetthi L, Saatci D et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection Nat Med. 2021 Dec;27(12):2144-2153.*

Emerging reports of rare neurological complications associated with COVID-19 infection and vaccinations are leading to regulatory, clinical and public health concerns. We undertook a self-controlled case series study to investigate hospital admissions from neurological complications in the 28 days after a first dose of ChAdOx1nCoV-19 (n = 20,417,752) or BNT162b2 (n = 12,134,782), and after a SARS-CoV-2-positive test (n = 2,005,280). There was an increased risk of Guillain-Barré syndrome (incidence rate ratio (IRR), 2.90; 95% confidence interval (CI): 2.15-3.92 at 15-21 days after vaccination) and Bell's palsy (IRR, 1.29; 95% CI: 1.08-1.56 at 15-21 days) with ChAdOx1nCoV-19. There was an increased risk of hemorrhagic stroke (IRR, 1.38; 95% CI: 1.12-1.71 at 15-21 days) with BNT162b2. An independent Scottish cohort provided further support for the association between ChAdOx1nCoV and Guillain-Barré syndrome (IRR, 2.32; 95% CI: 1.08-5.02 at 1-28 days). There was a substantially higher risk of all neurological outcomes in the 28 days after a positive SARS-CoV-2 test including Guillain-Barré syndrome (IRR, 5.25; 95% CI: 3.00-9.18). Overall, we estimated 38 excess cases of Guillain-Barré syndrome per 10 million people receiving ChAdOx1nCoV-19 and 145 excess cases per 10 million people after a positive SARS-CoV-2 test. In summary, although we find an increased risk of neurological complications in those who received COVID-19 vaccines, the risk of these complications is greater following a positive SARS-CoV-2 test.

24. *Garcia-Grimshaw M, Michel-Chavez A, Vera-Zertuche JM et al. Guillain-Barre syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clinical Immunology 2021: 230: 108818.*

Vaccines are the most effective strategy to mitigate the global impact of COVID-19. However, vaccine hesitancy is common, particularly among minorities. Guillain-Barré syndrome (GBS) is the most common autoimmune illness of the peripheral nervous system, occurring at an incidence of 1.1/100,000 worldwide. A causal link between mRNA vaccines and GBS has not been previously evaluated. We analyzed a cohort of 3,890,250 Hispanic/Latinx recipients of the BNT162b2 mRNA vaccine (613,780 of whom had already received both doses) for incident GBS occurring within 30 days from vaccine administration. Seven cases of GBS were detected among first-dose recipients, for an observed incidence of 0.18/100,000 administered doses during the prespecified timeframe of 30 days. No cases were reported after second-dose administration. Our data suggest that, among recipients of the BNT162b2 mRNA vaccine, GBS may occur at the expected community-based rate; however, this should be taken with caution as the current incidence of GBS among the unvaccinated population against COVID-19 is still undetermined. We hope that this preliminary data will increase the public perception of safety toward mRNA-based vaccines and reduce vaccine hesitancy.

25. *Shemer A, Pras E, Einan-Lifshitz A et al. Association of COVID-19 Vaccination and Facial Nerve Palsy: A Case-Control Study. JAMA Otolaryngology-- Head & Neck Surgery 2021: 147(8): 739-743.*

Importance: Peripheral facial nerve (Bell) palsy has been reported and widely suggested as a possible adverse effect of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine. Israel is currently the leading country in vaccination rates per capita, exclusively using the BNT162b2 vaccine, and all residents of Israel are obligatory members of a national digital health registry system. These factors enable early analysis of adverse events.
Objective: To examine whether the BNT162b2 vaccine is associated with an increased risk of acute-onset peripheral facial nerve palsy.
Design, setting, and participants: This case-control study was performed from January 1 to February 28, 2021, at the emergency department of a tertiary referral center in central Israel. Patients admitted for facial nerve palsy were matched by age, sex, and date of admission with control patients admitted for other reasons.
Exposures: Recent vaccination with the BNT162b2 vaccine.
Main outcomes and measures: Adjusted odds ratio for recent exposure to the BNT162b2 vaccine among patients with acute-onset peripheral facial nerve palsy. The proportion of patients with Bell palsy exposed to the BNT162b2 vaccine was compared between groups, and raw and adjusted odds ratios for exposure to the vaccine were calculated. A secondary comparison with the overall number of patients with facial nerve palsy in preceding years was performed.
Results: Thirty-seven patients were admitted for facial nerve palsy during the study period, 22 (59.5%) of whom were male, and their mean (SD) age was 50.9 (20.2) years. Among recently vaccinated patients (21 [56.7%]), the mean (SD) time from vaccination to occurrence of palsy was 9.3 (4.2 [range, 3-14]) days from the first dose and 14.0 (12.6 [range, 1-23]) days from the second dose. Among 74 matched controls (2:1 ratio) with identical age, sex, and admittance date, a similar proportion were vaccinated recently (44 [59.5%]). The adjusted odds ratio for exposure was 0.84 (95% CI, 0.37-1.90; P = .67). Furthermore, analysis of the number of admissions for facial nerve palsy during the same period in preceding years (2015-2020) revealed a relatively stable trend (mean [SD], 26.8 [5.8]; median, 27.5 [range, 17-35]).
Conclusions and relevance: In this case-control analysis, no association was found between recent vaccination with the BNT162b2 vaccine and risk of facial nerve palsy.

26. Wan EYF, Chui CSL, Lai FTT et al. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. Lancet Infect Dis. 2022 Jan;22(1):64-72.

Background: Bell's palsy is a rare adverse event reported in clinical trials of COVID-19 vaccines. However, to our knowledge no population-based study has assessed the association between the inactivated SARS-CoV-2 vaccines and Bell's palsy. The aim of this study was to evaluate the risk of Bell's palsy after BNT162b2 and CoronaVac vaccination.
Methods: In this case series and nested case-control study done in Hong Kong, we assessed the risk of Bell's palsy within 42 days following vaccination with BNT162b2 (Fosun-BioNTech [equivalent to Pfizer-BioNTech]) or CoronaVac (from Sinovac Biotech, Hong Kong) using data from voluntary surveillance reporting with the Hospital Authority, the COVID-19 Vaccine Adverse Event Online Reporting system for all health-care professionals, and the Hospital Authority's territory-wide electronic health records from the Clinical Data Analysis and Reporting System. We described reported cases of Bell's palsy among vaccine recipients (aged 18-110 years for CoronaVac and aged 16-110 years for BNT162b2). We compared the estimated age-standardised incidence of clinically confirmed cases among individuals who had received the CoronaVac or BNT162b2 vaccination (up to 42 days before presentation) with the background incidence in the population. A nested case-control study was also done using conditional logistic regression to estimate the odds ratio (OR) for risk of Bell's palsy and vaccination. Cases and controls were matched (1:4) by age, sex, admission setting, and admission date.

Findings: Between February 23 and May 4, 2021, 451 939 individuals received the first dose of CoronaVac and 537 205 individuals received the first dose of BNT162b2. 28 clinically confirmed cases of Bell's palsy were reported following CoronaVac and 16 cases were reported following BNT162b2. The age-standardised incidence of clinically confirmed Bell's palsy was 66·9 cases per 100 000 person-years (95% CI 37·2 to 96·6) following CoronaVac vaccination and 42·8 per 100 000 person-years (19·4 to 66·1) for BNT162b2 vaccination. The age-standardised difference for the incidence compared with the background population was 41·5 (95% CI 11·7 to 71·4) for CoronaVac and 17·0 (-6·6 to 40·6) for BNT162b2, equivalent to an additional 4·8 cases per 100 000 people vaccinated for CoronaVac and 2·0 cases per 100 000 people vaccinated for BNT162b2. In the nested case-control analysis, 298 cases were matched to 1181 controls, and the adjusted ORs were 2·385 (95% CI 1·415 to 4·022) for CoronaVac and 1·755 (0·886 to 3·477) for BNT162b2.
Interpretation: Our findings suggest an overall increased risk of Bell's palsy after CoronaVac vaccination. However, the beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the risk of this generally self-limiting adverse event. Additional studies are needed in other regions to confirm our findings.

27. *Massoud F, Ahmad SF, Hassan AM et al. Safety and tolerability of COVID-19 vaccine among Patients with Epilepsy (PWE) in a tertiary hospital in Kuwait: A patient Survey Epilepsia 2021: 62(SUPPL 3): 80.*

Background: People with epilepsy (PwE) were concerned about the safety of the novel 2019 Coronavirus Disease (COVID-19) vaccines.
Objective: This study aimed to assess the side effects experienced by PwE following vaccination with COVID-19 vaccines and to identify the causes of vaccine hesitation.
Methods: We administered a questionnaire to PwE, who visited the epilepsy clinic at Ibn Sina Hospital in Kuwait during the first two working weeks of April 2021. It included socio-demographic, epilepsy status, and vaccination data. In addition, we asked those who were not vaccinated yet about the reasons and their plan.
Results: A total of 111 PwE were surveyed, with 82 being vaccinated and 29 being unvaccinated. Out of the 82 vaccinated, 66 (80.5%) reported at least one side effect. Patients who received the Pfizer BioNTech mRNA vaccine (BNT162b2) (first, second dosage); and the Oxford-AstraZenecaa chimpanzee adenovirus-vectored vaccine (ChAdOx1nCoV-19) (first dose) had the following reactions: Pain at the injection site (40%, 67.6%), 43.8%, fatigue (47%, 32.4%), 46.9%, Headache (33.3%, 35.3%), 34.4% and Myalgia (40%, 35%), 50% respectively. Local site effects, including pain (67.6% vs. 40%, p = < 0.001) and redness (26.5% vs 6.7%, p = 0.019), were more statistically significantly after the second dose of BNT162b2 vaccine compared to the first dose of the same vaccine. While there was no significant difference in systemic side effects frequencies between the two doses of the BNT162b2 vaccine. The systemic side effects were more statistically significantly after the first dose of ChAdOx1nCoV-19 compared to the first dose of the BNT162b2 vaccine and those included fever (56.3% vs 13.3%, p = < 0.001), chills (37.5% vs 6.7%, p = < 0.001), myalgia (50% vs 40%, p = < 0.001) and arthralgia (25% vs 6.7%, p = 0.021). The local site reactions were not significantly different between the first doses of both vaccines. Among the subgroup who had vaccine-related side effects, 66.7% were females, 90.9% were 55 or younger, 63.6% were on polytherapy, 74% had side effects for one day or less, and 95% were symptoms free by the end of the first-week post-vaccination. Symptoms were mild in 68% of the patients and moderate in 29.3%. Most patients (93.9%) did not report seizure worsening after vaccination. The relative risk of seizure worsening after the first and second doses of BNT162b2 and the first dose of ChAdOx1nCoV-19 vaccines was 1.027 (95% CI 0.891-1.183), 1.019 (95% CI 0.928-1.119), and 1.026 (95% CI 0.929-1.134) respectively. After the first dose of BNT162b2, one patient reported the

development of status epilepticus. Among the non-vaccinated group, 34.9% were still indecisive, while 37.9% rejected the vaccination. Fear of adverse effects (42.9%) and fear of epilepsy worsening (23.8%) were the main reasons for vaccine hesitation.
Conclusions: This study shows that the two vaccines under consideration (BNT162b2 and ChAdOx1nCoV-19) have a good safety profile and a low risk of epilepsy worsening among a cohort of PwE in Kuwait.

28. Lotan I, Wilf-Yarkon A, Friedman Y et al. Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis: Early experience from a tertiary multiple sclerosis center in Israel. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 283-284.

Background: Although the COVID-19 vaccines are currently recommended for people with multiple sclerosis (MS), the fact that they were not specifically tested in people with MS raises uncertainty regarding the safety of the vaccines in this population. The COVID-19 vaccination campaign began in Israel in December 2020 using the BNT162b2 (Pfizer) vaccine as its sole vaccine. Israel is currently the leading country in the world in the percentage of its population that received both doses of the vaccine. Objective: To report real-life safety data of the BNT162b2 COVID-19 vaccine in a cohort of MS patients. Methods: An anonymous survey was distributed to 425 MS patients. Participants were asked general demographic and disease-related questions and specific questions regarding the safety profile of the COVID-19 vaccine. Results: 262 of 425 MS patients (61.6% response rate) completed the questionnaire. The median age was 42 years (range 22-79 years); 199 were females (75.9%), and 66 participants (25.2%) had associated comorbidities. 198 participants (75.6%) were treated with disease-modifying therapies (DMTs). 239 participants (91.2% of the responders) received the BNT162b2 COVID-19 vaccine. Of these, 182 (76.1%) were < 55 years old, and 57 (23.9%) were > 55 years old. 136 participants (56.9%; 52.5% of those 55 years; p=0.1517) reported immediate adverse events. 36 participants (15.1%) reported new or worsening neurological symptoms following the vaccination, the most frequent being sensory disturbances (21 participants, 58.3%). Most symptoms occurred within the first 24 hours after vaccination and resolved within three days. 28 participants (77.8%) didn't require any medication to treat their symptoms. Conclusions: This survey indicates an overall favorable safety profile of the BNT162b2 vaccine in people with MS. These data should be confirmed in further prospective, large-scale studies.

29. Lotan I, Wilf-Yarkoni A, Friedman Y et al Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis (MS): Early experience from a tertiary MS center in Israel. European Journal of Neurology 2021: 28(11): 3742-3748.

Background and purpose: Although the COVID-19 vaccines are currently recommended for people with multiple sclerosis (MS), the fact that they were not specifically tested in people with MS raises uncertainty regarding their safety in this population. The purpose of this study was to report real-life safety data of the BNT162b2 COVID-19 vaccine in a cohort of MS patients.
Methods: An anonymous survey was distributed to 425 MS patients. Participants were asked general demographic and disease-related questions and specific questions regarding the safety profile of the COVID-19 vaccine.
Results: Of the 425 MS patients, 262 completed the questionnaire. The median (range) participant age was 42 (22-79) years, 199 participants were women (75.9%), and 66 participants (25.2%) had associated comorbidities. A total of 198 participants (75.6%) were treated with disease-modifying therapies. In all, 239 participants (91.2% of the responders) had received the BNT162b2 COVID-19 vaccine. Of these, 182 (76.1%) were aged <55 years, and 57 (23.9%) were aged >55 years. Adverse events were reported by 136 participants (56.9%; 52.5% of those aged <55 years and 40.3% of those aged >55 years; p = 0.1517) and 36 participants (15.1%)

reported new or worsening neurological symptoms following the vaccination, the most frequent being sensory disturbances (21 participants, 58.3%). Most symptoms occurred within the first 24 h after vaccination and resolved within 3 days. A total of 28 participants (77.8%) did not require any medication to treat their symptoms.
Conclusions: This survey indicates an overall favorable safety profile of the BNT162b2 vaccine in people with MS. These data should be confirmed in further prospective, large-scale studies.

30. *Chou S, Kaviani K, Ropero B et al Incidence of multiple sclerosis relapses and pseudorelapses following mRNA COVID-19 vaccination. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 220-221.*

The coronavirus disease 2019 (COVID-19) pandemic has created an urgency for an effective vaccine. The current approved mRNA vaccines offered by Pfizer-BioNTech (BNT162b2) and ModernaTX (mRNA-1273) have shown few side effects in general population studies. People living with multiple sclerosis (MS) were not specifically represented in the above studies. The MS community is extremely interested in knowing, how these vaccines are tolerated by this population. We retrospectively identified 102 consecutive MS patients at our center that had been fully vaccinated against COVID-19 with the current mRNA vaccines. We compared the reported side effects (SE) with the clinical trial data from Pfizer-BioNtech and ModernaTX. In addition to local and systemic reactogenicity, we recorded clinical relapses and pseudo-relapses to encompass any neurological SE. Overall, our patient population reported significantly less SE for both vaccine variants as compared with general population studies, except for a higher incidence of fever in mRNA-1273 recipients (25% vs. 16%). Of the 62 patients that received the BNT162b2 vaccine variant, there were 2 cases of pseudo-relapse (3.2%). Of the 40 patients that received the mRNA-1273 vaccine, there were 4 patients that reported a pseudo-relapse (10%). Recovery to pre-vaccination neurological baseline occurred in all subjects within 96h without receiving specific treatments. No clinical relapses occurred in association with these vaccines. There was no association between a patient's disease-modifying therapy, age, sex, or race and their risk of suffering from a pseudo-relapse after COVID-19 vaccination. In summary, the risk for clinical relapses was absent in our cohort. The risk of transient neurological worsening was very low (average 5.9%). Our data may help inform patients and clinicians about the tolerability and safety of COVID-19 mRNA vaccines in people living with MS.

31. *Millan-Pascual J, Valero-Lopez G, Lopez-Tovar IA et al Serological response to SARS-CoV-2 vaccination in multiple sclerosis patient in a real-life experience. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 767-768.*

Introduction:
Vaccination against COVID-19 has been widely recommended for patients with multiple sclerosis (MS), although the effect of different disease-modifying treatments (DMTs) on said immunization is not well known. Some studies begin to point out a relationship between DMTs of greater efficacy with a lower rate of seroprotection.
Objectives:
To assess serological response to SARS-CoV-2 vaccination in MS patients receiving disease-modifying treatments (DMTs) in a real-life setting.
Methods:
Anti-spike protein-based serology was measured in 191 patients with MS and 6 patients with neuromyelitis optica spectrum disorder (NMOSD). Patients were either untreated or under treatment with different DMTs. A group of healthy subjects similarly vaccinated served

as control. The percent of subjects that developed protective antibodies, the antibody-titer, and lymphocyte counts were evaluated.

Results:

Patients and controls were vaccinated with different available vaccines BNT162b2 (68.6%), mRNA-1273 (5.4%), ChAdOx1-S (20.7%) and Ad26COVS1 (4.3%). Protective serological response was observed in 100% of controls, NMOSD, untreated (n=19), Interferon-beta (n=17), Glatiramer-acetate (n=15), Cladribine (n=11), Dimethyl-fumarate (n=15), Teriflunomide (n=29) and Natalizumab (n=25) patients. 100% was also observed in Alemtuzumab (n=11) patients but none received treatment dose in last year. Serological response was observed in 42%, 44% and 0% of Fingolimod (n=12), Ocrelizumab (n=26) and Rituximab (n=6) patients respectively. Time from the last dosing was related to serological response in anti-CD-20 therapies; age, disease duration, disease phenotype, vaccine used, or lymphocyte counts did not affect humoral response to COVID-19 vaccination.

Conclusions:

Anti-CD20 therapies and Fingolimod seem to condition a lower humoral response to vaccines against SARS-CoV-2. Vaccination prior initiation of these DMTs medication administration would be recommendable whenever possible.

32. Briggs FBS, Mateen FJ, Schmidt H et al COVID-19 Vaccination Reactogenicity in Persons With Multiple Sclerosis. Neurology neuroimmunology & neuroinflammation 2022: 9(1).

Background and Objectives

There are limited data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine reactogenicity in persons with multiple sclerosis (PwMS) and how reactogenicity is affected by disease-modifying therapies (DMTs). The objective of this retrospective cross-sectional study was to generate real-world multiple sclerosis–specific vaccine safety information, particularly in the context of specific DMTs, and provide information to mitigate specific concerns in vaccine hesitant PwMS.

Methods

Between 3/2021 and 6/2021, participants in iConquerMS, an online people-powered research network, reported SARS-CoV-2 vaccines, experiences of local (itch, pain, redness, swelling, or warmth at injection site) and systemic (fever, chills, fatigue, headache, joint pain, malaise, muscle ache, nausea, allergic, and other) reactions within 24 hours (none, mild, moderate, and severe), DMT use, and other attributes. Multivariable models characterized associations between clinical factors and reactogenicity.

Results

In 719 PwMS, 64% reported experiencing a reaction after their first vaccination shot, and 17% reported a severe reaction. The most common reactions were pain at injection site (54%), fatigue (34%), headache (28%), and malaise (21%). Younger age, being female, prior SARS-CoV-2 infection, and receiving the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vs BNT162b2 (Pfizer-BioNTech) vaccine were associated with experiencing a reaction after the first vaccine dose. Similar relationships were observed for a severe reaction, including higher odds of reactions among PwMS with more physical impairment and lower odds of reactions for PwMS on an alpha4-integrin blocker or sphingosine-1-phosphate receptor modulator. In 442 PwMS who received their second vaccination shot, 74% reported experiencing a reaction, whereas 22% reported a severe reaction. Reaction profiles after the second shot were similar to those reported after the first shot. Younger PwMS and those who received the mRNA-1273 (Moderna) vs BNT162b2 vaccine reported higher reactogenicity after the second shot, whereas those on a sphingosine-1-phosphate receptor modulator or fumarate were significantly less likely to report a reaction.

Discussion

SARS-CoV-2 vaccine reactogenicity profiles and the associated factors in this convenience sample of PwMS appear similar to those reported in the general population. PwMS on specific DMTs were less likely to report vaccine reactions. Overall, the short-term vaccine reactions experienced in the study population were mostly self-limiting, including pain at the injection site, fatigue, headache, and fever.

33. Alonso R, Leguizamón, F; Silva BA et al Safety of COVID-19 vaccines in patients with multiple sclerosis from Latin America Multiple Sclerosis Journal 2021: 27(2 SUPPL): 695-696.

Introduction:
Patients with MS (pwMS) are currently receiving different COVID-19 vaccines in several Latin American countries. However, questions arise around the safety of these vaccines and whether vaccination might increase the risk of relapse activity. Therefore, we aimed to assess the safety and occurrence of relapses following COVID-19 vaccination in Latin American pwMS.
Methods:
A web-based survey was completed by 207 pwMS from Latin America to assess for adverse events associated with COVID-19 vaccination between February 1 and April 30, 2021.
Results:
All participants received the first dose and 84 the second. The different vaccines administered were inactivated virus vaccines [(IVV);CoronaVac, BBIBP-CorV)] in 117 (56.5%) patients, adenovirus vector vaccines [(AdV);Gam-COVID-Vac, AZD1222] in 53 (25.6%) and mRNA vaccines (BNT162b2) in 37 (17.9%). The mean follow-up after vaccination was 24 ± 16 days. Three (1.4%) patients reported having COVID-19 infection after vaccination (all occurring after the first dose). Any adverse events were reported in 61 (29.5%) and 23 (27.4%) individuals after the first and second doses respectively. These included pain at the injection site, headache, fever, flu-like symptoms, fatigue, and muscle or joint pain. A lower frequency of adverse events was found with IVV (x?=7.2, p=0.03). Four (1.9%) patients reported an MS relapse, all occurring after an IVV first dose. Mean time to relapse 18 ± 13 days. None of these patients had stopped or postponed their MS treatment before vaccination.
Conclusion:
COVID-19 vaccines seem to be safe for pwMS from Latin America. No major safety signals appeared in this patient reported study.

34. Alroughani R, Al-Hashel J, Abokalawa F et al COVID-19 vaccination in people with multiple sclerosis. The Kuwait experience: Multiple Sclerosis Journal 2021: 27(2 SUPPL): 785.

Background:
Two vaccine (BNT162b2 and ChAdOx1 nCoV-19) have been approved to be used in Kuwait since December 2021
Objective:
To assess the safety of the vaccination in MS patients and to determine the occurrence of relapses following COVID-19 vaccination in MS patients.
Methods:
MS patients were contacted by phone, WhatsApp, or through face-to-face interview and were invited to complete a web-based questionnaire. Demographic, clinical, medications, administration of first and second vaccine doses, symptoms following vaccine, worsening of preexisting MS symptoms and occurrence of relapse were recorded
Results:

482 MS patients answered the web-based questionnaire. Between January 2021 and 20 May 2021, 240 (49.8%) MS patients received at least one dose of the approved vaccination. Their mean age was 37.27 +8.95 and most of them 146 (60.8%) were females. 159 received first dose and 81 received the second dose. 126 revived BNT162b2 vaccine and 114 received ChAdOx1 nCoV-19. There was one case of COVID-19 infection encountered after the first dose of BNT162b2 vaccine. Nine cases reported worsening of preexisting MS symptoms after vaccine. One patient reportedrelapse after first BNT162b2 vaccine dose. The most common adverse events of COVID-19 vaccine were pain at the injection site, fatigue, low grade fever and body ache. 28 Patients on anti CD20 needed to postpone vaccine or reschedule their medications.
Conclusion:
Both BNT162b2 and ChAdOx1 nCoV-19 are safe for MS patients. There is nNo increased risk of relapse activity or worsening of preexisting MS symptoms were recorded.

35. *Menascu S, Dreyer-Alster S, Dolev M et al. Safety and efficacy of COVID-19 Pfizer-BNT162b2 m-RNA vaccine in young MS population Multiple Sclerosis Journal 2021: 27(2 SUPPL): 255-256.*

Introduction:
As the vaccination against coronavirus disease 2019 (COVID-19) becomes available worldwide, risks related to vaccinating patients with multiple sclerosis (MS) need to be carefully assessed.
Objective:
Characterize safety and occurrence of immediate relapses following COVID-19 vaccination in young MS patients up to 30 years of age.
Methods:
We assessed the safety of BNT162b2-COVID-19 vaccination in young MS patients. Patients were contacted by phone, email, WhatsApp, or face-to-face encounters. Follow-up was conducted in the MS Center to record any occurrence of acute relapses
Results:
The safety profile of COVID-19 vaccination was compared between 21 very young and 71 young MS patients, median (25-75 IQR) age 18.7 (18.1 - 19.8) vs. 26.5 (24.2 - 28.3) years, $p<0.001$. One patient (4.8%) in the very young age group was infected with SARS-COV-2 following the first vaccine dose; no cases of COVID-19 infection were noted during the follow-up, median (range) 85 (7 - 116) days after the second vaccine dose. The percent of patients with any adverse event was higher in the very young age group, after the first and the second vaccine doses, 76.2% and 80.9% vs. 52.1% and 59.1%, respectively. Adverse events profile was characterized by increased rates of pain at the injection site fatigue, and headache in the very young age group, after the first and after the second vaccine doses. No events of face tingling or facial palsy were recorded in either age group. No increased risk of relapse activity was noted in both groups.
Conclusions:
The COVID-19-BNT162b2 vaccine is safe for young MS patients. The frequency of adverse events was higher in the very young age group, and more so after the second vaccine dose.

36. *Dreyer-Alster S, Dolev M, Menascu S et al 2021 COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by May 2021. Multiple Sclerosis Journal 2021: 27(2 SUPPL): 253-254.*

Introduction:
We have previously reported (Achiron A, et al. Mult Scler. 2021. PMID 33856242) that the BNT162b2 vaccine against coronavirus disease 2019 (COVID-19) proved safe for multiple

sclerosis (MS) patients, with no increased risk of relapse activity. Since our previous report, further data has accumulated, and the follow-up period was extended.

Objectives:

Revalidate safety and occurrence of immediate relapses following COVID-19 vaccination in a large cohort of MS patients.

Methods:

We assessed the safety of BNT162b2 COVID-19 vaccination in adult MS patients. Patients were questioned regarding adverse events via phone, WhatsApp, email, or face-to-face encounters. Follow-up was conducted in the MS Center to record any occurrence of acute relapses.

Results:

Between December 2020 and April 2021, 911 MS patients received the first vaccine dose and 888 completed the second dose. Four cases of COVID-19 infection were encountered after the first dose. The adverse event profile of COVID-19 vaccine was mainly characterized by pain at the injection site (23.1% and 15.6% of patients following first and second dose, respectively), fatigue (10.3%, 19.4%), and headache (5.5%, 8.1%). An acute relapse was noted in 1.5% of patients adjacent to the first dose. Within a follow-up period of up to 4 months from second vaccine dose, 3.1% of patients experienced an acute relapse, median 41 days from second dose. The rate of acute relapses during the follow-up period was similar between vaccinated and nonvaccinated MS patients (4.6%). Younger age (18-55 years), lower disability (Expanded Disability Status Scale ≤3.0), and treatment with immunomodulatory medication were associated with a higher frequency of adverse events.

Conclusions:

COVID-19 BNT162b2 vaccine is safe for MS patients. No increased risk of acute relapse activity was noted following vaccination.

37. Barda N, Dagan N, Ben-Shlomo Y et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. New England Journal of Medicine. 2021 Aug 25.

BACKGROUND

Preapproval trials showed that messenger RNA (mRNA)–based vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had a good safety profile, yet these trials were subject to size and patient-mix limitations. An evaluation of the safety of the BNT162b2 mRNA vaccine with respect to a broad range of potential adverse events is needed.

METHODS

We used data from the largest health care organization in Israel to evaluate the safety of the BNT162b2 mRNA vaccine. For each potential adverse event, in a population of persons with no previous diagnosis of that event, we individually matched vaccinated persons to unvaccinated persons according to sociodemographic and clinical variables. Risk ratios and risk differences at 42 days after vaccination were derived with the use of the Kaplan–Meier estimator. To place these results in context, we performed a similar analysis involving SARS-CoV-2–infected persons matched to uninfected persons. The same adverse events were studied in the vaccination and SARS-CoV-2 infection analyses.

RESULTS

In the vaccination analysis, the vaccinated and control groups each included a mean of 884,828 persons. Vaccination was most strongly associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% confidence interval [CI], 1.55 to 12.44; risk difference, 2.7 events per 100,000 persons; 95% CI, 1.0 to 4.6), lymphadenopathy (risk ratio, 2.43; 95% CI, 2.05 to 2.78; risk difference, 78.4 events per 100,000 persons; 95% CI, 64.1 to 89.3), appendicitis (risk ratio, 1.40; 95% CI, 1.02 to 2.01; risk difference, 5.0 events per 100,000 persons; 95% CI, 0.3 to 9.9), and herpes zoster infection (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24.2). SARS-CoV-2 infection was associated with a

substantially increased risk of myocarditis (risk ratio, 18.28; 95% CI, 3.95 to 25.12; risk difference, 11.0 events per 100,000 persons; 95% CI, 5.6 to 15.8) and of additional serious adverse events, including pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia.

CONCLUSIONS

In this study in a nationwide mass vaccination setting, the BNT162b2 vaccine was not associated with an elevated risk of most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). The risk of this potentially serious adverse event and of many other serious adverse events was substantially increased after SARS-CoV-2 infection.

38. *Furer V, Zisman D, Kibari A et al. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. Rheumatology. 2021 Apr 12.*

Objectives

As global vaccination campaigns against COVID-19 disease commence, vaccine safety needs to be closely assessed. The safety profile of mRNA-based vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) is unknown. The objective of this report is to raise awareness to reactivation of herpes zoster (HZ) following the BNT162b2 mRNA vaccination in patients with AIIRD.

Methods

The safety of the BNT162b2 mRNA vaccination was assessed in an observational study monitoring post-vaccination adverse effects in patients with AIIRD (n = 491) and controls (n = 99), conducted in two Rheumatology Departments in Israel.

Results

The prevalence of HZ was 1.2% (n = 6) in patients with AIIRD compared with none in controls. Six female patients aged 49 ± 11 years with stable AIIRD: rheumatoid arthritis (n = 4), Sjogren's syndrome (n = 1), and undifferentiated connective disease (n = 1), developed the first in a lifetime event of HZ within a short time after the first vaccine dose in 5 cases and after the second vaccine dose in one case. In the majority of cases, HZ infection was mild, except a case of HZ ophthalmicus, without corneal involvement, in RA patient treated with tofacitinib. There were no cases of disseminated HZ disease or postherpetic neuralgia. All but one patient received antiviral treatment with a resolution of HZ-related symptoms up to 6 weeks. Five patients completed the second vaccine dose without other adverse effects.

Conclusion

Epidemiologic studies on the safety of the mRNA-based COVID-19 vaccines in patients with AIIRD are needed to clarify the association between the BNT162b2 mRNA vaccination and reactivation of zoster.

39. *Furer V, Zisman D, Elkayam O. Comment on: Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series: reply. Rheumatology (Oxford, England). 23 Sep 2021.*

DEAR EDITOR, We would like to respond to the comment by Mungmunpuntipantip and Wiwanitkit relating to the article published by our group, entitled 'Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series'. Herpes zoster is indeed a common comorbidity in patients suffering from

autoimmune inflammatory rheumatic diseases (AIIRD) and therefore it is challenging to postulate the direct causality to vaccination based on the cluster of cases.
Following the publication of the above article, the authors received numerous mails all over the world with reports of post-vaccination herpes zoster occurrence in both immunocompetent and immunocompromised patients (personal communication). Furthermore, accumulating evidence has recently emerged confirming the increased incidence of herpes zoster infection following mRNA-based COVID-19 vaccination in immunocompetent subjects, as reported in case series by Psichogiou from Greece and a large-scale population-based study from Israel. In the latter, the BNT162b2 mRNA vaccinated and control groups, including a mean of 884 828 persons each, were followed for 42 days after vaccination. Vaccination was strongly associated with herpes zoster infection: risk ratio, 1.43; 95% CI: 1.20, 1.73; risk difference, 15.8 events per 100 000 persons; 95% CI: 8.2, 24.2. Interestingly, data on >240 000 SARS-CoV-2 infected persons were assessed to estimate the effects of a documented SARS-CoV-2 infection on the incidence of adverse events. SARS-CoV-2 infection was not estimated to have a meaningful effect on the incidence of herpes zoster infection. In summary, the present epidemiological data points out that herpes zoster might represent a potential adverse event of mRNA SARS-CoV-2 vaccination, with the limitation of the lack of dermatopathological assessment in most cases. In our opinion, reactivation of herpes zoster following SARS-CoV-2 vaccination should be considered by the medical community and vaccination for herpes zoster should be offered when appropriate.

40. *Xu S, Huang R, Sy LS, Glenn SC, Ryan DS, Morrissette K, Shay DK, Vazquez-Benitez G, Glanz JM, Klein NP, McClure D, Liles EG, Weintraub ES, Tseng HF, Qian L. COVID-19 Vaccination and Non-COVID-19 Mortality Risk - Seven Integrated Health Care Organizations, United States, December 14, 2020-July 31, 2021. MMWR Morb Mortal Wkly Rep. 2021 Oct 29;70(43):1520-1524. doi: 10.15585/mmwr.mm7043e2. PMID: 34710075; PMCID: PMC8553028.*

By September 21, 2021, an estimated 182 million persons in the United States were fully vaccinated against COVID-19.* Clinical trials indicate that Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Janssen (Johnson & Johnson; Ad.26.COV2.S) vaccines are effective and generally well tolerated (1-3). However, daily vaccination rates have declined approximately 78% since April 13, 2021†; vaccine safety concerns have contributed to vaccine hesitancy (4). A cohort study of 19,625 nursing home residents found that those who received an mRNA vaccine (Pfizer-BioNTech or Moderna) had lower all-cause mortality than did unvaccinated residents (5), but no studies comparing mortality rates within the general population of vaccinated and unvaccinated persons have been conducted. To assess mortality not associated with COVID-19 (non-COVID-19 mortality) after COVID-19 vaccination in a general population setting, a cohort study was conducted during December 2020-July 2021 among approximately 11 million persons enrolled in seven Vaccine Safety Datalink (VSD) sites.§ After standardizing mortality rates by age and sex, this study found that COVID-19 vaccine recipients had lower non-COVID-19 mortality than did unvaccinated persons. After adjusting for demographic characteristics and VSD site, this study found that adjusted relative risk (aRR) of non-COVID-19 mortality for the Pfizer-BioNTech vaccine was 0.41 (95% confidence interval [CI] = 0.38-0.44) after dose 1 and 0.34 (95% CI = 0.33-0.36) after dose 2. The aRRs of non-COVID-19 mortality for the Moderna vaccine were 0.34 (95% CI = 0.32-0.37) after dose 1 and 0.31 (95% CI = 0.30-0.33) after dose 2. The aRR after receipt of the Janssen vaccine was 0.54 (95% CI = 0.49-0.59). There is no increased risk for mortality among COVID-19 vaccine recipients. This finding reinforces the safety profile of currently approved COVID-19 vaccines in the United States.

41. Shapiro Ben David S, Shamir-Stein N, Baruch Gez S et al. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. Clinical Immunology 2021: 232: 108860.

Background: Since July 13, 2021, a third SARS-CoV-2 vaccine BNT162b2 was approved in Israel to immunocompromised and seniors 60 years of age or older. We aimed to evaluate vaccine's reactogenicity.
Methods: A retrospective cohort, using electronic surveys sent to booster vaccine recipients, during July 20-August 10, 2021.
Results: 17,820 participated in the survey, with a response rate of 30.2%. 3195 (17.9%) were immunocompromised. Fatigue, myalgia and fever were the most frequent systemic side effects reported (19.6%, 9.2% and 8.1% respectively among immunocompromised; 21.3%, 9.9% and 9.2% respectively among seniors). 67.3% of immunocompromised and 62% of seniors reported experiencing a better or a similar response to the third dose, compared to the second.
Conclusions: Local and systemic reactions after third BNT162b2 vaccine, reported by immunocompromised and seniors, were similar to those observed following previous vaccines and mostly self-resolved. These findings may aid promoting confidence among vaccine providers and recipients.

42. Bar-On Y M, Goldberg Y, Mandel M et al. Protection of BNT162B2 vaccine booster against Covid-19 in Israel. New England Journal of Medicine 2021: 385(15): 1393-1400.

BACKGROUND
On July 30, 2021, the administration of a third (booster) dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) was approved in Israel for persons who were 60 years of age or older and who had received a second dose of vaccine at least 5 months earlier. Data are needed regarding the effect of the booster dose on the rate of confirmed coronavirus 2019 disease (Covid-19) and the rate of severe illness.
METHODS
We extracted data for the period from July 30 through August 31, 2021, from the Israeli Ministry of Health database regarding 1,137,804 persons who were 60 years of age or older and had been fully vaccinated (i.e., had received two doses of BNT162b2) at least 5 months earlier. In the primary analysis, we compared the rate of confirmed Covid-19 and the rate of severe illness between those who had received a booster injection at least 12 days earlier (booster group) and those who had not received a booster injection (nonbooster group). In a secondary analysis, we evaluated the rate of infection 4 to 6 days after the booster dose as compared with the rate at least 12 days after the booster. In all the analyses, we used Poisson regression after adjusting for possible confounding factors.
RESULTS
At least 12 days after the booster dose, the rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3); the rate of severe illness was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). In a secondary analysis, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days by a factor of 5.4 (95% CI, 4.8 to 6.1).
CONCLUSIONS
In this study involving participants who were 60 years of age or older and had received two doses of the BNT162b2 vaccine at least 5 months earlier, we found that the rates of confirmed Covid-19 and severe illness were substantially lower among those who received a booster (third) dose of the BNT162b2 vaccine.

43. Bensouna I, Caudwell V, Kubab S et al. SARS-CoV-2 Antibody Response After a Third Dose of the BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. Am J Kidney Dis. 2021 Sep 8;S0272-6386(21)00833-7.

Rationale & Objective
Recent studies showed that antibody titers after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the dialysis population are diminished as compared with the general population, suggesting the possible value of a third booster dose. We characterized the humoral response after 3 doses of the BNT162b2 vaccine in patients treated with either maintenance hemodialysis (HD) or peritoneal dialysis (PD).
Study Design
Case series.
Setting & Participants
69 French patients (38 HD and 31 PD) treated at a single center who received 3 doses of the BNT162b2 vaccine.
Findings
Humoral response was evaluated using plasma levels of anti-SARS-CoV-2 spike protein S1 immunoglobulin measured after the second dose and at least 3 weeks after the third dose of the BNT162b2 vaccine. Patients (median age 68 years [interquartile range (IQR), 53-76 years], 65% men) had a median anti-S1 antibody level of 284 [IQR, 83-1190] AU/mL after the second dose, and 7,554 [IQR, 2,268-11,736] AU/mL after the third dose. Three patients were nonresponders (anti-S1 antibody level < 0.8 AU/mL), and 12 were weak responders (anti-S1 antibody level 0.8-50 AU/mL) after the second vaccine dose. After the third dose, 1 of the 3 initial nonresponders produced anti-spike antibody, and all the 12 initial weak responders increased their antibody levels. Patients with a greater increase in anti-S1 antibody levels after a third dose had lower antibody levels after the second dose, and a longer time interval between the second and the third dose. Adverse events did not seem to be more common or severe after a third vaccine dose.
Limitations
Observational study, small sample size. Relationship between antibody levels and clinical outcomes is not well understood.
Conclusions
A third dose of the BNT162b2 vaccine substantially increased antibody levels in patients receiving maintenance dialysis and appeared to be as well tolerated as a second dose.

44. Borobia AM, Carcas AJ, Perez-Olmeda M et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet 2021: 398(10295): 121-130.

Background: To date, no immunological data on COVID-19 heterologous vaccination schedules in humans have been reported. We assessed the immunogenicity and reactogenicity of BNT162b2 (Comirnaty, BioNTech, Mainz, Germany) administered as second dose in participants primed with ChAdOx1-S (Vaxzevria, AstraZeneca, Oxford, UK).
Methods: We did a phase 2, open-label, randomised, controlled trial on adults aged 18-60 years, vaccinated with a single dose of ChAdOx1-S 8-12 weeks before screening, and no history of SARS-CoV-2 infection. Participants were randomly assigned (2:1) to receive either BNT162b2 (0·3 mL) via a single intramuscular injection (intervention group) or continue observation (control group). The primary outcome was 14-day immunogenicity, measured by immunoassays for SARS-CoV-2 trimeric spike protein and receptor binding domain (RBD). Antibody functionality was assessed using a pseudovirus neutralisation assay, and cellular immune response using an interferon-γ immunoassay. The safety outcome was 7-day reactogenicity, measured as solicited local and systemic adverse events. The primary analysis included all

participants who received at least one dose of BNT162b2 and who had at least one efficacy evaluation after baseline. The safety analysis included all participants who received BNT162b2. This study is registered with EudraCT (2021-001978-37) and ClinicalTrials.gov (NCT04860739), and is ongoing.
Findings: Between April 24 and 30, 2021, 676 individuals were enrolled and randomly assigned to either the intervention group (n=450) or control group (n=226) at five university hospitals in Spain (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men). 663 (98%) participants (n=441 intervention, n=222 control) completed the study up to day 14. In the intervention group, geometric mean titres of RBD antibodies increased from 71·46 BAU/mL (95% CI 59·84-85·33) at baseline to 7756·68 BAU/mL (7371·53-8161·96) at day 14 (p<0·0001). IgG against trimeric spike protein increased from 98·40 BAU/mL (95% CI 85·69-112·99) to 3684·87 BAU/mL (3429·87-3958·83). The interventional:control ratio was 77·69 (95% CI 59·57-101·32) for RBD protein and 36·41 (29·31-45·23) for trimeric spike protein IgG. Reactions were mild (n=1210 [68%]) or moderate (n=530 [30%]), with injection site pain (n=395 [88%]), induration (n=159 [35%]), headache (n=199 [44%]), and myalgia (n=194 [43%]) the most commonly reported adverse events. No serious adverse events were reported.
Interpretation: BNT162b2 given as a second dose in individuals prime vaccinated with ChAdOx1-S induced a robust immune response, with an acceptable and manageable reactogenicity profile.

45. *Longlune N, Nogier MB, Miedougé M et al High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrology Dialysis Transplantation 2021: 36(9): 1704-1709.*

Background: Patients with chronic kidney disease, dialysis patients and kidney transplant patients are at high risk of developing severe coronavirus disease 2019 (COVID-19). Data regarding the immunogenicity of anti-severe acute respiratory syndrome coronavirus 2 messenger RNA (anti-SARS-CoV-2 mRNA) vaccines in dialysis patients were published recently. We assessed the immunogenicity of anti-SARS-CoV-2 mRNA vaccine in dialysis patients.
Patients and methods: One hundred and nine patients on haemodialysis (n = 85) or peritoneal dialysis (n = 24) have received two injections of 30-µg doses of BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) that were administered intramuscularly 28 days apart. Those who were still seronegative after the second dose were given a third dose 1 month later. Anti-SARS-CoV-2 antibodies were tested before and after vaccination.
Results: Ninety-one out of the 102 patients who had at least a 1-month follow-up after the second (n = 97) or the third (n = 5) vaccine doses had anti-SARS-CoV-2 antibodies. The seroconversion rate was 88.7% (86 out of 97 patients) among SARS-CoV-2 seronegative patients at the initiation of vaccination. Receiving immunosuppressive therapy was an independent predictive factor for non-response to vaccination.
Conclusion: Due to high immunogenicity and safety of mRNA vaccines, we strongly recommend prioritizing a two-dose vaccination of dialysis patients. A third dose can be required in non-responders to two doses. When possible, patients waiting for a kidney transplantation should be offered the vaccine before transplantation.

46. *Russo G, Lai Q, Poli L et al SARS-COV-2 vaccination with BNT162B2 in renal transplant patients: Risk factors for impaired response and immunological implications. Clin Transplant. 2021 Sep 26;e14495.*

Solid organ transplant patients are at a higher risk for poor CoronaVirus Disease-2019 (COVID-19)-related outcomes and have been included as a priority group in the vaccination strategy

worldwide. We assessed the safety and efficacy of a two-dose vaccination cycle with mRNA-based COVID-19 vaccine (BNT162b2) among 82 kidney transplant outpatients followed in our center in Rome, Italy. After a median of 43 post-vaccine days, a SARS-CoV-2 anti-Spike seroprevalence of 52.4% (n = 43/82) was observed. No impact of the vaccination on antibody-mediated rejection or graft function was observed, and no significant safety concerns were reported. Moreover, no de novo HLA-donor-specific antibodies (DSA) were detected during the follow-up period. Only one patient with pre-vaccination HLA-DSA did not experience an increased intensity of the existing HLA-DSA. During the follow-up, only one infection (mild COVID-19) was observed in a patient after receiving the first vaccine dose. According to the multivariable logistic regression analysis, lack of seroconversion after two-dose vaccination independently associated with patient age ≥60 years (OR = 4.50; $P = .02$) and use of anti-metabolite as an immunosuppressant drug (OR = 5.26; $P = .004$). Among younger patients not taking anti-metabolites, the seroconversion rate was high (92.9%). Further larger studies are needed to assess the best COVID-19 vaccination strategy in transplanted patients.

47. *Grupper A, Rabinowich L, Schwartz D et al Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. American Journal of Transplantation 2021: 21(8): 2719-2726.*

COVID-19 is associated with increased morbidity and mortality in transplant recipients. There are no efficacy data available regarding these patients with any of the available SARS-CoV-2 vaccines. We analyzed the humoral response following full vaccination with the BNT162b2 (Pfizer-BioNTech) in 136 kidney transplant recipients, and compared it to 25 controls. In order to exclude prior exposure to the virus, only participants with negative serology to SARS-CoV-2 nucleocapsid protein were included. All controls developed a positive response to spike protein, while only 51 of 136 transplant recipients (37.5%) had positive serology ($p < .001$). Mean IgG anti-spike level was higher in the controls (31.05 [41.8] vs. 200.5 [65.1] AU/mL, study vs. control, respectively, $p < .001$). Variables associated with null humoral response were older age (odds ratio 1.66 [95% confidence interval 1.17-2.69]), high-dose corticosteroids in the last 12 months (1.3 [1.09-1.86]), maintenance with triple immunosuppression (1.43 [1.06-2.15]), and regimen that includes mycophenolate (1.47 [1.26-2.27]). There was a similar rate of side effects between controls and recipients, and no correlation was found between the presence of symptoms and seroconversion. Our findings suggest that most kidney transplant recipients remain at high risk for COVID-19 despite vaccination. Further studies regarding possible measures to increase recipient's response to vaccination are required.

48. *Yeshurun M, Pasvolsky O, Shargian L et al. Humoral serological response to the BNT162b2 vaccine after allogeneic haematopoietic cell transplantation. Clin Microbiol Infect. 2021 Oct 29;S1198-743X(21)00606-6.*

Objectives: To assess the humoral immune response to the BNT162b2 vaccine after allogeneic haematopoietic cell transplantation (HCT).
Methods: This is a prospective cohort study. The SARS-CoV-2 IgGII Quant (Abbott©) assay was performed 4-6 weeks after the second BNT162b2 vaccine for quantitative measurement of anti-spike antibodies.
Results: The cohort included 106 adult patients. Median time from HCT to vaccination was 42 (range 4-439) months. Overall, 15/106 (14%, 95% confidence interval (CI) 7-21%) were seronegative despite vaccination, 14/52 patients on immunosuppression (27%, 95%CI 19-35%) compared to only 1/54 patients off immunosuppression (1.8%, 95%CI 1-4%) (p 0.0002). The proportion of seronegative patients declined with time; it was 46% (6/13) during the first year, 12.5% (3/24) during the second year and 9% (6/69) beyond 2 years from transplant. Patients

with acute graft-versus-host disease (GVHD) (odds ratio (OR) 3.3, 95%CI 0.97-11.1, p 0.06) and moderate to severe chronic GVHD (OR 5.9, 95%CI 1.2-29, p 0.03) were more likely to remain seronegative. Vaccination was well tolerated by most patients. However, 7% (7/106) reported that GVHD-related symptoms worsened within days following vaccination.
Conclusion: A significant proportion of allogeneic HCT recipients receiving immunosuppression demonstrated an inadequate humoral response to the BNT162b2 vaccine. These patients should be recognized and instructed to take appropriate precautions. Recipients who were off immunosuppression had a humoral response that was comparable to that of the general population.

49. *Ram R, Hagin D, Freund T et al. Safety and efficacy of the BNT162B2 MRNA Covid-19 vaccine in patients after allogeneic HCT and CD19-based CAR-T therapy - A single center prospective cohort study. 26th Congress of the European Hematology Association, EHA 2021. Virtual. Publication: HemaSphere 2021: 5(SUPPL 2): 101.*

Background
The Pfizer/BioNTech BNT162b2 vaccine, employing mRNA technology, has been recently approved by both the FDA and EMA for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, demonstrating a 94.6% protection rate in a phase 3 study. While this vaccine is recommended by the FDA, EBMT and ASH-ASTCT for immunosuppressed patients, data regarding protection efficacy and safety in patients undergoing immunologic cell therapy are scarce.
Aims
We aimed to evaluate efficacy and toxicity of the BNT162b2 vaccine in patients that underwent hematopoietic cell transplantation and CAR-T therapy.
Methods
All patients under active treatment at the long-term follow-up HCT clinic (n=124) at the Tel Aviv Sourasky Medical Center, were evaluated for immunologic recovery (CD19+, CD4+, and CD8+ cell blood levels) pre-vaccination and were recommended to receive the commercial vaccination based on the EBMT recommendations. Patients were prospectively followed for vaccination-safety profile (laboratory tests, GVHD monitoring, and symptom-based questionnaire). We evaluated the humoral immune response to vaccine, 7-14 days after the second vaccine dose, by *in vitro* quantitative determination of anti-SARS-CoV-2S antibodies using Elecsys® assay and cellular immune response by ELISpot, estimating IL-2 and IFN-gamma secretion in response to a pool of lyophilized SARS-COV-2 S and M peptides (PepTivator; Miltenyi). The trial was approved by the local Ethics Committee and was registered by the clinical trials network (NCT04724642).
Results
From 23-Dec-2020 all sequential patients (allogeneic, n=101 and CAR-T, n=23) were assessed for eligibility based on the EBMT recommendations (Version 5.0, Feb 21, 2021). Of those, 100 patients were eligible and 79 patients (allogeneic, n=65 and CAR-T, n=14) were vaccinated per-protocol. Characteristics of patients are depicted in **Table 1**. Overall, the 2 vaccine doses were well tolerated. Adverse events were reported in 39% of allogeneic HCT recipients (4.6% grade ≥3) and 32% of CART recipients (7% grade ≥3). All events resolved within few days, with the exception of 1 secondary graft rejection which is still under investigation. Among the CAR-T group, 5 patients (36%) had humoral antibody response. Patients with CD19+ lymphocytes >0 had a higher likelihood to develop antibodies compared to those with B cell aplasia (67% vs. 12.5%, p=.036). Among the allogeneic HCT group - 47 patients (81%) had a humoral antibody response. Incidence of positive serology was lower in patients with concomitant high intensity immunosuppressive therapy (IST) compared to those with low intensity IST (69% vs. 94%, p=.016). Linear regressions identified that male sex (beta=-.380, p=.012) and high intensity IST

(beta=-.497, p=.014) were associated with lower antibody titer, while age, months from HCT, intensity of conditioning, low CD19 cell count, and active GVHD did not predict response. Analysis of peptide induced cytokine release by ELISpot is ongoing and will be presented at the EHA meeting.

Conclusion
Humoral response to the BNT162b2 mRNA COVID-19 vaccine in CAR-T patients with B cell aplasia is significantly impaired, while overall response in patients after allogeneic HCT is encouraging. Patients on concomitant high intensity IST had impaired humoral response to BNT162b2. Longer follow-up is mandatory to test persistence of antibodies, and general preventive practices should be continued until more data are available.

50. Ali H, Ngo D, Aribi A et al. Safety and Tolerability of SARS-CoV2 Emergency-Use Authorized Vaccines for Allogeneic Hematopoietic Stem Cell Transplant Recipients. Transplantation and Cellular Therapy 2021: 27(11): 938.e1-938.e6.

The safety and efficacy of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) emergency-use authorized (EUA) vaccines have been confirmed in the general population. However, there are no data on its safety and tolerability or efficacy in recipients of allogeneic hematopoietic stem cell transplant (HCT). We performed this study to identify the incidence of adverse events following SARS-CoV2 EUA vaccines, the incidence of new-onset graft-versus-host disease (GVHD) or worsening of existing GVHD after EUA vaccine administration, and the incidence SARS-CoV2 positivity in vaccinated HCT patients. We retrospectively reviewed 113 HCT patients who received at least one dose of EUA vaccine to describe the safety and tolerability, any impact on GVHD, and the incidence of SARS-CoV2 PCR positivity after vaccination. Patients received either Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines. Patients were included if they were 18 years or older and had received at least one dose of vaccine in the post-HCT setting. Most patients presented with myalgias/arthralgias (first dose, 7.7%; second dose, 14.6%), fatigue (first dose, 15.4%; second dose, 29.2%), and injection site pain (first dose, 40.4%; second dose, 43.8%). Other side-effects experienced by patients included nausea, vomiting, diarrhea, headache, and injection-site rash and swelling. Liver function abnormalities occurred in 18.6% of patients. Neutropenia, thrombocytopenia, and lymphopenia occurred in 13.3%, 11.5%, and 8.8% of patients, respectively. Forty percent of patients had active chronic GVHD at the time of vaccination, and worsening chronic GVHD occurred in 3.5% of the patients. New chronic GVHD developed in 9.7% of patients after vaccination. The SARS-CoV2 EUA vaccines were well tolerated in allogeneic HCT recipients.

51. Ram R, Hagin D, Kikozashvilli N et al. Safety and Immunogenicity of the BNT162b2 mRNA COVID-19 Vaccine in Patients after Allogeneic HCT or CD19-based CART therapy-A Single-Center Prospective Cohort Study Transplantation and Cellular Therapy 2021: 27(9): 788-794.

Data are scarce regarding both the safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients undergoing immune cell therapy; thus, we prospectively evaluated these two domains in patients receiving this vaccine after allogeneic hematopoietic cell transplantation (HCT; n = 66) or after CD19-based chimeric antigen receptor T cell (CART) therapy (n = 14). Overall, the vaccine was well tolerated, with mild non-hematologic vaccine-reported adverse events in a minority of the patients. Twelve percent of the patients after the first dose and 10% of the patients after the second dose developed cytopenia, and there were three cases of graft-versus-host disease exacerbation after each dose. A single case of impending graft rejection was summarized as possibly related. Evaluation of immunogenicity showed that 57% of patients after CART infusion and 75% patients after allogeneic HCT had evidence of humoral

and/or cellular response to the vaccine. The Cox regression model indicated that longer time from infusion of cells, female sex, and higher $CD19^+$ cells were associated with a positive humoral response, whereas a higher $CD4^+/CD8^+$ ratio was correlated with a positive cellular response, as confirmed by the ELISpot test. We conclude that the BNT162b2 mRNA COVID-19 vaccine has impressive immunogenicity in patients after allogeneic HCT or CART. Adverse events were mostly mild and transient, but some significant hematologic events were observed; hence, patients should be closely monitored.

52. *Davidov-Derevyanko Y, Tsaraf K, Ezra OC et al. Safety and efficacy of BNT162b2 mRNA vaccine among liver transplant recipients Hepatology 2021: 74(SUPPL 1): 336A-337A.*

Background:
BNT162b2 mRNA vaccine has been shown to be safe and effective in healthy subjects. The safety and efficacy of this vaccine in liver transplant (LT) recipients is still a subject of evaluation. The objective of this study was to assess the safety and efficacy of BNT162b2 mRNA vaccine among LT recipients.
Methods:
Immune response of two dose of BNT162b2 mRNA vaccine in 76 LT recipients was compared to 174 age-matched immunocompetent subjects with no exposure to SARS-CoV-2 infection. Postvaccination IgG antibodies against the RBD of SARS-CoV-2 IgG S-protein serology and neutralizing antibodies (NA) to the BNT162b2 mRNA vaccine were determined at least 14 days after the second dose of vaccine. AB titer ≥1.1 was considered protective. Side effects were monitored during study period.
Results:
Following the administration of the BNT162b2 mRNA two dose vaccines, LT recipients (median age 64 (range 22-83 years), 56.6% males) showed reduced immune response as compared with immunocompetent controls (72% vs. 94.2%, $p<0.0001$). The geometric mean of titer IgG antibody of SARS-CoV-2 and NA was significantly lower in LT recipients who received combine immunosuppression (combination of CNI and prednisone, and/or MMF and/or everolimus) vs CNI monotherapy 1.1±3.1 vs. 3.5±2.1, $p<0.0001$, 59.0±3.2 vs. 256.0±4.7, $p=0.002$. In multivariate analysis, the antibody response was reduced in LT recipients who received combined immunosuppression and in those with impaired renal function. Overall most self-reported side effects that were detected in 39 (51%) LT recipients were mild. The immune response did not correlate with more severe side effects. The side effects occurred more often in women than in men.
Conclusion:
Compared with immunocompetent subjects, liver transplant recipients had reduced immune response. Factors affecting serological antibodies response include renal function and type of immunosuppression used. Side effects were mild in most cases and more often in women. The durability of immune response to BNT162b2 mRNA vaccine among LT recipients needs further investigation.

53. *Rabinowich L, Grupper A, Baruch R et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. Journal of Hepatology 2021: 75(2): 435-438.*

Background & aims: Two SARS-CoV-2 mRNA vaccines were approved to prevent COVID-19 infection, with reported vaccine efficacy of 95%. Liver transplant (LT) recipients are at risk of lower vaccine immunogenicity and were not included in the registration trials. We assessed vaccine immunogenicity and safety in this special population.
Methods: LT recipients followed at the Tel-Aviv Sourasky Medical Center and healthy volunteers were tested for SARS-CoV-2 IgG antibodies directed against the Spike-protein (S)

and Nucleocapsid-protein (N) 10-20 days after receiving the second Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine dose. Information regarding vaccine side effects and clinical data was collected from patients and medical records.
Results: Eighty LT recipients were enrolled. Mean age was 60 years and 30% were female. Twenty-five healthy volunteer controls were younger (mean age 52.7 years, p = 0.013) and mostly female (68%, p = 0.002). All participants were negative for IgG N-protein serology, indicating immunity did not result from prior COVID-19 infection. All controls were positive for IgG S-protein serology. Immunogenicity among LT recipients was significantly lower with positive serology in only 47.5% (p <0.001). Antibody titer was also significantly lower in this group (mean 95.41 AU/ml vs. 200.5 AU/ml in controls, p <0.001). Predictors for negative response among LT recipients were older age, lower estimated glomerular filtration rate, and treatment with high dose steroids and mycophenolate mofetil. No serious adverse events were reported in either group.
Conclusion: LT recipients developed substantially lower immunological response to the Pfizer-BioNTech SARS-CoV-2 mRNA-based vaccine. Factors influencing serological antibody responses include age, renal function and immunosuppressive medications. The findings require re-evaluation of vaccine regimens in this population.

54. Ou MT, Boyarsky, Moter JD et al. Safety and Reactogenicity of 2 Doses of SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients. Transplantation 2021: 105(10): 2170-2174.

Background: We studied the safety and reactogenicity SARS-CoV-2 mRNA vaccines in transplant recipients because immunosuppressed patients were excluded from vaccine trials.
Methods: US transplant recipients were recruited into this prospective cohort study through social media; those who completed the full vaccine series between December 9, 2020 and March 1, 2021 were included. We collected demographics, medical history, and safety information within 7 d after doses 1 and 2 (D1, D2). Associations between characteristics and reactions were evaluated using modified Poisson regression.
Results: We studied 741 transplant recipients who underwent BNT162b2 (54%) or mRNA-1273 (46%) vaccination. Median (interquartile range) age was 60 (44-69) y, 57% were female, and 10% were non-White. Although local site reactions decreased after D2 (85% D1 versus 78% D2, P < 0.001), systemic reactions increased (49% D1 versus 69% D2, P < 0.001). Younger participants were more likely to develop systemic symptoms after D1 (adjusted incidence rate ratio [aIRR] per 10 y = 0.850.900.94, P < 0.001) and D2 (aIRR per 10 y = 0.910.930.96, P < 0.001). Participants who experienced pain (aIRR = 1.111.662.47, P = 0.01) or redness (aIRR = 1.833.928.41, P < 0.01) were more likely to develop an antibody response to D1 of mRNA vaccines. No anaphylaxis, neurologic diagnoses, or SARS-CoV-2 diagnoses were reported. Infections were minimal (3% after D1, <0.01% after D2). One patient reported incident acute rejection post-D2.
Conclusions: In solid organ transplant recipients undergoing mRNA vaccination, reactogenicity was similar to that reported in the original trials. Severe reactions were rare. These early safety data may help address vaccine hesitancy in transplant recipients.

55. Peled I, Ram E, Lavee J et al. BNT162b2 vaccination in heart transplant recipients: Clinical experience and antibody response. Journal of Heart & Lung Transplantation 2021: 40(8): 759-762.

Background
Data on the safety and efficacy of SARS-CoV-2 vaccines in immunocompromised populations are sparse.
Methods

We conducted a prospective study of 77 heart transplant (HT) recipients vaccinated with two doses of BNT162b2 vaccine and monitored for adverse events following both doses, the receptor-binding domain (RBD) IgG response, and neutralizing antibodies.
Results
BNT162b2 vaccination was associated with a low rate of adverse events, characterized mostly by pain at the injection site. By a mean 41 days post second dose there were no clinical episodes of rejection, as suggested by a troponin leak or allograft dysfunction. At a mean 21 days following the second dose, IgG anti-RBD antibodies were detectable in 14 (18%) HT recipients. Immune sera neutralized SARS-CoV-2 pseudo-virus in 8 (57%) of those with IgG anti-RBD antibodies. Immunosuppressive regimen containing mycophenolic acid was associated with lower odds of an antibody response (OR = 0.12, $p = 0.042$).
Conclusions
Whether a longer time-frame for observation of an antibody response is required after vaccination in immunosuppressed individuals remains unknown.

56. *Ferrari L, Caldara F, Teti E et al. Systematic evaluation of the tolerability of two doses of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in a diverse cohort of people with HIV (PWH). HIV Medicine 2021: 22(SUPPL 3): 221-222.*

Purpose: CIn the pivotal BNT162b2 trials, common side effects in the 7 days after vaccination were injection site pain, tiredness, headache, muscle/joint pain, chills and fever (dose-2 > dose-1). Reported data comprised only ~60 vaccine recipients with HIV. We systematically evaluated solicited and unsolicited side effects after two vaccine doses (3 weeks apart) in PWH diverse for risk group, HIV history and comorbidities. omorbidities are the most important risk factor for poor outcome of COVID-19 among HIV-positive patients – data from Euroguidelines in Central and Eastern Europe Network Group.
Method: Consecutive PWH attending for vaccination prospectively completed a structured questionnaire reporting side effects experienced in the 7 days after each vaccine dose. Findings were related to data from the total BNT162b2 trial population (ref: FDA submission, Nov 2020)
Results: In this interim analysis, the population totalled 145 PWH. Baseline characteristics: 74% males, median age 49 years (IQR 41–58), 80% Italy-born, 41% MSM, 16% IDU, 54% smokers, 26% prior AIDS-diagnoses, 99% on ART, 92% viral load <50 copies/ml, median nadir CD4 count 270 cells/mm3 (66–444), current CD4 count 722 cells/mm3 (493–956), CD4:CD8 ratio 0.8 (0.6–1.2). Prevalent comorbidities: hypertension (26%), cardiovascular disease (10%), diabetes (6%), chronic renal disease (4%). Prior COVID-19 diagnosis: 7%. After dose-1 vs. dose-2, solicited local and systemic reactions overall occurred in 76% vs. 63% ($P = 0.03$) and 55% vs. 64% ($P = 0.06$), respectively. Figures 1–2 show side effects by dose, severity and duration. Unsolicited symptoms (>1% of participants) comprised light-headedness, nausea, loss of appetite, and oral disturbances, typically mild-moderate and short-lived. One patient developed a superficial thrombophlebitis (upper leg) on day 8 after dose-1 immediately following a 3hr car journey. There were no serious adverse events.
Conclusions: The BNT162b2 vaccine was well tolerated. Injection site swelling, fatigue, muscle/joint aches and fever increased in incidence after dose-2. Side effects were similar to those reported in general trial populations, albeit with significantly less injection site pain and headache. The study, including pre- and post-vaccination antibody testing, is ongoing.

57. *De Vito A, Coradduzza D, Colpani A et al. Development of SARS-CoV- 2 IgG after first dose of mRNA vaccine in people living with HIV HIV Medicine 2021: 22(SUPPL 3): 210-211.*

Purpose: We aimed to evaluate the development of SARS-CoV-2 antibodies in people with HIV (PWH) after the first dose of the vaccine.

Method: We enrolled PWH, who received mRNA vaccine (Comirnaty®). We evaluated the presence of SARS-CoV-2 antibodies before the first dose and second dose.
The presence of antibodies was evaluated with LIAISON® SARS-CoV-2 TrimericS IgG by DiaSorin. In addition, we correlated the level of antibodies with clinical and viro-immunological data. A positive response was considered for IgG title >33.8 BAU/mL.
We performed a Spearman's rank correlation coefficient to evaluate the correlation between SARS-CoV-2 IgG and clinical-viro-immunological variables.
Results: We enrolled 192 patients with a median age of 53.4(IQR 45.6–58.0) years. Clinical and viro-immunological characteristics are summarized in Table 1.
At baseline, 20 (10.4%) subjects resulted have been previously infected by SARS-CoV-2. At the second blood sample, 173(90.1%) patients have developed antibodies (BAU >38.3 UI/mL). People with a history of IDU, CD4 nadir<200 copies/mL, and detectable HIV-RNA had a significantly lower title of antibodies ($P = 0.004$; $P = 0.005$; $P = 0.029$, respectively). CD4 nadir was associated with the level of antibodies, in particular people with <200 cells/mm^3 had a lower level of antibodies. Also, IDU, smoker, and a detectable HIV-RNA were associated with lower IgG development
Among people with previous infection, 16(80%) had antibodies levels above the assay measuring range (2080 BAU/mL). No patients without previous SARS-COV-2 infection achieved antibodies level over 2080 BAU/mL. One-hundred-thirty-one (68.2%) PWH complained adverse events, in particular 112(58.3%) developed shoulder's pain, 36(18.7%) malaise, 21(10.9%) fever, 24(12.5%) headache, 5(2.6%) nausea, 8(4.2%) diarrhea. People with previous SARS-CoV-2 infection had a higher prevalence of adverse events, particularly fever (45% vs. 5.8%, $P < 0.001$).
Conclusions: After 21 days from first SARS-CoV-2 vaccine administration, >90% of patients developed antibodies. However, PWH with a CD4 nadir <200 copies/mL had achieved a lower response and should be closely monitored.

58. Bergman P, Blennow O, Hansson L et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine. 2021 Dec;74:10370.

Background: Patients with immunocompromised disorders have mainly been excluded from clinical trials of vaccination against COVID-19. Thus, the aim of this prospective clinical trial was to investigate safety and efficacy of BNT162b2 mRNA vaccination in five selected groups of immunocompromised patients and healthy controls.
Methods: 539 study subjects (449 patients and 90 controls) were included. The patients had either primary (n=90), or secondary immunodeficiency disorders due to human immunodeficiency virus infection (n=90), allogeneic hematopoietic stem cell transplantation/CAR T cell therapy (n=90), solid organ transplantation (SOT) (n=89), or chronic lymphocytic leukemia (CLL) (n=90). The primary endpoint was seroconversion rate two weeks after the second dose. The secondary endpoints were safety and documented SARS-CoV-2 infection.
Findings: Adverse events were generally mild, but one case of fatal suspected unexpected serious adverse reaction occurred. 72.2% of the immunocompromised patients seroconverted compared to 100% of the controls (p=0.004). Lowest seroconversion rates were found in the SOT (43.4%) and CLL (63.3%) patient groups with observed negative impact of treatment with mycophenolate mofetil and ibrutinib, respectively.
Interpretation: The results showed that the mRNA BNT162b2 vaccine was safe in immunocompromised patients. Rate of seroconversion was substantially lower than in healthy controls, with a wide range of rates and antibody titres among predefined patient groups and

subgroups. This clinical trial highlights the need for additional vaccine doses in certain immunocompromised patient groups to improve immunity.

APPENDIX 6A REGULATORY AUTHORITIES REQUEST(S)

PSUR ASSESSMENT REPORT (AR)
PROCEDURE NO. EMEA/H/C/PSUSA/00010898/202106

As part of this Procedure, the PRAC requested the MAH to address the following 10 issues in the next PSUR:

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

Response

As of 21 December 2021, 307,601 cases were downloaded from EudraVigilance and 297,489 cases (96.7,5% of the total downloaded cases, 84,238 serious and 213,251 non serious) were included in the data tabulations presented in the PSUR.

The remaining 10,112 cases downloaded from EudraVigilance in the reporting period are not included in the data tabulations of this PSUR as they have not yet completed case processing; these include reports downloaded immediately prior to the data lock point. These reports will be included in the subsequent PSURs as Pfizer applies a late condition process that retrieves from the global safety database cases not included in the previous PSURs.

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

The table below provides updates on the corrective actions that have been or are being initiated with progress update as of 19 December 2021 to manage the volume of adverse event cases received:

Description of Action	**Case Type(s) within scope of action**	**Action status (proposed / completed / congoing)**	**Completion Date/Due Date**	**Responsible party (internal Pfizer group and/or third-party)**
Implementation of a machine-based translation tool to manage cases with non-English source data for use by Global AE data entry vendors	Spontaneous Post-Marketing (PM) AEs from global markets reported in non-English language. This includes cases from Health Authorities, Patients and HCPs, etc.	Completed	29 Mar 2021	Pfizer
Argus case batch routing. Allows users to route cases in batches to different workflow stages rather than individually to reduce manual efforts.	All Spontaneous PM AEs for all products.	Completed	16-Apr-2021	Pfizer

Description of Action	Case Type(s) within scope of action	Action status (proposed / completed / congoing)	Completion Date/Due Date	Responsible party (internal Pfizer group and/or third-party)
VESPA (Vaccine Engine Specialized Process Automation): Transmits a copy of vaccine-related safety cases from the Argus Safety system to a third-party vendor (Indegene) which allows for automation of case processing, followed by a final check by case reviewers and medical reviewers before returning back to the Pfizer safety database for distribution.	Initial single suspect COVID-19 vaccine AEs from the following sources: MHRA (serious and non-serious post marketing spontaneous) EVWEB, nonserious spontaneous US COVAES (Online reporting portal) non-serious spontaneous Japan COVAES Non-serious spontaneous. To date over 230,000 cases have been processed via VESPA.	Completed	Initial deployment of NS cases completed 16 April 2021 (approximately 1000 cases/day). Serious cases from MHRA deployed 16 Sep 2021.	Third party Indegene and Pfizer
VESPA language translation workflow - enables processing of non-English cases through VESPA. Text provided in non-English language is automatically translated, via a machine translation tool, and then verified by local language speaking Pfizer colleagues within the Drug Safety Units. The translated source is then sent to Indegene for processing.	Non-English language Spontaneous PM-COVID-19 Vaccine cases from the online reporting portal in Japan	Completed	4 Oct 2021	Pfizer
Auto-acceptance of Follow-up cases received from MHRA. The process updates follow-up E2B reports received from the MHRA in a queue and automatically updates the Argus case information based on the information in the incoming E2B report.	Follow up cases in workflow from MHRA.	Completed	20 May 2021	Pfizer
Auto-acceptance of COVID-19 vaccine cases received from BioNTech via E2B.	Initial E2B COVID-19 vaccine cases from China, Hong Kong, Macau and Taiwan.	Completed	20 May 2021	Pfizer

Description of Action	Case Type(s) within scope of action	Action status (proposed / completed / congoing)	Completion Date/Due Date	Responsible party (internal Pfizer group and/or third-party)
Implement activation of Argus Auto-Submission for select reporting rules, eliminating manual submission activities.	Post marketing foreign cases (excluding from interventional clinical trials) with a submission destination to MHRA. Since implementation of auto submission 267, 515 cases have been submitted to MHRA. Since implementation of auto submission 86, 076 cases have been submitted to Health Canada (HC).	Completed Completed	28 May 2021 22 Oct 2021	Pfizer
Deploy improvements to the initial BOT solution allowing for a fully automated and efficient process to manage downloading of EVWeb ICSRs from EudraVigilance.	Serious and Non-serious initial and follow up cases for all products from EVWEB. Since deployment of the BOT enhancements (08-Jul-2021) 431,076 XML files have been downloaded from EVWEB (up to and including 10-Dec-2021).	Completed	08 Jul 2021	Pfizer
COVID-19 Hub Streamlined Workflow: Technical creation of a dedicated workflow for COVID-19 vaccine cases in ARGUS.	Global spontaneous PM serious and non-serious AEs for the COVID-19 vaccine As of 12 Dec 2021, > 154, 000 cases managed in streamlined workflow.	Completed	26 Jul 2021	Pfizer
BOT solution for assignment and auto-completion of data entry of select fields and routing in Argus for further processing.	Serious initial COVID-19 ICSRs from EVWEB for 5 high volume countries (Germany, France, Italy, Spain and the Netherlands). Since implementation until 12 Dec 2021, 14,640 serious ICSRs have been data entered.	Completed	17 Sep 2021	Pfizer
Deployment of auto-listedness functionality to BNT162B2 in Argus. Allows auto-population of listedness assessments in the Core, SmPC and	All spontaneous PM cases for the COVID-19 vaccine from all sources.	Completed	1 Nov 2021	Pfizer

Description of Action	Case Type(s) within scope of action	Action status (proposed / completed / congoing)	Completion Date/Due Date	Responsible party (internal Pfizer group and/or third-party)
United States Prescribing Information fields in the global safety database.				
Route to Distribution (RTD) Phase I: Streamlined processing of non-serious cases that originated from Health Authorities. This solution required technical changes to ARGUS to allow for reduced workflow steps	Initial EVWEB Non-serious PM cases for COVID-19 vaccine.	Completed: As of 12 Dec, more than 93,500 cases were processed via this solution.	Technical solutions deployed 15 Nov 2021	Pfizer
Enhancement of auto-narrative feature. This tool is used to generate a draft narrative requiring only minimal editing during case processing.	All products and all sources – spontaneous and solicited, initial and follow-up cases.	Completed	29 Nov 2021	Pfizer
RTD Phase 2 BOT enabled date entry that assigns a case to a single user and subsequent routing to distribution	Initial and follow up HA Non-serious PM cases for COVID-19 vaccine.	Ongoing	14 Mar 2022	
Pfizer continuously assess resource needs. Following implementation of technology and process efficiency and through continuous monitoring of the AE reporting rate for COVID-19 vaccine, continue to assess the need for and onboard additional resources to help manage the increased volume of AE reports received associated with the COVID-19 vaccine	N/A	Ongoing: As of 31 Dec, > 2400 contractor and vendor resources will have been onboarded.	N/A	Pfizer

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

Serious cases

- Fatal / Life Threatening.

- All other serious.

Non-serious cases

- Non-serious AESI cases for external targets (Health Authority/License Partner).
- Non-serious cases (non AESI) for external targets (Health Authority/License Partner).
- Non-serious highest days open AESI followed by non-serious with no AESI

Within the same prioritization, cases including AESI terms should be completed first.

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

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

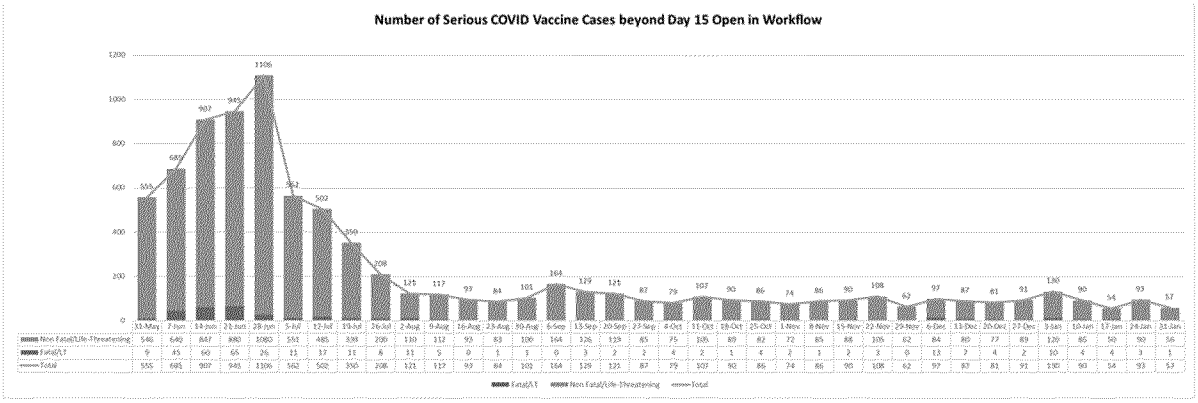
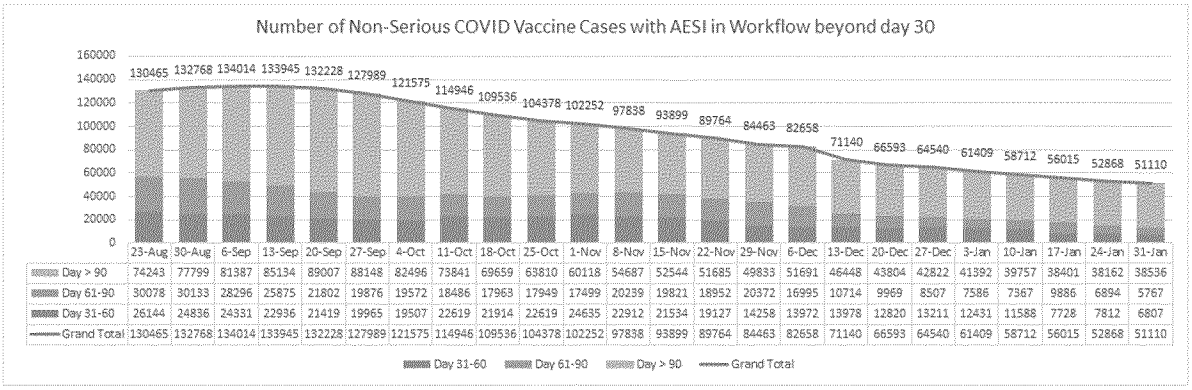


Figure 2. Non-Serious COVID Vaccine Cases with AESI in Workflow beyond Day 30



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

Response

The MAH has now provided in Appendix 6B the O/E analyses for all processed cases, along with sensitivity analyses that include the processed plus the backlog cases, as presented in the MSSRs (now SBSRs). Analyses were conducted using 21- and 42-days risk windows for all AESIs, with an additional 14-day risk window provided for myocarditis and myocarditis/pericarditis.

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

Response

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

A DCA Performance Monthly Report is generated to include a summary and a detailed report by product of the DCA review findings and any actions taken if a specific issue or concern was identified to ensure DCA follow-up. The response rate and the clinical significance of the information received through the special follow up is not routinely tracked in this process, and thus it cannot be described in this response.

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

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

– initial report was from a regulatory authority source (43,590; 58.7%),

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

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

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

As part of the routine PV and safety surveillance and risk management activities, the MAH is continuously monitoring the use and value of the risk management measures, including but not limited to the special follow up activities. The MAH plans to conduct further evaluation of DCA effectiveness in the coming future with the objective of analyzing the response rate and clinical and safety value of the responses received in the follow up activities and will report results and/or recommended actions in future aggregate reports or Risk Management Plan as appropriate.

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

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

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

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

a. if the safety profile of Comirnaty when administered with different time intervals between dose 1, 2 and 3 than the recommended posology is consistent with the known safety profile.

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

Response

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

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

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

Post-Authorization Data

- Number of cases: 4595 (0.7% of 657,528 cases, the total PM dataset).
- MC cases (1543), NMC cases (3052).
- Country of incidence (≥ 2%): US (2044), UK (936), Netherlands (444), France (221), Italy (205), Spain (144) and Germany (108).
- Subjects' gender: female (3386), male (1118) and unknown (91).
- Subjects' age in years (n = 4384), range: 12-100, mean: 55.5, median: 55.0.
- Medical history (n = 2813): the most frequently (≥50 occurrences) reported medical conditions included Hypertension (459), Disease risk factor (317), Drug hypersensitivity (296), Asthma (263), Hypothyroidism (158), Hypersensitivity (149), Food allergy (129), Diabetes mellitus (125), Depression (115), Atrial fibrillation (91), Immunodeficiency (81), Gastrooesophageal reflux disease (79), Type 2 diabetes mellitus (76), Anxiety (75), Migraine (72), Obesity (69), Arthritis, Rheumatoid arthritis (68 each), Seasonal allergy (63), Chronic obstructive pulmonary disease (58), Blood cholesterol increased (57) and Pain (50).
- COVID-19 Medical history: the most frequently (≥4 occurrences) reported COVID-19 (171), Suspected COVID-19 (120), Asymptomatic COVID-19, COVID-19 pneumonia, Post-acute COVID-19 syndrome and SARS-CoV-2 test positive (4 each).
- Co-suspects (n = 272): the most frequently (≥2 occurrences) reported co-suspect vaccines/medications included influenza vaccine (137), influenza vaccine inact sag 4V (23), hepatitis A vaccine (18), influenza vaccine inact split 4V (16), influenza vaccine

inact sag 3V (12), adalimumab, influenza vaccine inact split 3V (8 each), diphtheria vaccine toxoid/ HIB vaccine/ pertussis vaccine/ polio vaccine inact/ tetanus vaccine toxoid, paracetamol (4 each), carbidopa/levodopa, imatinib mesilate, levothyroxine sodium, ocrelizumab, pneumococcal vaccine polysacch 23V and prednisone (2 each).

- Number of events: 24,610.
- Event seriousness[1]: serious (6846), non-serious (17,771).
- Most frequently reported PTs (≥2%): Immunisation[2] (3473), Headache (1081), Off label use (1069), Fatigue (991), Pyrexia (970), Chills (773), Myalgia (619), Pain (595), Pain in extremity (581), Lymphadenopathy (579), Vaccination site pain (568), Nausea (526), Arthralgia (512) and Malaise (497).
- Event outcome[3]: fatal (360), resolved/resolving (9403), resolved with sequelae (322), not resolved (5484), unknown (9158).
- Event seriousness and clinical outcome and the most frequently (≥ 2%) reported AEs were compared between the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the remaining PM dataset in Table 2 and Table 3, respectively.

Table 2. Comparison of the Event Seriousness and Clinical Outcome in Cases Involving 3 Doses of BNT162b2 Administered with Time Intervals Different from Recommended Posology and in the Remaining PM Dataset

	3 Doses Administered with Time Intervals Different from Recommended Posology No. of AEs (%)	Remaining PM Dataset* No. of AEs (%)
Event seriousness		
Serious	6846 (27.8)	524,791 (24.4)
Non-serious	17,771 (72.2)	1,624,556 (75.6)
Clinical Outcome		
Fatal	360 (1.5)	12,307 (0.6)
Resolved/resolving	9403 (38.2)	1,021,922 (47.1)
Resolved with sequelae	322 (1.3)	23,389 (1.1)
Not resolved	5484 (22.3)	541,657 (25.0)
Unknown	9158 (37.2)	569,800 (26.3)
Total number of events	**24,610****	**2,149,347****

* The cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology have been excluded from the overall dataset; these cases are referred as "Remaining PM Dataset".
**Multiple episodes of the same PT event may be reported with different seriousness and/or different clinical outcome.

[1] Multiple episodes of the same event may be reported with a different seriousness within a case making the sum of the events seriousness exceeding the total number of events.

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

[3] Multiple episodes of the same event may be reported with a different clinical outcome within a case making the sum of the events seriousness exceeding the total number of events.

Table 3. Comparison of the Most Frequently (≥ 2%) Reported AEs in Cases Involving 3 Doses of BNT162b2 Administered with Time Intervals Different from Recommended Posology and in the Remaining PM Dataset

MedDRA SOC MedDRA PT	**3 Doses Administered with Time Intervals Different from Recommended Posology** **No. of AEs (AERP%)** **No. of Cases=4595**	**Remaining PM Dataset*** **No. of AEs (AERP%)** **No. of Cases =652,933**
Surgical and medical procedures		
Immunisation[4]	3473 (75.6)	18,239 (2.8)
Nervous system disorders		
Headache	1080 (23.5)	133,959 (20.5)
Dizziness	306 (6.7)	37,676 (5.8)
Injury, poisoning and procedural complications		
Off label use	1069 (23.3)	20,980 (3.2)
Product use issue	120 (2.6)	3894 (0.6)
General disorders and administration site conditions		
Fatigue	990 (21.6)	108,489 (16.6)
Pyrexia	970 (21.1)	105,157 (16.1)
Chills	773 (16.8)	52,750 (8.1)
Pain	595 (13.0)	37,348 (5.7)
Vaccination site pain	567 (12.3)	21,896 (3.4)
Malaise	497 (10.8)	81,101 (12.4)
Vaccination site swelling	219 (4.8)	21,896 (3.4)
Asthenia	214 (4.7)	20,984 (3.2)
Vaccination site erythema	191 (4.2)	12,910 (2.0)
Swelling	189 (4.1)	9115 (1.4)
Axillary pain	170 (3.7)	5930 (0.9)
Chest pain	155 (3.4)	17,373 (2.7)
Feeling abnormal	140 (3.1)	7879 (1.2)
Peripheral swelling	129 (2.8)	6784 (1.0)
Vaccination site warmth	122 (2.7)	7941 (1.2)
Influenza like illness	92 (2.0)	12,564 (1.9)
Vaccination site inflammation	92 (2.0)	8237 (1.3)
Musculoskeletal and connective tissue disorders		
Myalgia	618 (13.5)	84,273 (12.9)
Pain in extremity	581 (12.6)	38,429 (5.9)
Arthralgia	512 (11.1)	56,099 (8.6)
Back pain	103 (2.2)	8361 (1.3)
Blood and lymphatic system disorders		
Lymphadenopathy	578 (12.6)	28,853 (4.4)
Lymph node pain	117 (2.6)	3618 (0.6)
Gastrointestinal disorders		
Nausea	526 (11.5)	55,215 (8.5)
Diarrhoea	206 (4.5)	20,675 (3.2)
Vomiting	202 (4.4)	15,721 (2.4)

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

Table 3. Comparison of the Most Frequently (≥ 2%) Reported AEs in Cases Involving 3 Doses of BNT162b2 Administered with Time Intervals Different from Recommended Posology and in the Remaining PM Dataset

MedDRA SOC MedDRA PT	**3 Doses Administered with Time Intervals Different from Recommended Posology No. of AEs (AERP%) No. of Cases=4595**	**Remaining PM Dataset* No. of AEs (AERP%) No. of Cases =652,933**
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	192 (4.2)	23,565 (3.6)
Cough	94 (2.1)	10,703 (1.6)
Skin and subcutaneous tissue disorders		
Pruritus	171 (3.7)	16,482 (2.5)
Rash	159 (3.5)	17,432 (2.7)
Erythema	130 (2.8)	9837(1.5)
Urticaria	105 (2.3)	10,016 (1.5)
Hyperhidrosis	97 (2.1)	7139 (1.1)
Cardiac disorders		
Palpitations	105 (2.3)	12,717 (1.9)
Metabolism and nutrition disorders		
Decreased appetite	99 (2.2)	5534 (0.8)
Total number of events	**24,610**	**2,148,816**

N: Number of cases; n=Number of events.
* The cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology have been excluded from the overall dataset; these cases are referred as "Remaining PM Dataset".

As shown in Table 2, no significances differences were observed in the proportions of event seriousness and clinical outcome between the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the overall PM dataset. There was a slightly higher proportion of fatal outcomes in the group with different time intervals compared to the remaining group. The comparatively low number of subjects in the group and selection bias for subjects most likely to receive a third dose are likely contributing factors.

The 101 cases reporting fatalities (360 fatal AEs) involved 97 elderly and 4 adult subjects. The most frequently (≥ 2%) reported AEs leading to death the subjects, who received 3 doses of BNT162b2 administered with time intervals different from recommended posology [Immunisation (65), Death (21), Sudden death (15), Off label use (11), Cardiac failure (10), Pyrexia (9) and Cardiac arrest (8)], are consistent with the most commonly reported fatal events in the remaining PM dataset, except for the PT Immunisation that is selected per case processing conventions to collect cases reporting third/booster doses[5] and the PT Off label use that is reported in this dataset due to the administration of dosages in unapproved time intervals.

[5] Please refer to Section 6.3.1.1.2.3 *Third Dose/Booster Dose.*

As shown in Table 3, in general, the most frequently reported events observed in these cases were consistent with those observed in the remaining population, apart from the PTs Immunisation and Off label use that are selected per case processing conventions to collect cases reporting third/booster doses and the PTs Chills, Pain, Vaccination site swelling, Pain in extremity and Lymphadenopathy that are consistent with the known reactogenicity of the vaccine and listed in Section 4.8 *Undesirable effects* of the CDS. In general, the proportion of events reported by the group with different intervals than recommended, is higher than the proportions in the remaining PM dataset. This may be due to the comparatively lower number of subjects in the different intervals group.

Among the 4595 cases, 1114 (468 serious and 646 non-serious) included PTs indicative of use of BNT162b2 in unapproved conditions: Off label use (1069), Product use issue (120) and Product administered to patient of inappropriate age (3). As shown in Table 4, there were no significant differences between the AEs co-reported along with the terms indicative of the off-label use in the cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology and the remaining cases reporting off-label use, apart from the PT Immunisation, which is selected per case processing conventions to collect cases reporting third/booster doses.

Table 4. Comparison of the Most Frequently (≥ 2%) AEs Co-reported with Off-Label PTs

MedDRA SOC MedDRA PT	**3 Doses Administered with Time Intervals Different from Recommended Posology No. of AEs (AERP%) No. of Cases=1114**	**Remaining PM Dataset No. of AEs (AERP%) No. of Cases =21,419***
Surgical and medical procedures		
Immunisation	1008 (90.5)	12823 (59.9)
Nervous system disorders		
Headache	192 (17.2)	4176 (19.5)
Dizziness	70 (6.3)	1168 (5.5)
Paraesthesia	28 (2.5)	512 (2.4)
Injury, poisoning and procedural complications		
Extra dose administered	64 (5.8)	365 (1.7)
Product use issue		
General disorders and administration site conditions		
Pyrexia	184 (16.5)	2765 (12.9)
Fatigue	179 (16.1)	3586 (16.7)
Pain	120 (10.8)	1646 (7.7)
Vaccination site pain	96 (8.6)	1695 (7.9)
Chills	93 (8.4)	2108 (9.8)
Malaise	89 (8.0)	1642(7.7)
Asthenia	60 (5.4)	668 (3.1)
Swelling	46 (4.1)	665 (3.1)
Peripheral swelling	44 (4.0)	689 (3.2)
Chest pain	43 (3.9)	681 (3.2)
Axillary pain	37 (3.3)	809 (3.8)
Vaccination site erythema	36 (3.2)	476 (2.2)
Feeling abnormal	35 (3.1)	350 (1.6)
Vaccination site swelling	34 (3.1)	518 (2.4)

Table 4. Comparison of the Most Frequently (≥ 2%) AEs Co-reported with Off-Label PTs

MedDRA SOC MedDRA PT	**3 Doses Administered with Time Intervals Different from Recommended Posology No. of AEs (AERP%) No. of Cases=1114**	**Remaining PM Dataset No. of AEs (AERP%) No. of Cases =21,419***
Chest discomfort	25 (2.2)	255 (1.2)
Illness	23 (2.1)	324 (1.5)
Influenza like illness	23 (2.1)	499 (2.3)
Musculoskeletal and connective tissue disorders		
Pain in extremity	129 (11.6)	2194 (10.2)
Myalgia	111 (10.0)	1856 (8.7)
Arthralgia	102 (9.2)	1697 (7.9)
Back pain	29 (2.6)	380 (1.8)
Blood and lymphatic system disorders		
Lymphadenopathy	130 (11.7)	2145 (10.0)
Lymph node pain	34 (3.1)	424 (2.0)
Gastrointestinal disorders		
Nausea	89 (8.0)	1942 (9.1)
Diarrhoea	54 (4.9)	840 (3.9)
Vomiting	46 (4.1)	694 (3.2)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	59 (5.3)	747 (3.5)
Cough	23 (2.1)	375 (1.8)
Skin and subcutaneous tissue disorders		
Rash	47 (4.2)	724 (3.4)
Pruritus	44 (4.0)	781 (3.6)
Erythema	32 (2.9)	471 (2.2)
Urticaria	23 (2.1)	277 (1.3)
Cardiac disorders		
Palpitations	37 (3.3)	578 (2.7)
Total number of events	**6609**	**123,415**

N= Number of cases; n=Number of events.
* The cases involving 3 doses of BNT162b2 administered with time intervals different from recommended posology have been excluded from the overall dataset; these cases are referred as "Remaining PM Dataset".

Conclusion

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

b. Safety profile of Comirnaty when used in heterologous vaccination schedules with other vaccines.

Please refer to subsections "Heterologous doses schedule (primary series with a specified non-BNT162b2 COVID-19 vaccine and booster with BNT162b2)" and "Third/Booster doses of BNT162b2 administered after an unspecified primary COVID-19 vaccination series" in Section 6.3.1.1.2.3. *Third Dose / Booster Dose.*

5. ***The MAH should present a cumulative review of exacerbation (flare-up) of pre-existing ai/inflammatory disorders in the next PSUR including data from, at least, the scientific literature and the post-marketing cases. A tabulated case summary to be presented, with the following columns to be included: case id, Eudravigilance case id, pts, patient age, patient gender, first dose to onset, medical history, concomitant medications, case comment, information dose, WHO causality assessment and the reasoning for the causality category.***

Response

Please refer to Appendix 6A.1.

6. Regarding O/E analyses for AESIs, the MAH is requested to clarify which terms have been considered for the background incidence estimate for the multiple concerned AESIs including haemorrhage when using the Pfizer internal data Healthcare.

Response

The following are the conditions for which the MAH has used Pfizer internal results from an analysis of the HealthCore claims database for background incidence rate estimates. Table 1 provides the HealthCore terms and operational definitions for each of these listed AESIs.

Acute myocardial infarction
Autoimmune thyroiditis
Multiple sclerosis
Haemorrhage
Giant cell arteritis
Polyneuropathy
Rheumatoid arthritis, polyarthritis

The HealthCore Integrated Research Database is a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from more than 50 million current and past health plan members in the US. The study time period included 01 January 2006 through 30 December 2019.

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
Acute myocardial infarction	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code [ICD-9-CM: 410.x; ICD-10-CM: I21.%, I22.%] Specific: [At least two outpatient physician claims (CPT starts with '99' AND placeflag in ('ER', 'OUT', 'OV', 'SNF')) at least two months apart, OR at least one inpatient physician claim (placeflag = 'INP')] with an appropriate diagnosis code(s) (see above), AND at least one of the following specific processes/treatments: At least one appropriate diagnosis by a cardiologist Diagnosis at least one day and no more than two months after a diagnostic test X-ray imaging of the chest and heart [CPT: 71010 through 71035, 93000, 3120F, 0178T, 0179T, 0180T, 93000, 93010, 93660, 0295T, 0298T, 93272, 93224 through 93229, 93268, 93270, 93271, 93272, 0295T, 0296T, 0297T, 0298T, 3022F, 93015 through 93024, 75571 through 75574, 75557 through 75565, 93451 through 93581; HCPCS: G8962; ICD-9 Proc: 87.49, 88.42, 88.43, 88.44,88.5x, 89.41 through 89.69; ICD-10 Proc: BB0DZZ, BB12ZZZ, BB13ZZZ, BB14ZZZ, BB16ZZZ, BB1CZZZ, BB1DZZZ, B3000ZZ, B3001ZZ, B300YZZ, B30P0ZZ, B30P1ZZ, B30PYZZ, B3100ZZ, B3101ZZ, B310YZZ, B31P0ZZ, B31P1ZZ, B31PYZZ, B4000ZZ, B4001ZZ, B400YZZ, B40D0ZZ, B40D1ZZ, B40DYZZ, B4100ZZ, B4101ZZ, B410YZZ, B41D0ZZ, B41D1ZZ, B41DYZZ, B3050ZZ, B3051ZZ, B305YZZ, B30T0ZZ, B30T1ZZ, B30TYZZ, B31S0ZZ, B31S1ZZ, B31SYZZ, B31T0ZZ, B31T1ZZ, B31TYZZ, B31UOZZ, B31U1ZZ, B31UYZZ, B3010ZZ, B3011ZZ, B301YZZ, B3020ZZ, B3021ZZ, B302YZZ, B30L0ZZ, B30L1ZZ, B30LYZZ, B30N0ZZ, B30N1ZZ, B30NYZZ, B3110ZZ, B3111ZZ, B311YZZ, B3120ZZ, B3121ZZ, B312YZZ, B31L0ZZ, B31L1ZZ, B31LYZZ, B31N0ZZ, B31N1ZZ, B31NYZZ, B2000ZZ, B2001ZZ, B200YZZ, B2010ZZ, B2011ZZ, B201YZZ, B2020ZZ, B2021ZZ, B202YZZ, B2030ZZ, B2031ZZ, B203YZZ, B2060ZZ, B2061ZZ, B206YZZ, B2100ZZ, B2101ZZ, B210YZZ, B2110ZZ, B2111ZZ, B211YZZ, B2120ZZ, B2121ZZ, B212YZZ, B2130ZZ, B2131ZZ, B213YZZ, B2160ZZ, B2161ZZ, B216YZZ, B2170ZZ, B2171ZZ, B217YZZ, B2180ZZ, B2181ZZ, B218YZZ, B21F0ZZ, B21F1ZZ, B21FYZZ, B2040ZZ, B20401ZZ, B204YZZ, B2140ZZ, B2141ZZ, B214YZZ, B2050ZZ, B2051ZZ, B205YZZ, B2150ZZ, B2151ZZ, B215YZZ, B2060ZZ, B2061ZZ, B206YZZ, B2160ZZ, B2161ZZ, B216YZZ, B2070ZZ, B2071ZZ, B207YZZ, B2080ZZ, B2081ZZ, B208YZZ, B20F0ZZ, B20F1ZZ, B20FYZZ, 4A12XSH, B210010, B210110, B210Y10, B211010, B211110, B211Y10, B212010, B212110, B212Y10, B213010, B213110, B213Y10, 4A030R1, 4A033R1, 4A130R1, 4A133R1, 4A13XR1, 4A03XB1, 4A130B1, 4A133B1, 4A13XB1, 4A04XB1, 4A143B0, 4A14XB1, 02HO02Z, 02HP32Z, 02HP42Z, 02HQ02Z, 02HQ32Z, 02HQ42Z, 4A020N6, 4A0239Z, 4A023N6, 4A1239Z, 02HR02Z, 02HR32Z, 02HR42Z, 02HV02Z, 02HV42Z, 4A03XR1, 4A13XR1, 4A040R1, 4A043R1, 4A04XR1, 4A140R0, 4A140R2, 4A140R3, 4A143R0, 4A143R2, 4A143R3, 4A12X92, 4A030JC, 4A033JC, 4A1209Z, 4A12X9Z, 4A0305C, 4A0335C, 4A1305C, 4A130JC, 4A1335C, 4A023N8, 02JA0ZZ, 02JA3ZZ, 02JA4ZZ, 02JY0ZZ, 02JY3ZZ, 02JY4ZZ, 02K80ZZ, 02K83ZZ, 02K84ZZ, 0WJD0ZZ, 0WJD3ZZ, 0WJD4ZZ, C2161ZZ, C216YZZ, C21G1ZZ, C21GDZZ, C21GSZZ, C21GYZZ, C21GZZZ, C21YYZZ, C23GKZZ, C23GMZZ, C23GQZZ, C23GRZZ, C23GYZZ, C23YYZZ, C2261ZZ, C226YZZ, C22G1ZZ, C22GDZZ, C22GKZZ, C22GSZZ, C22GYZZ, C22GZZZ, C22YYZZ, C2561ZZ, C256YZZ, C25YYZZ Electrocardiogram (ECG) [CPT: 93000, 3120F, 0178T, 0179T, 0180T, 93000, 93010, 93660, 0295T, 0298T, 93268, 93270 through 93272, 93224 through 93229, 93268, 93270 through 93272, 0295T, 0296T, 0297T, 0298T; ICD-9 Proc: 89.51, 89.52, 89.53; ICD-10 Proc: 4A020%].

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
Acute myocardial infarction *Cont'd*	Echocardiogram [CPT: 3022F; ICD-9 Proc: 88.72; ICD-10 Proc:] B240YZZ, B240ZZ4, B240ZZZ, B241YZZ, B241ZZ4, B241ZZZ, B244YZZ, B244ZZ4, B244ZZZ, B245YZZ, B245ZZ4, B245ZZZ, B24BYZZ, B24BZZ4, B24BZZZ, B24CYZZ, B24CZZ4, B24CZZZ, B24DYZZ, B24DZZ4, B24DZZZ Stress test [CPT: 93015 through 93024; HCPCS: G8962; ICD-9 Proc: 89.4; ICD-10 Proc:] 4A02XM4, 4A12XM4 Cardiac computed tomography (CT) [CPT: 75571 through 75574; ICD-9 Proc: 87.41; ICD-10 Proc:] B22600Z, B2260ZZ, B22610Z, B2261ZZ, B226Y0Z, B226YZZ, B226ZZZ Magnetic resonance imaging (MRI) [CPT: 75557 through 75565; ICD-9 Proc: 88.92; ICD-10 Proc:] B236Y0Z, B236YZZ, B236ZZZ Coronary catheterization [CPT: 93451 through 93581; ICD-9 Proc: 37.21 through 37.23; ICD-10 Proc:] 4A020N6, 4A023N6, 4A020N7, 4A023N7, 4A020N8 Procedures Coronary bypass surgery [CPT: 33510 through 33548; ICD-9 Proc: 36.1x, 39.66; ICD-10 Proc:] 0210%, 0211%, 0212%, 0213%, 5A1221Z Heart valve repair [CPT 33405 through 33406, 33411 through 33413, 33413, 33475, 33420 through 33427, 33430, 33465, 33470 through 33474, 33496, 33660 through 33665; ICD-9-CM proc 35.03, 35.13, 35.25, 35.26; ICD-10 Proc:] 027H0ZZ, 027H3ZZ, 027H4ZZ, 02CH3ZZ, 02CH4ZZ, 02NH3ZZ, 02NH4ZZ, 027H04Z, 027H0DZ, 027H0ZZ, 02NH0ZZ, 02QH0ZZ, 02RH07Z, 02RH08Z, 02RH0KZ, 02RH47Z, 02RH48Z, 02RH4KZ, 02RH0JZ, 02RH4JZ Implantable cardioverter-defibrillators (ICDs) [CPT: 93289 through 93296; ICD-9 Proc: 37.94, 37.95, 37.96, 37.97, 37.98; ICD-10 Proc:] 02H60KZ, 02H63KZ, 02H64KZ, 02H70KZ, 02H73KZ, 02H74KZ, 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ, 02PA0MZ, 02PA3MZ, 02PA4MZ, 02PAXMZ, 0JH608Z, 0JH638Z, 0JH808Z, 0JH838Z, 0JPT0PZ, 0JPT3PZ, 02H40KZ, 02H44KZ, 02H60KZ, 02H63KZ, 02H64KZ, 02H70KZ, 02H73KZ, 02H74KZ, 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ,02HN0KZ, 02HN3KZ, 02HN4KZ, 0JH608Z, 0JH638Z, 0JH808Z, 0JH838Z, 02PA0MZ, 02PA3MZ, 02PA4MZ, 02PAXMZ Cardiac resynchronization therapy (CRT) or biventricular pacing [CPT 33224, 33225, 33226; ICD-9-CM proc 00.50 through 00.54; ICD-10 Proc:] 02H40JZ, 02H43JZ, 02H44JZ, 02H60JZ, 02H63JZ, 02H64JZ, 02HK0JZ, 02HK3JZ, 02HK4JZ, 02HL0JZ, 02HL3JZ, 02HL4JZ, 0JH607Z, 0JH637Z, 0JH807Z, 0JH837Z, 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ, 0JH609Z, 0JH639Z, 0JH809Z, 0JH839Z, 02H43JZ, 02H43KZ, 02H40MZ, 02PA0MZ, 02PA3MZ, 02PA4MZ, 0JPT0PZ, 0JPT3PZ. Heart pumps (left ventricular assist devices [LVADs]) [CPT: 33975 through 33976, 33978, 33979, 33990, 33991; ICD-9 Proc: 37.62 through 37.68; ICD-10 Proc:] 02HA0RZ, 02HA3RZ,02HA4RZ, 5A02116, 5A02216, 02WA0QZ, 02WA0RS, 02WAORZ, 02WA3QZ, 20WA3RS, 02WA3RZ, 02WA4QZ, 02WA4RS, 02WA4RZ, 02PA0QZ, 02PA0RS, 02PA0RZ, 02PA3QZ, 02PA3RZ, 02PA4QZ, 02PA4RS, 02PA4RZ, 02HA0RZ, 02HA4RZ, 5A02116, 5A02216, 02HA0QZ, 02HA3QZ, 02HA4QZ, 02HN0MZ, 02HN3MZ, 02HN4MZ, 02QA0ZZ, 02QA3ZZ, 02QA4ZZ,

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
Acute myocardial infarction *Cont'd*	0KXF0ZZ, 0KXG0ZZ, OPT10ZZ, OPT20ZZ, 02HAORJ, 02HA3RJ, 02HA3RZ, 02HA4RJ, 5AO2116, 5A0211D, 5A02216, 5A0221D Heart transplant [CPT: 33935, 33945; ICD-9 Proc 33.6x, 37.51; ICD-10 Proc:] 02YA0Z0, 02YA0Z1, 02YA0Z2 Treatments Aldosterone antagonists [GPI: 3625x] Angiotensin-converting enzyme (ACE) inhibitor [GPI: 3610x] Angiotensin II receptor blockers (ARBs) [GPI: 3615x] Beta blockers [GPI: 33x] Digoxin [GPI: 9300002x] Diuretics [GPI: 37x]
Autoimmune thyroiditis HealthCore term: Thyroiditis (limited to acute presentation)	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code [ICD-9 CM: 245.0x, 245.4x, 245.9x; ICD-10 CM: E06.0]. Note: Acute thyroiditis will exclude any evidence of chronic thyroiditis OR appropriate diagnosis code(s) for Hashimoto's thyroiditis during the baseline period. Specific: At least two outpatient physician claims (CPT starts with '99' AND placeflag in ('ER', 'OUT', 'OV', 'SNF')) at least four weeks apart with an appropriate diagnosis code(s) (see above), AND at least one pharmacy dispensing of any of the following specific processes/treatments: Diagnosis at least one day and no more than two months after a diagnostic thyroid panel (thyroid stimulating hormone [TSH], free triiodothyronine (T3), free thyroxin (T4)) [see above] Treatments Thyroid medication Antithyroid agents (i.e. methimazole, propylthiouracil) [see above] Thyroid hormones (i.e. levothyroxine sodium, liothyronine sodium, liotrix, thyroid, thyroid strong, thyroid [pork]) [see above] Iodine following radioactive ablation [see above]
Multiple sclerosis	At least two physician claims with an appropriate diagnosis code(s) (see above) at least four weeks apart, AND no prior diagnosis of optic neuritis [ICD-9 CM: 377.3x; ICD-10 CM: H46.%], AND at least one of the following specific processes/treatments: At least one diagnosis by a neurologist At least one diagnosis at least one day and no more than two months after magnetic resonance imaging (MRI) of the spine [CPT 72141, 72142, 72146, 72147, 72148, 72149, 72156, 72157, 72158; ICD-9 Proc 88.93; ICD-10 Proc: B03BY0Z, B03BYZZ, B03ZZZ, BR30Y0Z, BR30YZZ, BR30ZZZ, BR31Y0Z, BR31YZZ, BR31ZZZ, BR32Y0Z, BR32YZZ, BR32ZZZ, BR33Y0Z, BR33YZZ, BR33ZZZ, BR37Y0Z, BR37YZZ, BR37ZZZ, BR39Y0Z, BR39YZZ, BR39ZZZ, BR3FY0Z, BR3FYZZ, BR3FZZZ] At least one diagnosis at least one day and no more than two months after computed tomography (CT) of the spine [CPT: 72125 through 72133] At least one pharmacy dispensing of any of the following specific treatments: Interferon-beta-1b or Interferon-beta-1a [GPI: 2170006050x, 6240306045x, 6240306050x; HCPCS: J1830, J1825, J1826, Q3025, Q3026] Glatiramer acetate [GPI: 624000x; HCPCS: J1595]

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
	Natalizumab [GPI: 624050x; HCPCS: C9126, J2323, Q4079]
Haemorrhage HealthCore term: Bleeding disorders, including acquired platelet deficiency, ecchymosis, idiopathic thrombocytopenia purpura (ITP), and thrombotic thrombocytopenia purpura	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code [ICD-9-CM: 283.11, 287.31, 446.6x, 782.7x; ICD-10-CM: D59.3, D69.3, M31.1, R23.3] with no diagnosis of hemophilia [ICD-9-CM: 286.0x through 286.4x, 286.52, V83.02; ICD-10-CM: D66, D67, D68.0, D68.1, D68.2, D68.311] Specific: [At least two outpatient physician claims (CPT starts with '99' AND placeflag in ('ER', 'OUT', 'OV', 'SNF')) at least two months apart, OR at least one inpatient physician claim (placeflag = 'INP')] with an appropriate diagnosis code(s) (see above), AND no diagnosis of hemophilia (see above) in the eligibility segment containing index date, AND no excluded diagnosis (see below), AND at least one of the following specific processes/treatments: Diagnosis by a hematologist Appropriate diagnosis at least one day and no more than two months after diagnostic test: Prothrombin time (PT) [CPT: 85610, 85611] Partial thromboplastin time (PTT): [CPT: 85730, 85732] Thrombin time [CPT: 85670, 85675] Fibrinogen [CPT: 85366, 85370, 85384, 85385] Platelet count [CPT: 85025, 85027, 85032] D-dimer levels [CPT: 85378, 85379, 85380] Diagnosis and treatment: Corticosteroids within two weeks after the first appropriate diagnosis code [see above] Vitamin K [GPI: 77204010x, 77204030x: HCPCS: J3430] Blood transfusion [see above] Intravenous immunoglobulin (IVIG) therapy [see above] Eltrombopag [GPI: 82405030x] Vincristine [GPI: 9684584130x, 2150002010x; HCPCS: J9370, J9371, J9375, J9380] Splenectomy [CPT: 38100, 38101, 38102, 38120; ICD-9 Proc: 41.43, 41.5x; ICD-10 Proc: 07BP0ZZ, 07BP3ZZ, 07BP4ZZ, 07TP0ZZ, 07TP4ZZ] Immunosuppression (azathioprine, cyclophosphamide, cyclosporin) [see above] Azathioprine Cyclophosphamide Cyclosporine
Giant cell arteritis HealthCore term: Temporal arteritis	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code [ICD-9 CM: 446.5x; ICD-10 CM: M31.6]. Specific: At least two outpatient physician claims (CPT starts with '99' AND placeflag in ('ER', 'OUT', 'OV', 'SNF')) at least two months apart with an appropriate diagnosis code(s), AND at least one of the following specific processes/treatments: Diagnosis by a neurologist Diagnosis at least one day and no more than two months after temporal artery biopsy [CPT: 37609] Diagnosis at least one day and no more than two months after ultrasound [CPT: 93886 through 93893; ICD-9-CM Proc: 88.71; ICD-10-CM Proc: B040ZZZ, BH4CZZZ, BW4FZZZ]

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
Polyneuropathy HealthCore term: Chronic inflammatory demyelinating polyradiculoneuropathy	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code [ICD-9 CM: 357.81; ICD-10 CM: G61.81] Specific: At least two outpatient physician claims (CPT starts with '99' AND placeflag in ('ER', 'OUT', 'OV', 'SNF')) at least two months apart, OR at least one inpatient physician claim (placeflag = 'INP')] with an appropriate diagnosis code(s) (see above), AND at least one of the following specific processes/treatments: At least one diagnosis by a neurologist Diagnosis at least one day and no more than two months after a diagnostic test or procedure Magnetic resonance imaging (MRI) of the spine [see above] Electromyography (EMG) [CPT: 95860 through 95864; ICD-9-CM Proc: 93.08; ICD-10-CM Proc: 4A0F33Z, 4A0FX3Z] Peripheral (sural) nerve biopsy [CPT: 64795; ICD-9-CM Proc: 04.11, 04.12; ICD-10-CM Proc Plasma exchange therapy/plasmapheresis [CPT: 36514, 36515, 36516; ICD-9-CM Proc: 99.07, 99.71; ICD-10-CM Proc: 30230J1, 30230K1, 30230L1, 30230M1, 30233J1, 30233K1, 30233L1, 30233M1, 30240J1, 30240K1, 30240L1, 30240M1, 30243J1, 30243K1, 30243L1, 30243M1, 30250J1, 30250K1, 30250L1, 30250M1, 30253J1, 30253K1, 30253L1, 30253M1, 30260J1, 30260K1, 30260L1, 30260M1, 30263J1, 30263K1, 30263L1, 30263M1, 6A550Z3, 6A551Z3] Treatment Corticosteroids within two weeks after the first appropriate diagnosis code [see above] Intravenous immunoglobulin (IVIG) therapy [see above]
Rheumatoid arthritis, polyarthritis HealthCore term: Arthritis (limited to new onset inflammatory arthritis, including polyarthritis and rheumatoid arthritis)	At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code. Individuals diagnosed with gout at baseline are excluded from analysis of this outcome [ICD-9 CM: 714.x; ICD-10 CM: M02.8%, M02.9, M05.%, M06.% M12.8%, M12.9, M13.0, M13.8%]. Specific: At least two outpatient physician claims at least two weeks apart OR at least one inpatient physician claim with an appropriate diagnosis code. Individuals diagnosed with gout at baseline are excluded from analysis of this outcome [ICD-9 CM: 714.x; ICD-10 CM: M02.8%, M02.9, M05.%, M06.% M12.8%, M12.9, M13.0, M13.8%] -AND- at least one pharmacy dispensing or medical claim of any of the following specific treatments: Abatacept [GPI: 6640x; HCPCS: C9230, J0129] Adalimumab [GPI: 66270015x; HCPCS: J0135] Anakinra [GPI: 6626x] Certolizumab pegol [GPI: 52505020x; HCPCS: C9249, J0718] Chlorambucil [GPI: 21101010x; HCPCS: S0172] Dexamethasone [GPI: 22100020x; HCPCS: C9256, J1094, J1100, J7312, J7637, J7638, J8540, S0173] Etanercept [GPI: 6629x; HCPCS: J1438] Gold Sodium Thiomalate [GPI: 66200030x; HCPC: J1600] Hydroxychloroquine [GPI: 13000020x] Hydrocortisone, oral or parenteral, within two weeks after the first appropriate diagnosis [GPI: 22100025x; HCPCS: J1700, J1710, J1720] Immunosuppressant drugs Azathioprine [GPI: 994060x; HCPCS: C9436, J7500, J7501] Cyclosporine [GPI: 99402020x; CPT: 80158; HCPCS: C9438, J7502, J7515, J7516]

Table 5. Terms and Operational Definitions for Selected AESIs using Pfizer Internal Data from HealthCore Claims Data for Background Incidence Rate Estimates

	Specific Case Definition
Rheumatoid arthritis, polyarthritis HealthCore term: Arthritis (limited to new onset inflammatory arthritis, including polyarthritis and rheumatoid arthritis) *Cont'd*	Methotrexate [GPI: 21300050x, 6625x; HCPCS: J8610, J9250, J9260] Infliximab [GPI: 52505040x; HCPCS: J1745] Leflunomide [GPI: 6628x] Methylprednisolone, oral or parenteral, within two weeks after the first appropriate diagnosis code [GPI: 22100030x; HCPCS: J1020, J1030, J1040, J1210, J2920, J2930, J7509] Penicillamine [GPI: 99200030x] Prednisolone within two weeks after the first appropriate diagnosis code [GPI: 22100040x; HCPCS: J7510, J2650] Prednisone within two weeks after the first appropriate diagnosis code [GPI: 22100045x; CPT: 4194F; HCPCS: J7506] Rituximab [GPI: 21353060x; HCPCS: J9310] Sulfasalazine [GPI: 52500060x] Tocilizumab [GPI: 6650x; HCPCS: C9264, J3262] Triamcinolone within two weeks after the first appropriate diagnosis code (see above)

Note: Treatments provided over the counter will not be captured in this database

7. ***Regarding pregnancy and lactation, the MAH is requested to:***
   a. ***define the strategies put in place to identify, manage and prioritize the pregnancy cases among the unlocked cases.***
   b. ***include all relevant publications during the reporting interval.***
   c. ***make all efforts to complete the follow-up of the pregnant woman cases.***
   d. ***describe with detail the relevant cases evaluated under signals or health authorities requests that concern breastfed children in section 'Use in pregnant/lactating women' of the PSUR.***

Response

For request a) and c), please refer to the response to PRAC commitment No. 1.

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

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

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

Response

Please refer to Appendix 6A.2.

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

Response

Please refer to Appendix 6A.3.

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

Response

The MAH will provide a cumulative review on the association between Comirnaty and subacute thyroiditis as a separate response latest by 04 March 2022.

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

The MAH should provide an updated age-stratified O/E analysis of herpes zoster, with a sensitivity analysis to account for the backlog of cases. The MAH is also requested to discuss possible mechanisms that could underpin herpes zoster reactivation following vaccination. (MS1/MS4)

Response

O/E analysis with sensitivity analysis to compensate for backlog cases was already implemented since the 8th SMSR (reporting period 01 July 2021 - 31 July 2021).

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.

Response

This request has been already addressed in the 1st SBSR and acknowledgment was provided in the AR (Procedure EMEA/H/C/005735/MEA/002.11). The same approach is used in the PSUR in Section 5.2 *Cumulative and Interval Patient Exposure from Marketing Experience.*

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

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

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

This request has been already addressed in the 1st SBSR. The same approach is used in the PSUR in Section 9.2 *Medication Errors* (for handling and dosing errors for the different vaccine formulations) and in Section 5.2 *Cumulative and Interval Patient Exposure from Marketing Experience* for number of third doses administered.

Please refer to subsection "Errors pertaining to the new formulation of BNT162b2 - Tris/Sucrose presentation" of the Section 9.2 *Medication Errors*, for an overview of the medication errors occurred with the new Tris/Sucrose presentation.

Overall, out of the 33,834 relevant medication error cases, there were 755 cases reporting events indicative of medication errors related to Tris/Sucrose paediatric formulation. This number is a good index of the effectiveness of the routine pharmacovigilance activities implemented by the MAH and detailed in Part III.1 of the EU-RMP in the subsection Potential Medication errors, considering that in the reporting period 47,038,200 pediatric tris/sucrose doses were shipped worldwide (Section 5.2 *Cumulative and Interval Patient Exposure from Marketing Experience*).

SIGNAL ASSESSMENT REPORT ON GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME WITH TOZINAMERAN EMA/PRAC/416198/2021 EPITT 19722 PROCEDURE NO: SDA 035

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

Response

See Appendix 6A.4 for details.

SIGNAL ASSESSMENT REPORT ON MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN FOR COVID VACCINES EMA/PRAC/473788/2021 EPITT 19732 PROCEDURE NO: SDA 038

The MAH should continue to closely monitor this safety issue and new cases of MIS-C/A should be reported in the MSSRs and PSURs, A dedicated questionnaire should be implemented to retrieve an appropriate level of information to facilitate the assessment of the cases. The MAHs should continue to closely monitor this safety issue. The MAH should focus on the well described index case(s) and less 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.

Response

See Appendix 6A.5 for details.

On 20 December 2021, a DCA Pfizer-BioNTech COVID-19 Vaccine Multisystem Inflammatory Syndrome in Pediatric and Adults was made effective.

SIGNAL ASSESSMENT ON ERYTHEMA MULTIFORME EMA/PRAC/398391/2021 EPITT 19721 PROCEDURE NO: SDA 034

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

Response

Signal detection activities for the COVID-19 mRNA vaccine occurs on a weekly basis. Published literature is reviewed weekly for individual case reports and broader signal detection purposes. In addition, observed versus expected analyses is conducted as appropriate as part of routine signal management activity. The MAH closely monitors monitor any new cases, patterns or trends of reporting erythema multiforme. Specific review of the incremental data is provided in Section 16.3.3.1.5 – *Dermatological AESIs*.

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.

Response

Please refer to Section 16.3.3.1.20. *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.

Please refer to Section 16.3.5.3. *Use in Pregnant/Lactating Women.*

APPENDIX 6A.1 EXACERBATION (FLARE-UP) OF PRE-EXISTING AI/INFLAMMATORY DISORDERS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
AER	Adverse Event Report
CDS	Core Data Sheet
CSP	Core Safety Profile
DLP	Data Lock Point
EMA	European Medicines Agency
FDA	(US) Food and Drug Administration
HA	Health Authority
HLT	(MedDRA) High Level Term
IBD	International Birth Date
LLT	(MedDRA) Lowest Level Term
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PT	(MedDRA) Preferred Term
RSI	Reference Safety Information
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematous
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	(MedDRA) System Organ Class

1. INTRODUCTION

The MAH received an updated PSUR Assessment Report from EMA PRAC on 30 December 2021 requesting a cumulative review of autoimmune/inflammatory disorder exacerbations reported following vaccination with COMIRNATY including data that have become available since the data-lock period of the 10th SMSR (30 September 2021) which also included a cumulative safety review of the topic.

The mechanisms of immune activation underlying exacerbations of immune conditions are unknown. Nevertheless, exacerbation of inflammatory or autoimmune conditions following infection is not a new concept and has been suggested and demonstrated in different settings. Exacerbations following vaccination has also been discussed in the scientific literature. Ishay Y et al [1] analyzed subjects with preexisting auto-inflammatory diseases and the likelihood of exacerbations following vaccination. In the same article the authors discuss the hypothesis of autoimmunity after vaccination. As a vaccine exerts its protective action by eliciting an immune response, it is hypothesized to initiate or exacerbate hyperinflammatory changes in certain settings. Some vaccine adjuvants – the substances lending immunogenicity to the vaccine – have been noted to act via induction and activation of the NLR (Nod-like receptor) pyrin domain containing 3 (NLRP3) inflammasome. mRNA vaccines, BNT162b2 included, exhibit a property of self-adjuvantation, with the mRNA acting as a carrier of coding for proteins that are recognized by endosomal toll-like receptors (TLRs) and cytosolic inflammasome components (MDA5, RIG-I, NOD2 and PKR), inciting inflammation and immunity.

The theory of molecular mimicry postulates that certain self-antigens share a structural similarity with the SARS-CoV-2 spike (S) protein and an immune response to S protein also targets these self-antigens. Notably, molecular mimicry has also been suggested as a mechanism in COVID-19 related immune phenomena, where viral proteins have elicited immune cross-reactivity with human tissue. This cross reactivity is dependent on environmental factors and genetic predisposition, such as immune tolerance deficit following aberrant major histocompatibility complex (MHC) class II antigen presentation to autoreactive T cells.

The adjuvant theory, or bystander effect, states that immune activation stems from the presence of an exposed autoantigen in the setting of a pro-inflammatory or pathogenic context. Exact characterization of the immune response triggered by the BNT162b2 vaccination has not been completely elaborated. Intracellular mRNA or the translated fragment of the SARS-CoV-2 spike protein may trigger components aimed at detecting danger associated molecular patterns, such as TLRs. Activation of TLR7 and TLR8 especially, and downstream signaling via type I interferon production, has been postulated as the driving mechanism. The spike protein fragment, itself likely to be inherently immunogenic, may be translocated to the plasma membrane. The context of a xenoprotein embedded in the plasma membrane of a cell in which TLRs and similar proteins have become activated, may trigger an immune response aimed at components of the cell. Similar effects have been implicated in viral infection. Whether any of these theories are true and whether a single theory explains all instances of post-vaccine autoimmunity remains unknown [1].

An observational study supports a similar reactogenicity profile of BNT162b2 in patients with autoimmune disorders. A cohort of 325 patients with various rheumatic and musculoskeletal diseases who received either BNT162b2 or mRNA-1273 were recruited using social media and asked to complete a questionnaire about local and systemic side effects they experienced during the first week following their first vaccine dose. Side effects were similar in severity and frequency to those of healthy patients in the vaccine trials, with 69% reporting at least 1 systemic side effect (most commonly fatigue). One patient reported confirmed COVID infection, 1 reported peripheral neuropathy, and none reported allergic reactions requiring epinephrine. Notably, most participants were female (96%) and white (89%), data were collected only after the first dose and the potential for participation bias are acknowledged.

And the possibility that treatment of underlying autoimmune conditions may affect the immune reaction to BNT162b2 has also been explored in some studies. In a study by Geisen et al [2], investigators measured arthritis activity prior to vaccination and after each vaccine dose; it was not found to be increased in these patients. Systemic side effects, however, tended to be milder among patients treated for inflammatory disease than in healthy controls. Available data from initial studies of COVID-19 vaccination in patients suggest that neither patients with immune-mediated inflammatory diseases (IMID) nor concurrent biologic use is a contraindication to vaccination. However, Wack S et al [3] showed that patients receiving biologics for their autoimmune conditions, and particularly those on B-cells depleting therapies, may produce diminished immune responses.

2. METHODOLOGY – POST-MARKETING SAFETY DATABASE

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality.

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

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

The search criteria were used in different steps:

1. The search criteria were applied to the medical history field to retrieve all cases with a medical history of autoimmune disease.

2. For the cases that reported autoimmune diseases in the medical history, the same search criteria was applied to the reported adverse events to retrieve cases reporting autoimmune disease in subjects with existing autoimmune comorbidity.

3. The cases retrieved in the search as per point 2 were reviewed for potential exacerbation/relapse/flare of the autoimmune disease coded both in the medical history and as an adverse event.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication

3. RESULTS – POST-MARKETING SAFETY DATABASE

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

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

In Table 1 below, the specific autoimmune diseases reported in the medical history and after vaccination are detailed.

Table 1. Autoimmune Disease Reported in the Medical History and After Vaccination

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

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

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

Alopecia Areata

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

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

Amyloidosis

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

Autoimmune Disease	Dose number	Clinical Outcome	Time to Onset (when reported)	AE Duration (when reported)
PT: Amyloidosis	Not reported	Not Resolved: Not reported Resolved/Resolving/Resolved with sequelae: Not reported Unknown: 1	Not reported	Not reported

Ankylosing spondylitis

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

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

Behcet's syndrome

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

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

Coeliac disease

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

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

Colitis ulcerative

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

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

Crohn's disease

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

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

Diabetes

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

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

Diabetes Fatal cases:
(AER#2021560240)

An 87-year-old female patient received BNT162b2 on 30Jan2021. Medical history included dementia and insulin-dependent diabetes mellitus. According to her doctor, the patient's condition was deteriorating both physically and mentally since the end of 2020. The patient's concomitant medications were not reported. The patient died from her insulin-dependent diabetes mellitus (not responding well to therapy) on 28Feb2021.

(AER#2021527624)

A 69-year-old female patient received BNT162b2 on 19Jan2021 as an initial dose and on 25Mar2021 as the second dose. Medical history included ketosis-prone diabetes mellitus, insulin-dependent diabetes, arterial hypertension, complete arrhythmia due to atrial fibrillation, kidney failure, sequelae cognitive disorders, stroke, sleep apnea, hypothyroidism, obesity, hyperuricaemia, deglutition disorder, hyponatraemia, hyperkalemia, swallowing disorders with currently rehydration by exclusive gastric tube. Concomitant medications included phenobarbital, oxazepam, mirtazapine, levothyroxine sodium, erythromycin, racecadotril, hyoscine, oxycodone hydrochloride, and insulin lispro. On 02Apr2021, the patient tested positive for COVID-19. On 06Apr2021, respiratory decompensation occurred,

dextro 5.8g/l, oxygen saturation 85%, heartbeat was 65, and blood pressure was 100/60. The patient was put under hospital care with oxygen 6L/min. The patient presented on arrival in a comatose state with concomitant hypoxia linked to COVID and especially a state of hyper osmolarity linked to a decompensation of her diabetes. Treatment was performed with rehydration for hyperosmolar coma, insulin therapy, and antibiotic therapy. Palliative comfort management was initiated given the patient's condition and the patient eventually died on 08Apr2021 despite the treatment. An autopsy was not performed. The reported cause of death was COVID-19, hyperosmolar (non-ketotic) coma and decompensation of diabetes.

Guillain-Barre syndrome

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

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

GBS Fatal case (AER# 2021381625):
A 76-year-old male patient received the first dose of BNT162b2 on 28Feb2021. The patient was diabetic and obese. Medical history also included heart disease with 2 stents (2009), hypertension, hyperlipidemia, coronary artery disease, prostate cancer from 2009, Guillain-Barre from Mar2020, hypertension, former smoker and was under multiple concomitant medication. Two weeks after receiving the vaccine, the patient presented to the physician's office with urinary incontinence, confusion, lethargy, decreased appetite and taste, weakness, and chills. He was admitted to the hospital and within a few days developed fever and thrombocytopenia; on the 5th hospital day he was diagnosed with Guillain-Barre Syndrome (confirmed by lumbar puncture). He was hospitalized for 2 weeks and received intravenous immune globulin for 5 days for Guillain-Barre Syndrome and was transferred to a nursing home. He was readmitted to the hospital with dehydration in 04Apr2021 and expired 2 days later (06Apr2021). Autopsy result showed that the patient died of acute renal failure/dehydration second to Guillain-Barre.

Henoch-Schoenlein purpura

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

Autoimmune Disease	Dose number	Clinical Outcome	Time to Onset (when reported)	AE Duration (when reported)
PT: Henoch-Schoenlein purpura	Dose 1: 6 Dose 2: 6	Not Resolved: 4 Resolved/Resolving/Resolved with sequelae: 8	Same day: 1 1-4 days: 5 6-7 days: 3	Not reported

Immune thrombocytopenia

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

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

Multiple Sclerosis

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

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

Multiple sclerosis Fatal case (AER#202101611411):
A 61-year-old female received BNT162b2 in 2021 (number of doses unknown). Relevant medical history included: "Multiple sclerosis" (unspecified if ongoing). The patient's concomitant medications were not reported. On 25Apr2021 the patient experienced multiple sclerosis relapse described as a flare, subileus, cerebrovascular accident described as apoplexy, dysphagia, aspiration, and infections. "After long-term ventilation and weaning-

failure, discharge from the respiratory care home, repeated aspirations, infections, final inpatient stay with subileus, apoplexy, and death on 16Sep2021. The reported cause of death was multiple sclerosis relapse. It was not reported if an autopsy was performed.

Myasthenia Gravis

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

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

Myasthenia gravis Fatal case (AER# 202101124956):
An 80-year-old female patient received BNT162B2 on 30May2021 (dose number unknown). Medical history included ongoing myasthenia gravis; concomitant medications were not reported. On an unspecified date in 2021, the patient experienced aggravated myasthenia gravis, difficulty swallowing, fatigue/ lassitude, and weight loss. Relatedness of COMIRNATY to the events Myasthenia gravis aggravated, swallowing disorder, Lassitude, and Weight loss was reported as unclassifiable by the regulatory authority (PEI).

Myelitis/ Transverse Myelitis

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

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

Polymyalgia Rheumatica

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

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

Psoriasis

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

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

Rheumatoid Arthritis

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

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

Rheumatoid arthritis Fatal case (AER# 2021436015): A 76-year-old female patient received the first dose of BNT162B2 on 15Mar2021. Medical history included ongoing rheumatoid arthritis; osteoporosis; depression. Concomitant medications included duloxetine for depression; prednisolone for adrenocortical steroid therapy; methotrexate for rheumatoid arthritis; alendronate for osteoporosis. The patient experienced possible liver thrombosis, in Mar2021 (date unspecified); urinary tract infection on 25Mar2021, abdominal pain, splenic infarction and bowel ischemia on 28Mar2021; aggravation of rheumatoid arthritis on 27Mar2021; disseminated intravascular coagulation. The patient was treated with antibiotics due to urinary tract infection and bowel operation was performed (entire colon was necrotic, only 2 meters of viable small intestine). The patient died on 31Mar2021. An autopsy was performed, and results included: The cause of death is considered as a result of Pyelonephritis, and consequences of this, sepsis and circulatory collapse. Reported causes of death were ischaemia bowel, disseminated intravascular coagulation and urosepsis. A physician associated with the inquest on the death stated the death was not considered related to the vaccine.

Sarcoidosis

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

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

Sjogren's syndrome

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

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

Systemic lupus erythematosus

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

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

Still's disease

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

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

Systemic scleroderma

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

Autoimmune Disease	Dose number	Clinical Outcome	Time to Onset (when reported)	AE Duration (when reported)
PT: Systemic scleroderma	Dose 1: 1 Dose 2: Not reported	Resolved: 1	2 days: 1	Not reported

Thyroiditis

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

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

Uveitis

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

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

Vasculitis

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

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

Vasculitis Fatal case (AER# 202101174757)

A 66-year-old male patient received the first dose of BNT162B2 on an unspecified date. Medical history included giant cell arteritis, stenosis, interstitial lung disease, tenderness, vasculitis, dehydration, headache, cortical blindness (admitted 14Aug2021), sciatica, hypoperfusion, visual disturbance, claudication, weakness, asthma and hypertension. Patient had seen Vascular in 2017 for leg pain which was atypical for intermittent claudication and diagnosed as sciatica; the ankle brachial pressure index was normal. Further investigation in May/June revealed bilateral inflammatory disease throughout his arterial extremities in lower limbs. He was referred to Rheumatology. Concomitant medications included beclometasone dipropionate taken for asthma from 20Feb2020 to an unspecified stop date; ramipril taken for hypertension from 01Aug2018 to an unspecified stop date. The patient experienced vasculitis in Feb2021; cortical blindness on 14Aug2021. The patient experienced bilateral anterior circulation ischaemic strokes, bilateral carotid artery occlusions, exercise tolerance, inflammatory disease, temporal tenderness, hypoperfusion, visual disturbance, weakness, giant cell arteritis, vomiting, intermittent claudication, headache, diarrhoea, middle cerebral artery infarct, all on an unspecified date. The patient underwent lab tests and procedures which included COVID-19 virus test: Negative COVID-19 test on 29Mar2021. COVID-19 infection status was negative during last admission 14Aug2021 until death on 21Aug2021. The patient has possible inflammatory pathology. Carotid artery ultrasound showed thickened temporal, frontal and axillary arteries. The outcome of exercise tolerance was unknown. The outcome of other events was fatal. The patient died on 21Aug2021. An

autopsy was not performed. Official cause of death was Bilateral anterior circulation ischaemic strokes and Bilateral carotid artery occlusions.

Vitiligo

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

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

3.1. Summation Of Post-Marketing AE Reports:

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

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

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

4. RESULTS - CLINICAL TRIAL DATA

Phase 2/3 Study C4591001 placebo-controlled unblinded adverse events in participants 16 years and older from dose 1 to 1 month after dose 2 (data cutoff date 13 March 2021) was also reviewed for the relevant adverse events. The data cutoff allows for a controlled comparison between the vaccine group and placebo group. A specific analysis of flare-ups of underlying conditions was not performed in the study.

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

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

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

Table 2 and Table 3 below report data described above. Medical history data are reported in Appendix 1.

Table 2. Number (%) of Subjects Reporting at Least 1 Adverse Event of a Potentially Aggravated Autoimmune Disease From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=2955)		Placebo (N[a]=2977)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	7 (0.2)	(0.1, 0.5)	4 (0.1)	(0.0, 0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Thrombocytopenia	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
ENDOCRINE DISORDERS	2 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Hypothyroidism	2 (0.1)	(0.0, 0.2)	0	(0.0, 0.1)
METABOLISM AND NUTRITION DISORDERS	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.1)
Diabetes mellitus	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.1)	(0.0, 0.2)	2 (0.1)	(0.0, 0.2)
Psoriatic arthropathy	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
Arthritis	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Arthritis reactive	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.1)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
Psoriasis	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)

Table 2. Number (%) of Subjects Reporting at Least 1 Adverse Event of a Potentially Aggravated Autoimmune Disease From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=2955)		Placebo (N[a]=2977)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Dermatitis	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.1)

Note: MedDRA (v23.1) coding dictionary applied.
a. N = number of subjects with prior autoimmune disease in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 01OCT2021 (13:53)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adae_s130_all_pd2_p3_aid

Table 3. Incidence Rates of at Least 1 Adverse Event of a Potentially Aggravated Autoimmune Disease From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age - Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=2955, TE[b]=11.0)			Placebo (N[a]=2977, TE[b]=11.0)		
System Organ Class Preferred Term	n[c]	IR (/100 PY)[d]	(95% CI[e])	n[c]	IR (/100 PY)[d]	(95% CI[e])
Any event	8	0.7	(0.3, 1.4)	8	0.7	(0.3, 1.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
Thrombocytopenia	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
ENDOCRINE DISORDERS	2	0.2	(0.0, 0.7)	2	0.2	(0.0, 0.7)
Hypothyroidism	2	0.2	(0.0, 0.7)	2	0.2	(0.0, 0.7)
GASTROINTESTINAL DISORDERS	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
Duodenal ulcer	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
Gastric ulcer	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
METABOLISM AND NUTRITION DISORDERS	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.3)
Diabetes mellitus	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	0.3	(0.1, 0.8)	2	0.2	(0.0, 0.7)
Arthritis	1	0.1	(0.0, 0.5)	1	0.1	(0.0, 0.5)
Arthritis reactive	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.3)
Psoriatic arthropathy	1	0.1	(0.0, 0.5)	1	0.1	(0.0, 0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
Interstitial lung disease	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	0.2	(0.0, 0.7)	1	0.1	(0.0, 0.5)
Dermatitis	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.3)
Psoriasis	1	0.1	(0.0, 0.5)	1	0.1	(0.0, 0.5)

Note: MedDRA (v23.1) coding dictionary applied.

a. N = number of subjects with prior autoimmune disease in the specified group.

b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of blinded follow-up. This value is the denominator for the incidence rate calculation.

c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.

d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.

Table 3. Incidence Rates of at Least 1 Adverse Event of a Potentially Aggravated Autoimmune Disease From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age - Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=2955, TE[b]=11.0)		Placebo (N[a]=2977, TE[b]=11.0)	
System Organ Class Preferred Term	n[c]	IR (/100 PY)[d] (95% CI[e])	n[c]	IR (/100 PY)[d] (95% CI[e])

e. 2-sided CI based on Poisson distribution.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 01OCT2021 (13:53)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adae_s131_d1unb_aid

4.1. Summation Of Clinical Study Data

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

5. ONGOING EPIDEMIOLOGY STUDIES

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

Study C4591008

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

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

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

Study C4591009

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

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

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

Study C4591010

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

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

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

Study C4591011

Study C4591011, Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization, is a secondary data collection study using data from the US Department of Defense military and civilian personnel and their families in the Military Health System.

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

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

Study C4591012

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

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

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

Study C4591021

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

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

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

Study C4591022

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

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

A summary of studies that analyzed adverse events and relapse in RA subjects that were administered COVID-19 vaccine is presented below.

6. RESULTS - LITERATURE REVIEW

The following database were scrutinized: BIOSIS Previews <1969 to 2021 Week 51>, Embase <1974 to 2021 December 16>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily from the 1946 to December 16, 2021. Single case reports will not be discussed, also articles focusing on willingness/positivity on vaccination will not be described. The most relevant articles that bring new information and overview on the topic will be discussed below.

The clinical trials of most COVID-19 vaccines allowed for patients with rheumatic disease to participate in the later stages of the trials but excluded patients on immunosuppressive agents. Therefore, it is not fully known whether vaccines might provoke flares of underlying rheumatic conditions as a result of immune activation or non-specific adjuvant effects. There are reports of other vaccines, such as those against tetanus, rubella, hepatitis B, and influenza, triggering rheumatoid arthritis, but causality has never been conclusive, and an association has never been reproduced in large, controlled studies. Molecular mimicry is thought to be one mechanism by which autoimmunity can occur, in which similarities between viral peptides and self-peptides can stimulate immune activation, but this has not been proven in rheumatoid arthritis.

Summaries of relevant studies are below:

- Rotondo et al [4] assessed, the safety profile of different types of COVID-19 approved vaccines (Astra-Zeneca and Pfizer/BioNtech) and the possible influence of immunosuppressive therapies in rheumatic disease (RD) patients. The study included subjects with autoimmune/chronic inflammatory RD (Au/cIn-RD) and with non-autoimmune/chronic inflammatory RD (no-Au/cIn- RD). The most frequently reported AEs after vaccination were site injection pain (17%), headache (12%), fever (12%), myalgia (10%) and fatigue (10%), reported with a lower incidence in older subjects and in those with complete control of RD. Relapses of the underlying Au/c-In-RD were recorded in 2.2% of patients after the first dose of vaccine. No relapses were observed after the second dose of vaccine. No safety issues were evident for any of the vaccines included in the study. The authors conclude that there is a low rate of disease relapse of Au/cIn-RD after the first dose of vaccine, as previously reported for influenza vaccines. In addition, a combination of immunosuppressive drugs seemed not interfere with the occurrence of AEs in Au/cIN-RD.

- Sattui et al [5] described early experiences of adults with systemic rheumatic disease who received the COVID-19 vaccine (Pfizer-BioNTech (53.2%), AstraZeneca (22.6%), Moderna (21.3%), Janssen/Johnson & Johnson (1.7%) and others (1.2%)). The author used an online, international survey of adults with systemic rheumatic disease who received COVID-19 vaccination from 2 April to 30 April 202. The majority (81.9%) reported communicating with clinicians about vaccination. Most (66.9%) were willing to temporarily discontinue DMARDs to improve vaccine efficacy, although many (44.3%) were concerned about rheumatic disease flares. After vaccination, the most reported patient-reported adverse events were fatigue/somnolence (33.4%), headache (27.7%), muscle/joint.

- Geisen et al [2] presented data on the efficacy and safety of anti-SARS-CoV-2 mRNA vaccines in a cohort of immunosuppressed patients as compared with healthy controls (42 healthy controls and 26 patients with Chronic inflammatory diseases). Antibody titres were assessed by ELISA before initial vaccination and 7 days after secondary vaccination. Disease activity and side effects were assessed prior to and 7 days after both vaccinations. Anti-SARS-CoV-2 antibodies as well as neutralising activity could be detected in all study participants. IgG titres were significantly lower in patients as compared with controls. Side effects were comparable in both groups. No severe adverse effects were observed, and no patients experienced a disease flare.

- Barbhaiya M et al [6] reported the interim results of a web-based survey evaluating systemic rheumatic disease (SRD) flare incidence post-SARS-CoV-2 vaccine. The survey was e-mailed to 3545 outpatients with SRDs seen at a large rheumatology division in New York City. A self-reported disease flare was defined as 'a sudden worsening of your rheumatology condition or arthritis' within 2 weeks of the vaccine. Pfizer (54.2%), Moderna (43.9 %), Janssen (1.5%) and Astra Zeneca (0.3%) vaccines were used. The interim data demonstrate that >85% of patients did not report an SRD flare post-SARS-CoV-2 vaccination.

- Yang M et al [7] described a prospective observational study examining the immunogenicity and safety profile of the Pfizer/BNT or Moderna vaccine in patients with immune-mediated diseases taking immunomodulatory medications (70 patients with autoimmune and inflammatory disease were enrolled). The authors concluded that patients with autoimmune and inflammatory disease experienced fever, fatigue and arthralgias mimicking flares with both frequency and severity appearing slightly greater than that of the reported results from the vaccine clinical trials.
- Bixio et al [8] performed a study focusing on COVID-19 vaccine safety and immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs), they have estimated an incidence of between 5% and 17% for RMD flares after COVID-19 vaccination. The results showed a low flare rate after the BNT162b2 COVID 19 vaccine in patients with RA in remission (6 patients: 7.8%; 95% confidence interval: 6.9-8.7%). The data were consistent with previous findings about Varicella-zoster virus (6.7%) and Hepatitis B virus (2.2%) vaccinations.

- Watad A et al [9] evaluated immune-mediated diseases (IMDs) flares or new disease onset within 28-days of SARS-CoV-2 vaccination at five large tertiary centers in countries with early vaccination adoption, three in Israel, one in UK, and one in USA. Overall, 27 cases of IMDs were included of which 23 (85.2%), two (7.4%), and two (7.4%) received the BNT-162b2, mRNA-1273 and ChAdOx1 vaccines, respectively). Of the relapsed cases, 75% were mild to moderate in severity and over 80% of cases had excellent resolution of inflammatory features, mostly with the use of corticosteroid therapy. They concluded that, despite the high population exposure in the regions served by these centers, IMDs flares or onset temporally associated with

SARS-CoV-2 vaccination appear rare. Of note, many of them are moderate in severity and responsive to therapy.

- Alfayadh N.M. et al [10] explored whether routine childhood vaccinations are associated with an increased risk of flares of arthritis activity in children with Juvenile idiopathic arthritis (JIA). They concluded that the risk of arthritis flares during the 90 days following immunization was reduced compared with patients' baseline risk and that routine childhood immunizations were not associated with arthritis flare onset in patients with JIA. The risk of arthritis flares in the 90 days following vaccination was lower than the baseline risk.

- Boekel L et al [11] describe the results of a questionnaire that assessed adverse events following COVID-19 vaccinations in patients with autoimmune diseases and healthy controls. The questionnaire was sent to patients with systemic autoimmune diseases who were enrolled in two ongoing prospective cohort studies (Netherlands Trial Register, trial ID NL8513 and NCT04498286). Between April 26, 2020 and March 1, 2021, all adult patients with systemic autoimmune diseases from the Amsterdam Rheumatology & Immunology Center (Amsterdam, Netherlands), and all adult patients with multiple sclerosis from the Amsterdam Multiple Sclerosis Center of Amsterdam UMC (Amsterdam, Netherlands) were invited to participate. Patients enrolled in the first study were asked (but not obliged) to recruit their own healthy control participant who was of the same sex and of comparable age (age difference <5 years). Data were collected via online questionnaires distributed via email. Analysis of the results of our questionnaire demonstrate that adverse events of COVID-19 vaccinations in patients with autoimmune diseases are comparable with controls, independent of the type of vaccine. Subjects were requested to send all adverse events reported within the first 7 days after vaccination, in addition Patients with rheumatic diseases and healthy controls were asked whether they experienced an increased number of joint complaints in the first 2 months after vaccination. The questionnaire was sent to 2515 patients with autoimmune diseases and 903 healthy controls, of whom 1780 patients and 660 controls completed the questionnaire. ChAdOx1 nCoV-19 (AstraZeneca) and BNT162b2 (Pfizer/BioNTech) were the most common vaccines in both patients and controls: 231 (46%) of 505 patients and 104 (51%) of 203 controls received the ChAdOx1 nCoV-19 vaccine and 209 (41%) patients and 90 (44%) controls received the BNT162b2 vaccine; 65 (13%) patients and 9 (4%) controls were vaccinated with CX-024414 (Moderna). The observed adverse events consisted of expected transient local or systemic reactions that were mostly self-limiting. The frequency of participants who reported adverse events was lower than that reported in clinical trials, but similar to a nationwide observational study on adverse events of COVID-19 vaccinations in the general population done in the UK. The data were consistent with previous studies that reported higher frequencies of adverse events in women and younger people. The authors conclude that COVID-19 vaccinations do not seem to trigger autoimmune disease flares, which is in accordance with data from previous small studies that assessed consequences of mRNA vaccines in patients with autoimmune diseases.

- Furer V et al [12] conducted a multicentre observational study to evaluate the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) compared with the general population. A total of 710 patients with AIIRD and 124 controls vaccinated with the two-dose regimen BNT162b2 mRNA vaccine were enrolled in the study. Serum IgG antibody levels against SARS-CoV- 2 spike S1/ S2 proteins were measured 2–6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/mL. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the second vaccine dose. The authors concluded that mRNA BNTb262 vaccine was immunogenic in the majority of patients with AIIRD (even though lower than in healthy controls), with an acceptable safety profile. Treatment with glucocorticoids, rituximab, MMF, and abatacept was associated with a significantly reduced BNT162b2-induced immunogenicity. There was no evidence of significant disease flares across different AIIRD.

- Connolly CM et al [13] evaluated disease flare and post-vaccination reactions in patients with rheumatic and musculoskeletal diseases (RMD) following two-dose SARS-CoV-2 mRNA vaccination (mRNA-1273 and BNT162b2). Participants completed questionnaires detailing local and systemic reactions experienced within 7 days of each vaccine dose (D1, D2), and one month after D2 detailing flare of RMD. A total of 11 percent reported flare requiring treatment; there were no reports of severe flares. Flare was associated with prior SARS-CoV-2 infection (IRR 2.09, p=0.02), flare in the six months preceding vaccination (IRR 2.36, p<0.001) and use of combination immunomodulatory therapy (IRR 1.95, p<0.001). The most frequently reported local and systemic reactions included injection site pain (D1 87%, D2 86%) and fatigue (D1 60%, D2 80%); reactogenicity increased after D2, particularly for systemic reactions. The authors concluded that flare of underlying RMD following SARS-CoV-2 vaccination was uncommon. There were no reports of severe flare. Local and systemic reactions typically did not interfere with daily activity.

- Machado et al [14] report published the results of the EULAR COVID-19 Vaccination (COVAX) Registry that is an observational registry launched on 5 February 2021. Data are entered voluntarily by clinicians or associated healthcare staff; patients are eligible for inclusion if they have a rheumatic and musculoskeletal diseases (RMDs) and have been vaccinated against SARS-CoV-2. As of 27 April 2021, 1519 patients were reported to the registry for a total of 28 countries, with France (60%) and Italy (13%) as the highest contributors. The majority (91%) had inflammatory RMDs. Inflammatory joint diseases accounted for 51% of cases, connective tissue diseases 19%, vasculitis 16%, other immune mediated inflammatory diseases 4%, and non-inflammatory/mechanical RMDs 9%. The most frequent individual diagnoses were rheumatoid arthritis (30%), axial spondyloarthritis (8%), psoriatic arthritis (8%), systemic lupus erythematosus (SLE, 7%) and polymyalgia rheumatica (6%). At the time of vaccination, 45% were taking conventional synthetic DMARDs, 36% biological DMARDs, 31% systemic glucocorticoids, 6% other immunosuppressants (azathioprine; mycophenolate; cyclosporine; cyclophosphamide; tacrolimus), and 3%

targeted synthetic DMARDs. The most frequent individual DMARDs were methotrexate (29%), TNF inhibitors (18%), antimalarials (10%) and rituximab (6%). The vaccines administered were: 78% Pfizer, 16% AstraZeneca, 5% Moderna and 1% other/unknown; 66% of cases received two doses and 34% one dose. Mean time from 1st and 2nd dose to case report was 41 days and 26 days, respectively. COVID-19 diagnosis after vaccination was reported in 1% of cases. Disease flares were reported by 5% of patients with inflammatory RMDs, with 1.2% classified as severe flares (vaccine type was not specified). Mean time from closest vaccination date to inflammatory RMD flare was 5 days (SD 5). The most common flare types were arthritis (2.5%), arthralgia (2.1%), cutaneous flare (0.8%) and increase in fatigue (0.8%). Potential vaccine side effects were reported by 31% of patients. The majority were typical early adverse events within 7 days of vaccination, namely pain at the site of injection (19%), fatigue (11%) and headache (7%). The author conclude that the majority of patients tolerated their vaccination well with rare reports of inflammatory RMD flare (5%; 1.2% severe) and very rare reports of severe adverse events (0.1%).

- Tzioufas A.G et al [15] report a study result that investigated humoral responses and safety of mRNA SARS-CoV-2 vaccines in systemic autoimmune and autoinflammatory rheumatic disease (SAARD) patients subjected or not to treatment modifications during vaccination. From February 1st, 2021, until June 30th, 2021, 2411 SAARD patients were eligible for recruitment in the study of whom 960 patients were enrolled. Among them, 737 had completed vaccination up to June 30th, 2021. Most patients (n = 659) were vaccinated with either Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273 vaccines. Patients with extended treatment modifications responded to vaccines similarly to controls as well as SAARD patients without immunosuppressive therapy (97.56% *vs 100%, p = 0.2468 and 97.56% vs* 97.46%, p > 0.9999, respectively). In contrast, patients with partial or without therapeutic modifications responded in 87.50% and 84.50%, respectively. Furthermore, SAARD patients with extended treatment modifications developed higher anti-SARS-CoV-2 antibody levels compared to those without or with partial modifications (median:7.90 *vs* 7.06 *vs* 7.1, p = 0.0003 and p = 0.0195, respectively). Mycophenolate mofetil (MMF), rituximab (RTX) and methotrexate (MTX) negatively affected anti-SARS-CoV-2 humoral responses. In 10.5% of vaccinated patients, mild clinical deterioration was noted; however, no differences in the incidence of deterioration were observed among the distinct treatment modification SAARD subgroups. Side-effects were generally comparable between SAARD patients and controls. Overall, the authors concluded that SAARD patients, mRNA SARS-CoV-2 vaccines are effective and safe, both in terms of side-effects and disease flares. Treatment with MMF, RTX and/or MTX compromises anti-SARS-CoV-2 antibody responses, which are restored upon extended treatment modifications without affecting disease activity.

- Fan et al [16] conducted a real-world survey to evaluate the safety profiles and disease flare in patients with AIIRDs (autoimmune inflammatory rheumatic diseases) who received any dose of inactivated COVID-19 vaccines in China. From 1 Aug 2021 to 15 Oct 2021, eligible participants completed a predefined 25-question-based

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

- Adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases were studied by Heshin-Bekenstein M et al 2021 and Maritsi D et al 2021. The authors performed a prospective multicenter study and examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. They concluded that BNTb262 mRNA COVID-19 vaccine have excellent safety profile in immunocompromised adolescents with Juvenile-onset AIIRD, with mild post vaccination side effects, similar to the safety profile of the healthy controls. No post vaccination COVID-19 illness was documented. Post vaccination disease activity was mostly kept stable. Details of the studies are reported below.

- Maritsi D et al [18] evaluated the safety and tolerability of the BNT162b2(Pfizer-BioNTech) COVID-19 vaccine in adolescent and young adult patients with juvenile idiopathic arthritis (JIA) on TNFi treatment. Methods: Study population: The study

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

- Heshin-Bekenstein M et al 2021 [17] evaluated the safety and immunogenicity of the BNT162b2 mRNA vaccine in adolescents with AIRD treated with immunosuppressive medications compared with healthy adolescents. The prospective multicenter study examined the safety and immunogenicity of the two-dose regimen BNT162b2 mRNA vaccine in adolescents aged 12-18 years diagnosed with juvenile-onset AIIRD including Juvenile Idiopathic Arthritis (JIA), connective tissues diseases (CTD) including systemic lupus erythematosus (SLE), systemic vasculitides and uveitis. Patients were evaluated 2-10 weeks after the second dose of the vaccine. Overall, 71 adolescents with AIIRD patients and 28 controls from 2 countries, 4 centers, participated in the study. The most common diagnosis in the AIIRD cohort was JIA (N=27), followed by SLE (N=14). The mean disease duration was 5.1±4.48 years (N=70). A total 84.5% (N=60) of the patients were treated with immunomodulatory medications. Post vaccination disease activity remained stable in 96.88% of the adolescents with AIIRD, and post vaccination treatment change was made in the minority of the patients (N=3, 4.84%). Both patients and controls have tolerated the vaccine well, with minimal side effects. There were no severe adverse events in both groups. No post vaccination infection with COVID-19 was documented in both groups. Seropositivity rate was 90.32% in adolescents with AIIRD and 100% in the healthy controls (N=28/31 vs. N=14/14; p=0.54). The level of the S1/S2 antibodies was significantly reduced in adolescents with AIIRD compared to controls.

Multiple sclerosis

Achiron A et al [19] assessed the safety of BNT162b2 COVID-19 vaccination in adult MS patients. Between 20 December 2020 and 25 January 2021, 555 MS patients received the first dose of BNT162b2 vaccine and 435 received the second dose. Safety profile of COVID-

19 vaccine was characterized by pain at the injection site, fatigue, and headache. No increased risk of relapse activity was noted over a median follow-up of 20 and 38 days after first and second vaccine doses, respectively. The rate of patients with acute relapse was 2.1% and 1.6% following the first and second doses, respectively, like the rate in non-vaccinating patients during the corresponding period. Mild increase in the rate of adverse events was noted in younger patients (18-55 years), among patients with lower disability (Expanded Disability Status Scale (EDSS) ⩽3.0), and in patients treated with immunomodulatory drugs. The authors concluded that overall COVID-19 BNT162b2 vaccine proved safe for MS patients and no increased risk of relapse activity was noted.

SLE

Izmirly PM et al [20] performed a study to analyze possible fares in SLE patients and healthy controls receiving a complete COVID-19 vaccine regimen (vaccine used: mRNA-both Moderna and Pfizer/BioNtech- and J&J). A total of 90 SLE patients and 20 healthy controls receiving a complete COVID-19 vaccine regimen were included. Overall, 11.4% of patients had a post-vaccination flare. In a multi-ethnic/racial study of SLE patients 29% had a low response to the COVID-19 vaccine which was associated with being on immunosuppression. Reassuringly, disease flares were rare. The author further underline that in aggregate analysis, despite apprehensions, the data presented did not support significantly increased anti-dsDNA autoantibody production or flares post-vaccination. Moreover, these results are consistent with a recent study which showed the majority of vaccinated SLE patients had no change or decrease in disease activity after COVID-19 vaccination as measured by Furer et al [12].

Tang et al [21] published a review on patients with SLE and concludes that AIIRD patients are not at greater risk of disease fares nor have a higher incidence of side effects following vaccination. There is no significant safety concern for the use of COVID-19 vaccines in patients with AIIRD and benefits of vaccination far outweigh the risks in patients with AIIRD, including SLE.

Felten R et al [22] performed a study where the primary objective was to assess the tolerance of COVID-19 vaccines in patients with SLE, including the risk of incident flare, from the patients' perspective (international vaccination against COVID in systemic lupus (VACOLUP) study). VACOLUP was a cross-sectional study based on a 43-question web-based survey, which took place between March 22, 2021, and May 17, 2021. The study included 696 participants from 30 countries. All patients received at least one dose of vaccine and 343 (49%) patients received a second dose. The most common vaccines were Pfizer-BioNTech (399 [57%] participants), Sinovac (156 [22%] participants), AstraZeneca (73 [10%] participants), and Moderna (57 [8%]). Side-effects were reported by 316 (45%) patients after the first vaccine dose and by 181 (53%) of 343 patients after the second vaccine dose, with no difference according to gender, age, or vaccine type. Patients who received both vaccine doses and reported side-effects after the first dose were more likely to report side-effects after the second dose than those who did not. An important finding of the study is that side-effects after COVID-19 vaccination in patients with SLE are common (around 50%) but do not impair daily functioning in most cases. No difference were found in the

occurrence of side-effects after receipt of mRNA vaccines compared with vaccines with other modes of action. The number of medically confirmed flares reported after COVID-19 vaccination was low. The short median time between vaccination and flare onset suggests that it might be difficult to distinguish actual SLE flares from common and expected post-vaccine side-effects, and therefore the 3% figure could be an overestimation of the actual flare rate. Vaccination is recommended for patients with rheumatic and musculoskeletal diseases according to the American College of Rheumatology, irrespective of disease activity and severity, except for those with severe and life-threatening illness (e.g., a patient receiving treatment in the intensive care unit for any condition). In conclusion, the VACOLUP study suggests that COVID-19 vaccination appears well tolerated in patients with SLE, with only a minimal risk of flare, if any, including after the mRNA vaccines.

Zavala-Flores E et al [23] studied post SARS-CoV-2 vaccine BNT162b2 (BioNTech & Pfizer) side effects in patients with systemic lupus erythematosus (SLE) immunized with the BNT162b2 vaccine from May 21 to June 30, 2021 performing a descriptive observational study. Of the total number of patients seen in the service, 100 received the vaccine's 1st dose, and 90 patients received the 2nd dose; 90% and 92.2% presented symptoms within 10 days after immunization (1st and 2nd doses, respectively), being pain at the inoculation site the most frequent (87%); most of the symptoms presented were of mild intensity. There were 27 episodes of post-immunization flare, 9% and 20% after the 1st and 2nd doses, respectively; the predominant type of flare was articular (85.1%), followed by dermal (18.5%). It was found that a history of renal involvement was associated with the risk of developing flare RR 0.38 (0.15–0.91) and the use of hydroxychloroquine and azathioprine prior to immunization 0.20 (0.06–0.63) and 7.96 (2.70–23.43) respectively. In 100 SLE patients immunized with BNT162b2 vaccine against SARS-CoV-2, 27% of SLE reactivation episodes occurred, two patients were hospitalized for flare severity, and none died. This study report similar results to those reported by Izmirly et al. who reported, in a multiethnic study, up to 11.5% of flare episodes in patients with lupus after SARS-Cov-2 immunization.

In addition, Sen, P et al [24] have designed a specific protocol to analyze efficacy and safety data of COVID-19. The study proposed is an ongoing international collaborative study involving 29 countries and over 110 investigators protocol of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study. The result of the study will shed additional light on the safety profile of COVID-19 vaccines available in the market in patients with autoimmune diseases.

7. SUMMARY AND CONCLUSION

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

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

It should be taken into consideration that some autoimmune diseases treatments, specifically immunomodulatory therapy (methotrexate, Jak inhibitor, abatacept, rituximab and cyclophosphamide), are recommended from American college of rheumatology guidance guidelines to be discontinued shortly before vaccination. Clearly this temporary discontinuation may influence a temporary flare up of the underlying autoimmune disease [25] due to change of immunomodulatory therapy rather than vaccination

Pfizer clinical study results do not demonstrate an imbalance between placebo and vaccine.

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

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

APPENDIX 1: MEDICAL HISTORY OF AUTOIMMUNE DISEASE IN PHASE 2/3 SUBJECTS ≥16 YEARS OF AGE SAFETY POPULATION

Table 4. Medical History – Autoimmune Disease – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21926)	Placebo (N[a]=21921)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)
Any medical history	2955 (13.5)	2977 (13.6)
Blood and lymphatic system disorders	17 (0.1)	21 (0.1)
Antiphospholipid syndrome	4 (0.0)	5 (0.0)
Haemolytic anaemia	0	3 (0.0)
Immune thrombocytopenia	6 (0.0)	10 (0.0)
Pernicious anaemia	7 (0.0)	2 (0.0)
Thrombotic thrombocytopenic purpura	0	1 (0.0)
Cardiac disorders	8 (0.0)	5 (0.0)
Cardiac amyloidosis	1 (0.0)	0
Myocarditis	2 (0.0)	0
Pericarditis	5 (0.0)	5 (0.0)
Endocrine disorders	1905 (8.7)	1964 (9.0)
Addison's disease	1 (0.0)	1 (0.0)
Autoimmune hypothyroidism	2 (0.0)	2 (0.0)
Autoimmune thyroiditis	73 (0.3)	58 (0.3)
Basedow's disease	28 (0.1)	22 (0.1)
Endocrine disorder	1 (0.0)	1 (0.0)
Hyperthyroidism	93 (0.4)	88 (0.4)
Hypothyroidism	1729 (7.9)	1808 (8.2)
Immune-mediated thyroiditis	0	1 (0.0)
Thyroid disorder	12 (0.1)	5 (0.0)
Thyroiditis	5 (0.0)	3 (0.0)
Eye disorders	8 (0.0)	9 (0.0)
Cogan's syndrome	0	1 (0.0)
Endocrine ophthalmopathy	0	1 (0.0)
Ocular pemphigoid	1 (0.0)	0
Optic neuropathy	1 (0.0)	1 (0.0)
Retinopathy	2 (0.0)	1 (0.0)

Table 4. Medical History – Autoimmune Disease – Phase 2/3 Subjects ⩾16 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21926)	Placebo (N[a]=21921)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)
Ulcerative keratitis	0	1 (0.0)
Uveitis	4 (0.0)	4 (0.0)
Gastrointestinal disorders	163 (0.7)	170 (0.8)
Chronic gastritis	13 (0.1)	19 (0.1)
Coeliac disease	45 (0.2)	49 (0.2)
Colitis	10 (0.0)	10 (0.0)
Colitis microscopic	8 (0.0)	7 (0.0)
Colitis ulcerative	24 (0.1)	28 (0.1)
Crohn's disease	17 (0.1)	16 (0.1)
Enteritis	1 (0.0)	0
Eosinophilic oesophagitis	10 (0.0)	9 (0.0)
Inflammatory bowel disease	2 (0.0)	5 (0.0)
Oesophageal achalasia	3 (0.0)	5 (0.0)
Oral lichen planus	1 (0.0)	2 (0.0)
Pancreatitis	28 (0.1)	18 (0.1)
Proctitis ulcerative	2 (0.0)	3 (0.0)
Hepatobiliary disorders	3 (0.0)	5 (0.0)
Cholangitis sclerosing	2 (0.0)	0
Hepatitis	0	4 (0.0)
Primary biliary cholangitis	1 (0.0)	1 (0.0)
Immune system disorders	15 (0.1)	17 (0.1)
Amyloidosis	1 (0.0)	1 (0.0)
Anti-neutrophil cytoplasmic antibody positive vasculitis	1 (0.0)	0
Autoinflammatory disease	1 (0.0)	0
Sarcoidosis	12 (0.1)	16 (0.1)
Infections and infestations	6 (0.0)	2 (0.0)
Encephalitis	4 (0.0)	2 (0.0)
Encephalomyelitis	1 (0.0)	0
Subacute endocarditis	1 (0.0)	0
Investigations	2 (0.0)	1 (0.0)

Table 4. Medical History – Autoimmune Disease – Phase 2/3 Subjects ⩾16 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21926)	Placebo (N[a]=21921)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)
Anti-platelet antibody positive	1 (0.0)	0
Anti-thyroid antibody positive	1 (0.0)	0
Antinuclear antibody positive	0	1 (0.0)
Metabolism and nutrition disorders	125 (0.6)	109 (0.5)
Diabetes mellitus	30 (0.1)	21 (0.1)
Diabetic ketoacidosis	1 (0.0)	3 (0.0)
Latent autoimmune diabetes in adults	1 (0.0)	0
Type 1 diabetes mellitus	94 (0.4)	86 (0.4)
Musculoskeletal and connective tissue disorders	349 (1.6)	334 (1.5)
Ankylosing spondylitis	8 (0.0)	7 (0.0)
Arthritis	243 (1.1)	232 (1.1)
Autoimmune arthritis	1 (0.0)	0
CREST syndrome	1 (0.0)	1 (0.0)
Inclusion body myositis	1 (0.0)	1 (0.0)
Juvenile idiopathic arthritis	2 (0.0)	2 (0.0)
Mixed connective tissue disease	2 (0.0)	0
Morphoea	1 (0.0)	1 (0.0)
Myositis	2 (0.0)	1 (0.0)
Polymyalgia rheumatica	7 (0.0)	3 (0.0)
Psoriatic arthropathy	5 (0.0)	6 (0.0)
Reynold's syndrome	1 (0.0)	0
Rheumatic disorder	1 (0.0)	1 (0.0)
Rheumatoid arthritis	42 (0.2)	34 (0.2)
Scleroderma	2 (0.0)	2 (0.0)
Sjogren's syndrome	5 (0.0)	7 (0.0)
Spondylitis	25 (0.1)	35 (0.2)
Spondyloarthropathy	5 (0.0)	1 (0.0)
Systemic lupus erythematosus	5 (0.0)	4 (0.0)
Undifferentiated connective tissue disease	0	1 (0.0)
Nervous system disorders	263 (1.2)	249 (1.1)
Anosmia	7 (0.0)	6 (0.0)
Autoimmune encephalopathy	1 (0.0)	0

Table 4. Medical History - Autoimmune Disease - Phase 2/3 Subjects ⩾16 Years of Age - Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21926)	Placebo (N[a]=21921)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)
Autonomic nervous system imbalance	0	2 (0.0)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	3 (0.0)
Cranial nerve disorder	0	1 (0.0)
Demyelination	1 (0.0)	0
Encephalopathy	0	3 (0.0)
Facial paresis	1 (0.0)	0
Guillain-Barre syndrome	1 (0.0)	1 (0.0)
Hashimoto's encephalopathy	0	1 (0.0)
IVth nerve paralysis	2 (0.0)	0
Mononeuritis	0	1 (0.0)
Multiple sclerosis	3 (0.0)	6 (0.0)
Myasthenia gravis	3 (0.0)	4 (0.0)
Narcolepsy	11 (0.1)	18 (0.1)
Neuralgic amyotrophy	1 (0.0)	0
Neuritis	1 (0.0)	2 (0.0)
Neuropathy peripheral	222 (1.0)	202 (0.9)
Optic neuritis	3 (0.0)	1 (0.0)
Radiculitis brachial	1 (0.0)	1 (0.0)
Relapsing multiple sclerosis	1 (0.0)	0
Stiff person syndrome	0	1 (0.0)
VIth nerve paralysis	2 (0.0)	0
Vocal cord paralysis	3 (0.0)	1 (0.0)
Vocal cord paresis	1 (0.0)	0
Renal and urinary disorders	17 (0.1)	18 (0.1)
Cystitis interstitial	14 (0.1)	10 (0.0)
Glomerulonephritis	0	1 (0.0)
Glomerulonephritis membranous	1 (0.0)	2 (0.0)
IgA nephropathy	1 (0.0)	1 (0.0)
Lupus nephritis	0	1 (0.0)
Nephritis	1 (0.0)	3 (0.0)
Reproductive system and breast disorders	11 (0.1)	5 (0.0)
Premature menopause	11 (0.1)	5 (0.0)

Table 4. Medical History - Autoimmune Disease - Phase 2/3 Subjects ⩾16 Years of Age - Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=21926) n[b] (%)	Vaccine Group (as Administered) Placebo (N[a]=21921) n[b] (%)
Respiratory, thoracic and mediastinal disorders	7 (0.0)	11 (0.1)
Idiopathic pulmonary fibrosis	0	2 (0.0)
Interstitial lung disease	2 (0.0)	1 (0.0)
Pulmonary fibrosis	5 (0.0)	7 (0.0)
Pulmonary sarcoidosis	0	1 (0.0)
Skin and subcutaneous tissue disorders	247 (1.1)	246 (1.1)
Alopecia areata	3 (0.0)	4 (0.0)
Chronic spontaneous urticaria	2 (0.0)	7 (0.0)
Cutaneous amyloidosis	0	1 (0.0)
Cutaneous lupus erythematosus	1 (0.0)	4 (0.0)
Dermatitis	43 (0.2)	29 (0.1)
Dermatomyositis	1 (0.0)	2 (0.0)
Erythema multiforme	0	1 (0.0)
Henoch-Schonlein purpura	1 (0.0)	0
Lichen planopilaris	0	1 (0.0)
Lichen planus	6 (0.0)	7 (0.0)
Lichen sclerosus	8 (0.0)	10 (0.0)
Palmoplantar keratoderma	1 (0.0)	0
Pityriasis lichenoides et varioliformis acuta	0	1 (0.0)
Psoriasis	153 (0.7)	157 (0.7)
Stevens-Johnson syndrome	1 (0.0)	1 (0.0)
Vitiligo	27 (0.1)	21 (0.1)
Vascular disorders	30 (0.1)	42 (0.2)
Giant cell arteritis	0	2 (0.0)
Kawasaki's disease	1 (0.0)	0
Raynaud's phenomenon	28 (0.1)	40 (0.2)
Vasculitis	1 (0.0)	0

Note: MedDRA (v23.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences of the same preferred term are counted only once.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:25) Source Data: admh Table Generation:

Table 4. Medical History – Autoimmune Disease – Phase 2/3 Subjects ⩾16 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21926)	Placebo (N[a]=21921)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)

01OCT2021 (15:21)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File:
./nda2_unblinded/C4591001_BLA_RR/admh_s002_all_p3_aid

REFERENCES

1. Ishay, Y., et al., *Autoimmune phenomena following SARS-CoV-2 vaccination.* Int Immunopharmacol, 2021. **99**: p. 107970.
2. Geisen, U.M., et al., *Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort.* Ann Rheum Dis, 2021. **80**(10): p. 1306-1311.
3. Wack, S., T. Patton, and L.K. Ferris, *COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: Review of available evidence.* J Am Acad Dermatol, 2021. **85**(5): p. 1274-1284.
4. Rotondo, C., et al., *Preliminary Data on Post Market Safety Profiles of COVID 19 Vaccines in Rheumatic Diseases: Assessments on Various Vaccines in Use, Different Rheumatic Disease Subtypes, and Immunosuppressive Therapies: A Two-Centers Study.* Vaccines (Basel), 2021. **9**(7).
5. Sattui, S.E., et al., *Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey.* RMD Open, 2021. **7**(3).
6. Barbhaiya M, L.J., Bykerk VP, et al, *Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City.* Ann Rheum Dis, 2021. **80**: p. 1352-1354.
7. M. Yang, P.K., D. Paez, A. Carvidi, M. Matloubian, M. Nakamura, L. S. Gensler, *REACTOGENICITY OF SARS-COV-2 VACCINES IN PATIENTS WITH AUTOIMMUNE AND INFLAMMATORY DISEASE.* Ann Rheum Dis, 2021.
8. Bixio, R., et al., *Incidence of Disease Flare After BNT162b2 Coronavirus Disease 2019 Vaccination in Patients With Rheumatoid Arthritis in Remission.* ACR Open Rheumatol, 2021. **3**(12): p. 832-833.
9. Watad, A., et al., *Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination.* Vaccines (Basel), 2021. **9**(5).
10. Alfayadh, N.M., et al., *Vaccinations Do Not Increase Arthritis Flares in Juvenile Idiopathic Arthritis: A Study of the Relationship between Routine Childhood Vaccinations on the Australian Immunisation Schedule and Arthritis Activity in Children with Juvenile Idiopathic Arthritis.* Int J Rheumatol, 2020. **2020**: p. 1078914.
11. Boekel, L., et al., *Adverse events after first COVID-19 vaccination in patients with autoimmune diseases.* The Lancet Rheumatology, 2021. **3**(8): p. e542-e545.
12. Furer, V., et al., *Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study.* Ann Rheum Dis, 2021. **80**(10): p. 1330-1338.
13. Connolly, C.M., et al., *Disease Flare and Reactogenicity in Patients With Rheumatic and Musculoskeletal Diseases Following Two-Dose SARS-CoV-2 Messenger RNA Vaccination.* Arthritis Rheumatol, 2022. **74**(1): p. 28-32.
14. Machado, P.M., et al., *Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry.* Ann Rheum Dis, 2021.
15. Tzioufas, A.G., et al., *A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with*

systemic autoimmune and autoinflammatory rheumatic diseases. J Autoimmun, 2021. **125**: p. 102743.

16. Fan, Y., et al., *Safety and disease flare of autoimmune inflammatory rheumatic diseases: a large real-world survey on inactivated COVID-19 vaccines.* Ann Rheum Dis, 2021.
17. Heshin-Bekenstein, M., et al., *Safety and immunogenicity of the BNT162B2 mRNA COVID-19 vaccine in adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases.* Pediatric Rheumatology 2021. **19** (SUPPL 1).
18. Maritsi, D., et al., *Safety and tolerability of the biontech COVID-19 vaccine in adolescent patients with JIA on TNFi.* Pediatric Rheumatology 2021. **19** (SUPPL 1).
19. Achiron, A., et al., *COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by February 2021.* Mult Scler, 2021. **27**(6): p. 864-870.
20. Izmirly, P.M., et al., *Evaluation of Immune Response and Disease Status in Systemic Lupus Erythematosus Patients Following SARS-CoV-2 Vaccination.* Arthritis Rheumatol, 2021.
21. Tang, W., et al., *The Use of COVID-19 Vaccines in Patients with SLE.* Curr Rheumatol Rep, 2021. **23**(11): p. 79.
22. Felten, R., et al., *Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study.* The Lancet Rheumatology, 2021. **3**(9): p. e613-e615.
23. Zavala-Flores, E., et al., *Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus.* Clin Rheumatol, 2021.
24. Sen, P., et al., *COVID-19 vaccination in autoimmune disease (COVAD) survey protocol.* Rheumatol Int, 2021.
25. Curtis, J.R., et al., *American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1.* Arthritis Rheumatol, 2021. **73**(7): p. 1093-1107.

APPENDIX 6A.2 CHRONIC URTICARIA/WORSENING OF PRE-EXISTING CHRONIC URTICARIA

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AER	Adverse Event Report
CDS	Core Data Sheet
CSP	Core Safety Profile
DLP	Data Lock Point
EMA	European Medicines Agency
FDA	(US) Food and Drug Administration
HA	Health Authority
HLT	(MedDRA) High Level Term
IBD	International Birth Date
LLT	(MedDRA) Lowest Level Term
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PT	(MedDRA) Preferred Term
RSI	Reference Safety Information
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	(MedDRA) System Organ Class

1. INTRODUCTION

In the PSUR Assessment Report (Procedure No. EMEA/H/C/PSUSA/00010898/202106), the PRAC requested the MAH to address the following issue in the next PSUR:

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

An overview of what is the Chronic urticaria (CU) state of art and literature analysis of CU and covid-19 infection and vaccination is reported below.

Urticaria, more commonly known as "hives", is a prevalent disorder that affects between 15 and 25% of the population at some point during their lifetimes. The condition tends to be more common in adults than in children and in woman than in men with peak occurrence in the third to fifth decades of life. This condition is marked by the onset of pruritic "wheals," which represent well-circumscribed areas of non-pitting edema with blanched centers and raised borders that involve only the superficial portions of the dermis and are seen in conjunction with surrounding erythema of the skin. Lesions can be as small as a few millimeters in diameter but can coalesce to form wheals as large as several centimeters wide. They often remit within 24 h since time of onset. Urticaria is classified as either acute or chronic (CU) depending on whether the onset of episodes lasts for less or >6 weeks in duration, respectively.[1]

CU can occur in response to drugs, physical stimuli, as part of inflammatory or inherited diseases, or can be idiopathic in nature. Chronic idiopathic urticaria is the most common type of CU, comprising up to 90% of all cases of CU. CU generally lasts 1 to 5 years but can have a prolonged course beyond 5 years in roughly 14% of patients. Individuals affected by CU have reported emotional distress, feelings of isolation and fatigue in response to their condition, like findings in patients with ischemic heart disease [2].

Currently, it is thought that up to 50% of CU is caused by autoimmune mechanisms. Autoantibodies to the high affinity IgE receptor are the most commonly identified offender, activating mast cells, basophils, and the complement system, resulting in the wheal and flare reaction. CU is hypothesized to occur because of a predisposition in the patient to develop autoimmune diseases. In concordance with this hypothesis, additional autoimmune diseases are observed in patients with CU. Thyroid disease, particularly hypothyroidism, is the most common additional autoimmune disease diagnosed. Furthermore, thyroid disease may directly exacerbate CU severity by activating the complement system Other autoimmune diseases that occur more frequently in patients with CU include rheumatoid arthritis, systemic lupus erythematosus, vitiligo, pernicious anemia, celiac disease, and Sjörgen's syndrome. In case reports, CU has been identified as part of a larger autoimmune phenotype. These associations support the theory that patients who develop CU do so because of an innate propensity to mount autoimmune reactions.[2]

Triggers of CSU can be identified in 10–20% of cases. These include stress, environmental conditions, medications, physical stimuli, infections, or autoantibodies.[3]

Prevalence of chronic urticaria is estimated to be anywhere from 0.5 to 5% in the general population but is not truly known, though incidence is thought to fall around 1.4% annually.

COVID-19 and chronic urticaria

The COVID-19 pandemic dramatically disrupts health care around the globe. Chronic urticaria (CU) frequently compromises patients' quality of life and stress can be a major factor. This becomes even more important in the current worldwide COVID-19 pandemic scenario.
Kocaturk E et al[4] evaluated the impact of the pandemic on chronic urticaria (CU) and its management with a cross-sectional, international, questionnaire-based, multicenter UCARE COVID-CU study aimed to assess the impact of the pandemic on patient consultations, remote treatment, changes in medications, and clinical consequences. Their results show that COVID-19 pandemic severely impairs CU patient care, with less than 50% of the weekly numbers of patients treated as compared to before the pandemic as almost half of responding UCARE physicians were involved in COVID-19 patient care, which negatively impacted on the care of urticaria patients. The rate of face-to-face consultations decreased by 62%. Cyclosporine and systemic corticosteroids, but not antihistamines or omalizumab, are used less during the pandemic. CU does not affect the course of COVID-19, but COVID-19 results in CU exacerbation in one of three patients, with higher rates in patients with severe COVID-19. The authors warned that long-term consequences of these changes, especially the increased use of remote consultations, require careful evaluation.

During the pandemic, patients' adherence to therapy has reduced due to both government-related and patient-related reasons. For patients with chronic urticaria, their adherence to therapy should be ensured by minimizing the risk of transmission of SARS-CoV-2.[5] Actually, there was not a scientific reason not to adhere to the therapy, and study from Koc Yildirim S et al showed trough a retrospective evaluation study of patients with chronic spontaneous urticaria using omalizumab during the COVID-19 pandemic that omalizumab treatment in CU patients during the COVID-19 pandemic does not increase the risk of COVID-19 infection and omalizumab can be used safely. Similar results were confirmed also from other literature articles[6,7,8]

Argolo et al performed a retrospective study including 140 patients and collected data from electronic medical records of patients with CU from April to July, 2020. Nervousness was reported by 80 patients (57.1%), of which 30% reported worsening of urticaria. The use of corticosteroids was more frequent among patients with emotional stress due to the pandemic (20%). Obesity was the other comorbidity most frequently seen in these patients with CU (35%). Of the 22 patients who visited the Emergency Room, 9 (40.9%), only five patients underwent specific investigation to COVID-19 and 2 (22.2%) of them tested positive. The author concluded that during the COVID-19 pandemic, CU patients presented more frequently new episodes of emotional stress and these were a factor associated with worsening urticaria and greater use of corticosteroids.[9]

Covid-19 vaccination and Chronic urticaria

Magen e et al studied the clinical cases of patients with new-onset Chronic spontaneous urticaria (CSU) and CSU in remission who relapsed within 3 months after BNT162b2 mRNA vaccination. All patients with a CSU diagnosis within 12 weeks of BNT162b2 mRNA vaccination were retrospectively identified and included in the new-onset CSU and the relapsed CSU groups. The first control group (CSU control group) retrospectively consisted of patients diagnosed with CSU in complete clinical remission for ≥ 6 months, with no CSU relapse after vaccination. The second control group (healthy control group) consisted of subjects who were fully vaccinated and without CSU, matched 1:2 for age and sex with patients with CSU. Twenty-seven patients were included in the relapsed CSU group, 32 patients in the new-onset CSU group, 179 patients in the CSU control group, and 476 subjects in the healthy control group. The relapsed CSU and new-onset CSU groups had more allergic comorbidities overall (19 [70.4%] and 13 [40.6%], respectively) than the CSU control group and the healthy control group (50 [27.9%] and 110 [23.1%], respectively; $p < 0.001$). Multiple logistic regression analysis showed that a positive autologous serum skin test result, overall allergic comorbidities, and basopenia were positively associated with the probability of CSU relapse within 3 months after BNT162b2 mRNA vaccination. The authors concluded that is possible that BNT162b2 mRNA vaccination serves as a provoking and/or relapsing factor of CSU in individuals with allergic diseases and/or predisposed autoimmunity.[10]

Alflen C et al reported two cases of CU that reported a flare after Moderna Covid-19 vaccine administration. The first case was a 49-year-old male who presented with a history of chronic spontaneous urticaria for the past twenty-eight years and his exacerbating factors include warm temperatures and sunlight, or spontaneously without evident trigger. The patient was being treated with omalizumab (Xolair) and 16 hours after the second dose of the Moderna COVID19 vaccine, the patient had a flare of urticaria identical to previous episodes (Alflen C et al 2021). The second case was a 74-year-old female who presented with a past medical history of allergic rhinitis and chronic spontaneous urticaria. The patient's CSU symptoms include angioedema of the upper lip. The patient had spontaneous angioedema for multiple years until her symptoms became controlled with a first generation H1 antihistamine. About 30 minutes after first dose of Moderna vaccine the subject experienced upper lip swelling and resolved within 30 minutes without pharmacological intervention.[11]

Brook GS et al presented a case of COVID-19 vaccine that induced chronic spontaneous urticaria (CSU) triggered by the AstraZeneca/Oxford COVID-19 vaccine in a patient with no history of CSU. A 60-year-old male with environmental allergies (potential anaphylactic reaction to immunotherapy for his environmental allergies over 30 years ago) and a history of asthma and received the first dose of the AstraZeneca/Oxford COVID-19 vaccine and five days later he developed erythema on his palms and cheeks followed by a pruritic rash on his scalp, face, neck, shoulders and armpits. He was recommended the use of an antihistamine followed by corticosteroid cream without success. The patient was seen in an allergy and immunology clinic and was diagnosed with CSU.[12]

2. METHODOLOGY

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality. The safety database was searched for all cases cumulatively to 18 December 2021 using MedDRA 24.1. the search was performed in 2 steps:

All cases reporting the PT: urticaria Chronic in the medical history

All cases retrieved from the previous listing were selected for the PT urticaria chronic as adverse event.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

3. RESULTS

3.1. Post Marketing Data

A total of 497 cases reported Chronic urticaria in the medical history. Fifteen cases among the 497 reported an adverse event of chronic urticaria. There were 11 females and 4 males. Age was reported as ranging from 21 to 73 years of age (mean: 43.3 years). Most cases (12) were reported by adults (≥ 18-<65 years) and 2 cases were reported by elderly (≥65) subjects.

Most cases were reported from United Kingdom (6) followed by France, Japan (2 cases each), Germany (1 case) and Lithuania (1 case). Ten cases were reported as non-serious and 5 as serious. Ten cases were not medically confirmed and 5 were medically confirmed. Eight

cases did not report concomitant medication, the other cases reported either antihistamine and/or corticosteroid therapy.

Four cases reported the flare after the 1st vaccine dose, 4 after the 2nd vaccine dose, 2 after the 3rd booster dose and the dose number was not reported for 5 cases.

Time to onset was reported for 11 cases and ranged between the same vaccination day to 16 days after vaccination (one additional case reported it as few days after vaccination and from the date may be from day 1-5). Time to onset was reported as:

- same vaccination day: 6 cases
- day 1-2: 2 cases
- day 6: 1 case
- day 10: 1 case
- day 16: 1 case

Details on the 15 relevant cases are provided beow:

AER Number Age/Sex Country	Dose / Time to onset	Medical History Concomitant medication	Events
[redacted] 47/M [redacted]	Dose 2/Not reported	Relapsing multiple sclerosis / Rheumatoid arthritis / Urticaria chronic Cortisone / glatiramer acetate	Relapsing multiple sclerosis, Urticaria chronic, Disease recurrence
[redacted] 23/F [redacted]	Dose 2/ same vaccination day	Fexofenadine / prednisolone	Hypersensitivity, Urticaria, Urticaria chronic, Condition aggravated, Dermatitis allergic, Vaccination site urticaria
[redacted] 32/F [redacted]	Dose 2/10 days	Suppressed lactation / Urticaria chronic Fexofenadine	Peripheral swelling, Urticaria chronic
[redacted] 61/M [redacted]	Dose 2/ same vaccination day	Hypertension / Urticaria chronic Not reported	Urticaria chronic
[redacted] 26/F [redacted]	Unknown/ 1	Asthma / Urticaria chronic Not reported	Angioedema, Urticaria chronic, Dizziness, Nausea, Pyrexia, Headache, Lip swelling, swelling face, Swelling
[redacted] 56/F [redacted]	Dose 3/ same vaccination day	Idiopathic angioedema / Immunodeficiency / Urticaria chronic Fexofenadine / omalizumab	Off label use, Interchange of vaccine products, Immunisation, Swelling, Lip swelling, Swelling face, Urticaria chronic
[redacted] 60/F [redacted]	Dose 1/unknown	Back pain / Inguinal hernia / Osteoarthritis / Osteoporosis / Urticaria chronic	Disease recurrence, Urticaria chronic
[redacted]	Dose 3/ same	Urticaria chronic	Off label use, Interchange of

AER Number Age/Sex Country	Dose / Time to onset	Medical History Concomitant medication	Events
46/F [redacted]	vaccination day	Not reported	vaccine products (Patient exhibited flare-up of her chronic urticaria during a previous vaccination with SPIKEVAX), Immunisation, Disease recurrence, Urticaria chronic, Influenza like illness, Vaccination site pain
[redacted] 36/F [redacted]	Unknown/unknown	Migraine / Suppressed lactation / Urticaria chronic Not reported	Migraine, Urticaria chronic
[redacted] 71/F [redacted]	Unknown/2	Urticaria / Urticaria chronic Fexofenadine / gabapentin	Vaccination site erythema, Vaccination site pruritus, Urticaria chronic, Urticaria
[redacted] 34/F [redacted]	Dose 1/ same vaccination day	Dermatitis contact / Migraine / Urticaria chronic Not reported	Anaphylactic reaction, Lip swelling, Pruritus, Urticaria chronic
[redacted] 21/M [redacted]	Unknown /few days	Idiopathic angioedema / Urticaria chronic Beclometasone / cetirizine	Rash, Urticaria, Dermatitis, Pain, Urticaria chronic, Condition aggravated
[redacted] 73/F [redacted]	Dose 1/6	Angioedema / Urticaria chronic Not reported	Angioedema, Rash, Oedema peripheral, Urticaria, Disease recurrence, Eyelid oedema, Urticaria chronic
[redacted] 39/M [redacted]	Unknown/16	Urticaria chronic Not reported	Urticaria chronic
[redacted] 30/F [redacted]	Dose 1/same vaccination day	Food allergy / Urticaria chronic Not reported	Urticaria chronic

3.2. Clinical Trial Data

Phase 2/3 Study C4591001 placebo-controlled unblinded adverse events in participants 16 years and older from dose 1 to 1 month after dose 2 (data cutoff date 13 March 2021) was also reviewed for the adverse event Chronic urticaria. In the Phase 2/3 safety population, Chronic Urticaria was reported in 0 of 21926 participants in the BNT162b2 group compared with 0 of 21921 participants in the placebo group. Four subjects reported Chronic urticaria in the medical history and none of these subjects reported a flare up of the underlying disease.

4. SUMMARY AND CONCLUSION

A total of 15 cases reported chronic urticaria relapse in subject that presented chronic urticaria as underlying disease. Eight among the 11 cases reporting the time to onset report a time to onset ranging from the same vaccination day to 2 days after vaccination suggesting

an allergic reaction to vaccine more than a relapse of chronic urticaria. This is evident also in some literature cases reported where the symptoms (lips edema) appeared 30 minutes after vaccination and disappear within half an hour (Alflen C et al 2021).

As mentioned in the introduction section, there has been hesitancy to vaccination for the patients with underlying Chronic urticaria. In addition, low adherence to therapy, nervousness as well as worsening of urticaria was frequently reported in these patients. Overall, during the COVID-19 pandemic, CU patients presented more frequently new episodes of emotional stress and these were a factor associated with worsening urticaria and greater use of corticosteroids. Overall, the number of cases reporting a relapse of chronic urticaria is low and the short time to onset suggest more an allergic response to the vaccine.

Urticaria is recognized as a causally associated reaction to BNT162b2. Based on the abundance of literature regarding the stress induced by the SARS-CoV-2 pandemic and chronic urticaria and given the very low number of cases (15) reporting a worsening of CU after more than 2 billion doses of BNT162B2 administered worldwide, CU is not considered a signal and safety updates to the product information and/or the risk management plan are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored with routine pharmacovigilance.

5. REFERENCES

1 Bracken SJ, Abraham S, MacLeod AS Autoimmune theories of chronic spontaneous urticaria. Frontiers in Immunology. March 2019;10: article 627

2 Fraser K, Robertson L Chronic urticaria and autoimmunity.. Skin Therapy Lett. 2013 Nov-Dec;18(7):5-9.

3 Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid- Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. Clin Rev Allergy Immunol. 2018;54(1):88–101

4 Kocaturk E et al The global impact of the COVID-19 pandemic on the management and course of chronic urticaria.

5 Aytekin G., Atayik E The effect of COVID-19 pandemic on treatment compliance and process of chronic urticaria patients receiving omalizumab treatment

6 Ayhan E, Ozturk M, An I, BekcIbasi M COVID-19 infection under omalizumab therapy for chronic spontaneous urticaria: three cases. International Journal of Dermatology. 60(2):253-254, 2021 Feb

7 Bostan E et al. The effect of COVID-19 on patients with chronic spontaneous urticaria treated with omalizumab and antihistamines: A cross-sectional, comparative study. Journal of Cosmetic Dermatology. 20(11):3369-3375, 2021 Nov

8 Abrahim Abduelmula et al Incidence of COVID-19 in Patients With Chronic Idiopathic Urticaria and Asthma on Omalizumab: A Multicentre Retrospective Cohort Study. J Cutan Med Surg. 2021 Sep 29

9 Argolo P., Pereira G., Pereira G.F., Kalil J., Motta A., Agondi R. Clinical conditions of patients with chronic urticaria during the pandemic caused by the 2019 Novel Coronavirus Disease (COVID-19).

10 Magen E, Yakov A, Green I, et al. Chronic spontaneous urticari after BNT162b2 mRNA (Pfizer-BioNTech) vaccination against SARS-CoV-2. Allergy Asthma Proc. January 2022; 43 (1):30-36.

11 Alfeln C, Birch K, Shilian R, et al. Two cases of well controlled chronic spontaneous urticaria triggered by the Moderna COVID-19 vaccine. Allergy & Rhinology. 12: 1-3, 2021.

12 Brooks S.G et al Chronic Spontaneous Urticaria Triggered by the AstraZeneca/Oxford COVID-19 Vaccine with Achieved Remission: A Case Report. Allergy & Rhinology Volume 13: 1–2 2022

APPENDIX 6A.3 POLYMYALGIA RHEUMATICA CUMULATIVE REVIEW

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

COVID-19	Coronavirus Disease 2019
MedDRA	Medical Dictionary for Regulatory Activities
PMR	Polymyalgia Rheumatica
CRP	C-reactive protein
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Coronavirus-2; virus causing the disease COVID-19
SMQ	Standardized MedDRA query
ESR	Erythrocyte Sedimentation Rate
GCA	Giant Cell Arteritis

1. INTRODUCTION

Reference is made to the PRAC Assessment Report to PSUR #1 (EMEA/H/C/PSUSA/00010898/202106), in which the following review was requested:

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

Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease of the elderly characterised by pain and stiffness in the neck and pelvic girdle. It is the second most common inflammatory rheumatic condition in people aged over 50 years, after rheumatoid arthritis (RA). Polymyalgia rheumatica can occur independently or in association with giant cell arteritis (GCA), the most common primary vasculitis in this age group.[1]

PMR typically presents in people over age 50, with incidence increasing with age. Annual incidence varies from 12 to 60 cases per 100,000 in different populations, with the highest rate in those of Northern European descent. Women are more often affected than men. PMR's etiology is not well understood.[2] Genetic and infectious associations have been investigated without conclusive results. Studies in various geographic regions have revealed increased numbers of certain polymorphisms for genes involved in the immune system, but they have not been consistently found across different populations of patients with PMR.

PMR typically presents in people over age 50, with incidence increasing with age. Annual incidence varies from 12 to 60 cases per 100,000 in different populations, with the highest rate in those of Northern European descent. Women are more often affected than men. PMR's etiology is not well understood 2. Genetic and infectious associations have been investigated without conclusive results. Studies in various geographic regions have revealed increased numbers of certain polymorphisms for genes involved in the immune system, but they have not been consistently found across different populations of patients with PMR.[3]

[1] Camellino D, Giusti A, Girasole G, Bianchi G, Dejaco C. Pathogenesis, Diagnosis and Management of Polymyalgia Rheumatica. *Drugs Aging*. Nov 2019;36(11):1015-1026.

[2] Mahmood SB, Nelson E, Padniewski J, Nasr R. Polymyalgia rheumatica: An updated review. *Cleve Clin J Med*. Aug 31 2020;87(9):549-556.

[3] Gonzalez-Gay MA, Amoli MM, Garcia-Porrua C, Ollier WE. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. *Semin Arthritis Rheum*. Aug 2003;33(1):38-48.

By far the strongest risk factor for PMR is increasing age. PMR is virtually unheard of in those under 50 years old and incidence of the disease becomes more common with each decade, with a peak incidence around 75 years. The reason for this is unclear. Ageing of the immune system (immunosenescence), ageing of the tissues and ageing of neurohumoral regulatory systems may all be involved. Based on the clustering of cases in space and time, it has been proposed that PMR may be triggered by infection in some cases. This could lead to persistent inflammation on a background of chronic low-grade inflammation secondary to decline in adaptive immunity and a compensatory increase in innate immune mechanisms. Neurohumoral mechanisms may also be involved.[4]

The typical presentation of PMR consists of pain in the shoulders and in the hips, often spreading to the arms and limbs. Pain can develop abruptly or progressively during the course of weeks. It is typically more intense during the night and in the first part of the day and is associated with prolonged morning stiffness. Patients often report malaise, fever and weight loss. Peripheral arthritis, especially at the level of the wrist and the knee, can be present. If the patient reports headache, jaw claudication or visual disturbance, treatment with glucocorticoids (GC) should be started promptly and GCA should be ruled out.[4]

At present, there is not a clear understanding of the aetiology and pathogenesis of PMR1. Many earlier studies on genetic and immunologic alterations in PMR were conducted in mixed cohorts of patients with PMR and GCA, making it hard to extrapolate the findings of these studies into isolated (sometimes called "pure") PMR. Even though the cause of polymyalgia rheumatica remains unknown, both genetic and environmental factors contribute to disease susceptibility and severity. Some studies show a cyclical pattern in incidence, which suggests an environmental infectious trigger, such as parvovirus B19, Mycoplasma pneumoniae, and Chlamydia pneumoniae. Polymyalgia rheumatica has a modest familial aggregation. It is linked to the HLA DR4 allele in white populations. Epigenetic changes and differential expression of genes that regulate the expression of inflammatory cytokines probably account for the variable disease phenotypes.[5]

The diagnosis of PMR is usually based on clinical presentation, namely pain and stiffness in the neck, shoulder and pelvic girdles, associated with prolonged morning stiffness that improves throughout the day. However, manifestations could have an insidious onset, sometimes start only on one side and become eventually bilateral.[1,4] Systemic features can be more pronounced than pain, raising the suspicion of a neoplastic or an infectious disease mimicking PMR. Physical examination may be unremarkable but may give clues to mimics of PMR (such as malignancy, deep seated infection or other inflammatory illness). Inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate

[4] Mackie SL. Polymyalgia rheumatica: pathogenesis and management. *Clinical Medicine*. 2013;13(4):398-400.

[5] Cornelia M. Weyand M, and Jo¨ rg J. Goronzy, MD. Giant-Cell Arteritis and Polymyalgia Rheumatica. *Ann Intern Med*. 2003;139:505-515.

(ESR) and plasma viscosity (PV) are typically elevated.[4] Increased ESR and CRP usually supports the diagnosis of PMR, however, 1.5–22.2% of patients with PMR present with normal acute-phase reactants (i.e. ESR ≤ 30 mm/h and CRP < 5 mg/L). Nevertheless, having both ESR and CRP negative is quite rare (0.52–1.2% of cases).

The primary differential diagnosis of PMR consists of elderly-onset RA, which might present with girdle pain and, if rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) are absent, the correct diagnosis is often made only during follow-up. Clues to the diagnosis of elderly-onset RA are the positivity of ACPA (because RF is commonly present in elderly people even in the absence of joint complaints), a refractory course of the disease and the presence of bone erosions, given that PMR-associated synovitis is usually non-erosive [51, 52]. Glucocorticoids are the cornerstone of PMR treatment, and despite the availability of new and sophisticated drugs, they remain unsurpassed in terms of resolution of symptoms and control of inflammation.[1]

Polymyalgia rheumatica and COVID-19 infection

Interleukin-6 (IL-6) is the main cytokine increased during PMR relapses. IL-6 is also the most frequently reported one to be increased during the so-called "cytokine storm" induced by severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) and the altered regulation of innate immunity induced by SARS-CoV-2 might represent a specific, ad hoc trigger for PM relapse.[6]

Sattui et al performed a retrospective study in adult patients (aged ≥18 years) diagnosed with COVID-19 between March 12, 2020, and April 12, 2021, who had a history of primary systemic vasculitis or polymyalgia rheumatica and were reported to the COVID-19 Global Rheumatology Alliance registry. A total of 1202 eligible patients identified in the registry, among them 374 (31.1%) patients had polymyalgia rheumatica. The study concluded that for patients with primary systemic vasculitis and polymyalgia rheumatica, severe COVID-19 outcomes were associated with variable and largely unmodifiable risk factors, such as age, sex, and number of comorbidities, as well as treatments, including high-dose glucocorticoids.[7]

Another study from Pablos JS et al[8], compared outcomes of a cohort of patients with rheumatic diseases with a matched control cohort to identify potential risk factors for severe COVID-19. The cohorts were composed of 456 rheumatics and non-rheumatic patients, in

[6] Manzo C, Castagna A, Ruotolo G. Can SARS-CoV-2 trigger relapse of polymyalgia rheumatica? *Joint Bone Spine*. May 2021;88(3):105150.

[7] Sattui SE, Conway R, Putman MS, et al. Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study. *The Lancet Rheumatology*. 2021;3(12):e855-e864.

[8] Pablos JL, Galindo M, Carmona L, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. *Ann Rheum Dis*. Dec 2020;79(12):1544-1549.

equal numbers. They also found that male sex and previous comorbidity (obesity, diabetes, hypertension, cardiovascular or lung disease) increased the risk in the rheumatic cohort by bivariate analysis.

2. METHODOLOGY

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality.

The Pfizer safety database was searched for all BNT162b2 vaccine cases received through 18 December 2021 using the MedDRA version 24.1 search criteria: PT: Polymyalgia rheumatica.

To analyze exacerbations (flares) of PMR, a two-step approach was used:

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

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

3. RESULTS – PMR CASES REPORTED AFTER BNT162B2 VACCINATION

A total of 628 cases were identified from the database using the search criteria mentioned above. Most cases were spontaneous reports (619, 98.6%) except for seven literature case reports (1.1%) and one clinical study report (0.2%). All cases were serious. A total of 323 cases (51.4%) were medically confirmed, while the remaining 305 cases (48.6%) were non-medically confirmed. The reported age ranged from 34 years to 95 years (mean 70.9, median 72.0, N=600), with the case distribution by age as shown in Table 1.

Table 1. Case Distribution by Age

Age Range	Number of Cases	Percentage (%)
31-50 years	19	3.0%
51-64 years	106	16.9%
65-74 years	261	41.6%
Greater than or equal to 75 years	219	34.9%
Unknown	23	3.7%

Of the 628 reports, 357 (56.8%) were females, 265 (42.2%) males, and in 6 (1.0%) cases sex was not reported. Most of the cases were reported from France (138, 22%), followed by United Kingdom (91, 14.5%) and Germany (83, 13.2 %). The top ten reporting countries are in Table 2.

Table 2. Top Ten Reporting Countries

Country	Number of Cases	Percentage (%)
France	138	22.0%
United Kingdom	91	14.5%
Germany	83	13.2%
Netherlands	47	7.5%
Sweden	38	6.1%
Finland	32	5.1%
Japan	31	4.9%
United states	31	4.9%
Italy	30	4.8%
Norway	26	4.1%

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

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

In 232 cases (36.7%), the events were reported after the first dose of the vaccination, in 332 cases (52.9%) after the second dose, in 25 cases (4%) after third dose (booster) and in 67 cases (10.7%) it was unspecified.

Among the 232 cases reporting the event after the first dose of the vaccination, time to onset was reported as detailed in table 3.

Table 3. Time to Onset After First Dose

Time to onset	Number of cases	Percentage (%)
Same day or day after	29	12.5%
2-7 days	64	27.6%
8-14 days	36	15.5%
15-21 days	22	9.5%
22-45 days	21	9.1%
>45 days	16	6.9%
Unknown	47	20.3%

Among the 332 cases reporting the event after the second dose of the vaccination, time to onset was reported as detailed in table 4.

Table 4. Time to Onset After Second Dose

Time to onset	Number of cases	Percentage (%)
Same day or day after	47	14.2%
2-7 days	61	9.3%
8-14 days	36	10.8%
15-21 days	23	7%
22-45 days	49	14.8%
>45 days	41	12.3%
Unknown	75	22.6%

Among the 25 cases reporting the event after the third dose of the vaccination (booster dose), time to onset was reported as detailed in table 5.

Table 5. Time to Onset After Second Dose

Time to onset	Number of cases	Percentage (%)
Same day or day after	1	4%
2-7 days	6	24%
8-14 days	2	8%
15-45 days	4	16%
Unknown	12	48%

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

The remaining dataset comprised 204 cases which were further analyzed by laboratory data provided, to identify those cases in which both CRP and ESR levels were elevated (CRP greater than 5 mg/L and ESR greater than 30 mm/hour). Although there are no clear diagnostic criteria for PMR, the CRP is nearly always elevated in PMR patients. The medical literature supports that an elevated ESR (greater than 30 mm/hour) occurs in >92% of patients at the time of diagnosis of PMR, while 99% of such patients have an increased serum CRP level (greater than 5 mg/L).[9,10]

CASES PROVIDING C-REACTIVE PROTEIN AND SEDIMENTATION RATE VALUES

Out the 204 reports, only 16 provided both CRP and ESR levels, increasing the likelihood that the cases are accurately assessed as PMR. Case detail for each report is provided in Table 6. Each case has been assessed based on the WHO-UMC causality assessment categories.

[9] Cantini F, Salvarani C, Olivieri I, et al. Erythrocyte sedimentation rate and C-reactive protein in the evaluation of disease activity and severity in polymyalgia rheumatica: a prospective follow-up study. *Semin Arthritis Rheum.* Aug 2000;30(1):17-24.

[10] Salvarani C, Cantini F, Niccoli L, et al. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective followup study. *Arthritis Rheum.* Feb 15 2005;53(1):33-38.

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 65/M [redacted] Dose 1 Not Recovered/Not Resolved 7 Days	Polymyalgia rheumatica, Gait inability, Inflammation, Pyrexia, Arthralgia, Myalgia Not Reported Not Reported	Pt received dose 1 on 20 June 2021. 7 days after vaccination he experienced pyrexia and pain in the right shoulder and right hip joint on the opposite side of the vaccination left arm. Blood tests on 19 July 2021 showed high inflammatory response, white blood cell (WBC): 9500, C-reactive protein (CRP): 12.24 mg /dL, Erythrocyte sedimentation rate (ESR): 80 mm/h. The diagnosis of polymyalgia rheumatica was made Corticosteroid treatment was started. Outcome was reported as not recovered. *Symptoms reported, lab data, CRP and ESR decreased following steroid initiation and plausible time to onset support the diagnosis of PMR. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*
[redacted] 74/M [redacted] Dose 1 and 2 Not Recovered/Not Resolved 4 Days	Polymyalgia rheumatica Benign prostatic hyperplasia / Chronic kidney disease / Hypertension Candesartan cilexetil, hydrochlorothiazide / dutasteride, tamsulosin hydrochloride	Pt received dose 1 on 14 April 2021 and dose 2 on 12 May 2021. Four (4) days after 1st dose, he developed inflammatory pain in the pelvic girdle. Shortly after the second dose of the vaccine, the pain migrated to the shoulder girdle while the pelvic girdle pain subsided. Laboratory tests revealed an inflammatory syndrome: ESR = 74 mm / h, CRP = 50 mg / l). A diagnosis of polymyalgia rheumatica was made, and corticosteroid treatment was started Outcome was reported as not recovered. *Symptoms reported, lab data and time to onset support the diagnosis of PMR, however no report of improvement with glucocorticosteroid treatment is unusual and an indicator that the diagnosis may be inaccurate Additionally, the patient's chronic renal disease may be playing a role in inflammation and symptomatology. F-up has been requested.* *WHO-UMC Causality Assessment: Unlikely*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 69/F [redacted] Dose 1 Unknown Not Reported	Polymyalgia rheumatica Not Reported Not Reported	This is a literature report describing a woman who complained of sudden bilateral pain in the shoulder and pelvic girdles associated with morning stiffness lasting > 2 hours, fever, and general malaise on an unspecified date after 1st dose vaccination. X-ray of the chest, shoulders, and pelvic region, revealing no pathologic findings; an abdominal ultrasound (US) showing mild hepatomegaly, and an 18-fluorodeoxyglucose positron emission tomography (18-FDG/PET) associated with total body computed tomography (CT) that excluded pathological findings in other sites. PMR was diagnosed. She was started on corticosteroid and her clinical manifestations and ADL quickly improved. *Symptoms reported and lab data along with the improvement after prednisone therapy may support a PMR diagnosis. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 46/M [redacted] Dose 1 Not Recovered/Not Resolved 16 Days	Giant cell arteritis, Impaired work ability, CSF protein increased, Polymyalgia rheumatica, Haematuria, Vasculitis Not Reported Not Reported	Pt received dose 1 on 14 June 2021. 16 days after vaccination pt experienced neck, shoulders, and head soreness that extended then to legs and arms. These symptoms lasted for 2-3 weeks and then pt also felt feverish and had elevated heart rate. A central nervous system infection was suspected, but no confirmation from cerebrospinal fluid was obtained for this. Mainly proteins were elevated in cerebrospinal fluid, but there was no sign of viral infection. Upon admission, CRP was 180 (unspecified unit) and urinary microhematuria and normocytic anemia were found. Body CT was performed on 22 July and no signs of malignancy or infection were found. During that time, neck-shoulder pain eased, but the pain migrated to the thighs and hip area. Lab data showed CRP at 257 (unspecified unit) and ESR up to 110. Rheumatoid serum, ANCA antibodies and myositis antibodies were negative. Prostate-specific antigen was normal. A muscle biopsy was performed from the left thigh and did not show abnormality. In a PET-CT scan, fluorodeoxyglucose-positive lymph nodes in both groins, somewhat pronounced glucose metabolism of large vessels in the proximal area of the thighs, and mild vasculitis were considered possible. Corticosteroid treatment was started, and the inflammatory values started to decrease. *Possible PMR case in the context of vasculitis. Patient age is not typical for PMR. In addition, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Possible*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 70/F [redacted] Dose 2 Recovering/Resolving Not Reported	Pyrexia, Arthralgia, Hyperhidrosis, Giant cell arteritis, Headache, Polymyalgia rheumatica, Cough, Night sweats, Weight decreased, Pain in extremity, Gait disturbance Palpitations / Supraventricular extrasystoles Not Reported	Pt received dose 2 on 28 May 2021. On 24 April 2021, the patient received vaccine dose 1 and experienced headache, temporal arteritis, felt abnormal, irritated and felt stabbing toward the jaw. On 31 May 2021, she developed a fever of 39.5 (unspecified unit) and had a small cough and was started on antibiotics. As symptomatology did not improve, she was hospitalized. and was started on corticosteroids in combination with osteoporosis prophylaxis. On 11 June 2021 lab tests were performed and included: stable C-reactive protein 81 and increased transaminase Urine: leukocytes 1+, erythrocytes 2+, protein 1+. Computed tomography of the neck/thorax/abdomen did not show evidence of lymphadenopathy or other pathology. Positron emission tomography (PET) scan on 14 June 2021 revealed a slight irregular accumulation of activity in the thoracic aorta, possibly vasculitis, but metabolism was obviously reduced due to use of high dose prednisone. A reactive bone marrow was observed. Working diagnosis was giant cell arteritis (temporal arteritis) with involvement of large vessels (aortitis). *Giant cell arteritis case with no shoulder pain and stiffness reported (clinical manifestations of PMR). Although prednisone therapy improved symptoms, major clinical manifestation of PMR are lacking. The case supports more a giant cell arteritis/vasculitis diagnosis. Of note, time to onset is not reported and this precludes a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 75/M [redacted] Dose 2 Recovering/Resolving 15 Days	Polymyalgia rheumatica Hypertension / Knee arthroplasty Lercanidipine hydrochloride / losartan potassium / spironolactone	Pt received dose 2 on 12 April 2021. Fifteen (15) days after vaccination the pt experienced asthenia and a few days later he had joint pain starting from the elbows and extending to the shoulder girdle, described as a periodic pain (more in the evening) that progressively increased in the lumbar spine, cervical and posterior surface of both thighs. A rheumatologist was consulted, and clinical examination showed limitation of forward movement in both shoulders. Lab tests performed 3 months after the symptomatology showed ESR= 35 mm, C-reactive protein = 44 mg / L, complete blood count normal, no monoclonal abnormality on protein electrophoresis. Final diagnosis was polymyalgia rheumatica. Outcome: recovering *This patient had shoulder, back, neck and leg pain which could be consistent with PMR. It is not clear if the limitation of shoulder movement is due to pain or weakness. Muscular weakness is not a feature of PMR. The labs were not done at the time of the symptoms, limiting the ability to interpret them. Further, treatment is not described as a factor of the recovery.* *WHO-UMC Causality Assessment: Unlikely*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 8 decade/M [redacted] Dose 2 Unknown Not Reported	Polymyalgia rheumatica, Chondrocalcinosis pyrophosphate Not Reported Not Reported	Pt received dose 2 on an unspecified date and about 2 to 3 weeks, he experienced pain in the neck or shoulder. Lab data were performed, and WBC was unspecified but reported as "a little high", CRP was "about 10 or less," ESR was "very high" (2-hour rate was "60 or 70"). The diagnosis of polymyalgia rheumatica and/or pseudogout of the cervical spine was postulated and the patient was started on corticosteroid without improvement. Therapy was changed to NSAIDs. On an unspecified date, the patient underwent an orthopedic surgery (unspecified). The outcome of the event was not provided. *Patient with pain in the neck and shoulder and ESR/CRP elevated about 2-3 weeks after vaccination. The lack of improvement after corticosteroid and orthopedic surgery suggests a different diagnosis than PMR.* *WHO-UMC Causality Assessment: Unlikely*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 78/F [redacted] Dose 2 Not Recovered/Not Resolved 5 Days	Polymyalgia rheumatica, Myalgia, Headache, Arthralgia, C-reactive protein increased Not Reported Apixaban	Pt received dose 2 on 27 May 2021 Five days (5) after the 2nd vaccination the subject experienced polymyalgia rheumatica, muscle ache, forehead headache, aching joints. Corticosteroid therapy was initiated. Lab included: CRP 5.69 mg/dl on an unspecified date. On 30 August 2021, CRP increased but unspecified, antinuclear antibody 1/160, haemoglobin: 11.9, platelet count: 276, ESR 52 (unspecified units). The outcome of the events polymyalgia rheumatica, muscle ache, forehead headache, aching joints was not recovered. *Headache could be suggestive of giant cell arteritis. Myalgia and joint pain were reported but anatomical location was not provided. The increased CRP and ESR were taken two months after initiation of the symptoms, limiting their usefulness for diagnosis. Further, the patient did not have symptomatic response to corticosteroids. Of note, medical history is not reported. The lack of clear details makes the case difficult to fully assess.* *WHO-UMC Causality Assessment: Unlikely*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 59/F [redacted] Dose 3 Unknown Not Reported	Immunisation, Joint swelling, Oedema peripheral, Myalgia, Blindness, Oedema peripheral, Peripheral swelling, Body temperature increased, Nausea, Joint swelling, Face oedema, Arthralgia, Pyrexia, Swelling face, Polymyalgia rheumatica, Arthritis, Iron deficiency, Anaemia COVID-19 / Specialist consultation, rheumatic disease Not Reported	Pt received dose 3 on 16 September 2021. Medical history included COVID-19 in October 2020 and rheumatic disease. On 16 September 2021, immediately after administration of the 3rd dose of the vaccine, the patient experienced transient swelling of the left ankle, ankle oedema, muscle pain and blindness. In the following days, she had swelling of both ankles foot oedema, swelling of the joints in the hand and arm. She was hospitalized. Laboratory data included increased ESR (unspecified), moderately nonspecifically elevated D-dimer (915 mcg / L), "low inflammatory parameters," mild sideropenic anemia. The patient was started on NSAIDs for PMR and responded very well at first, but then the swelling reappeared. X-rays of the wrists and feet were normal. Lab data on 30 September 2021 showed normal leukocyte count, lymphocytes and monocytes increased, ESR increased (unspecified), CRP 37 (unspecified unit). X-ray of the right foot showed initial arthrosis. There were no reliable signs of arthritis of the upper ankle on the right or left, there is a small amount of fluid in the synovial cavity of the right and left upper ankle, no signs of thickening or hyperaemia of the synovium. Clinical condition begins to slowly improve with etoricoxib. *While the patient's symptoms are not the classic symptoms of PMR although the details may be indicative of another underlying rheumatic disease which is mentioned in the medical history, but not specified. The report of blindness suggests an underlying pathology not reported in the medical history. Of note, concomitant meds and time to onset were not reported which preclude a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 65/F [redacted] Dose 2 Recovering/Resolving 7 Days	Polymyalgia rheumatica, Multisystem inflammatory syndrome, Arthralgia, Red blood cell sedimentation rate increased Not Reported Not Reported	Pt received dose 2 on 07 June 2021 and 7 days later was reported to have PMR, hip pain, inflammatory syndrome, red blood cell sedimentation rate increased. The patient underwent the following laboratory tests and procedures: anti-cyclic citrullinated peptide antibody: negative; blood fibrinogen: 6.27g/l; c-reactive protein: 11 mg/l; full blood count: normal, magnetic resonance imaging abdominal: (09 August 2021) no signs of arthropathy, red blood cell sedimentation rate increased: 51 mm at hour 1; rheumatoid factor: negative. Unspecified therapeutic measures were taken and the patient was recovering at the time of the reporting. *Lack of detail on symptoms and treatment precludes a proper medical assessment.* *WHO-UMC Causality Assessment: Unclassifiable*
[redacted] 71/M [redacted] Dose 2 Not Recovered/Not Resolved 28 Days	Polymyalgia rheumatica Hyperlipidaemia / Hypertension Atorvastatin / lisinopril / lisinopril dihydrate / tamsulosin hydrochloride	Pt received dose 2 on 06 March 2021. Twenty-eight (28) days later the patient had fever (T 100, unspecified unit) and started having pain in the hip area then down his legs to calves. It spread to the shoulders and finally to neck. He also had severe morning stiffness. The same day, lab tests showed ESR at 52 mm/hr, CRP at 32.3 (unspecified unit) and creatinine (CR) was 363 (normal range 71-331). He was diagnosed with polymyalgia rheumatica. Treatment with prednisone (15mg) daily was started and within few days, symptoms improved. The outcome of the event polymyalgia rheumatica was reported as not recovered at the time of the reporting. *The details provided are not inconsistent with PMR, however they may also be consistent with infection.* *WHO-UMC Causality Assessment: Unlikely*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 67/M [redacted] Dose 1 Recovering/Resolving 7 Days	Polymyalgia rheumatica, C-reactive protein increased, Gamma-glutamyltransferase increased, Red blood cell sedimentation rate increased Hypertension Irbesartan	Pt received dose 1 on 07 March 2021 7 days after vaccination he experienced PMR. On 02 April 2021, C-reactive protein increased (40.15 mg/l), gamma-glutamyl transferase increased (GammaGT): 65 IU/l and ESR was 35 mm. Pt underwent computerised tomogram which did not reveal abnormalities On 22 April 2021, positron emission tomogram showed appearance of metabolically active rhizomelic pseudo-polyarthritis of, the lumbar interspinous bursae and the right knee. The pt was recovering from the events at the time of the reporting. *Patient was diagnosed with PMR 7 days after D1, however it was 1-2 months later when supportive labs and imaging were conducted. Treatment was not described. These factors hinder assessment of the case.* *WHO-UMC Causality Assessment: Unclassifiable*
[redacted] 74/M [redacted] Dose 1 Not Recovered/Not Resolved Not Reported	Polymyalgia rheumatica Not Reported Not Reported	Pt received dose 1 on 13 April 2021. On an unspecified date, he experienced polymyalgia rheumatica and was hospitalized from 04 May 2021 to rule out a cerebral event. About 1.5 weeks after vaccination, he had dyspnea (when walking) and loss of power in both thighs. The disease gradually changed to proximal pain, stiffness and loss of power. Increased CRP and SED rate were noted. He was diagnosed with PMR and was started on corticosteroids. The patient underwent lab tests and procedures which included CRP: 25 mg/l on 04 May 2021, 55 mg/l on 14 May 2021, RBC SED: 40 on 14 May 2021 Units: mm/h. The pt did not recover from the event at the time of the reporting. *The reported muscle weakness is not a feature of PMR. Medical history and concomitant medication would be helpful in assessing this case.* *WHO-UMC Causality Assessment: Unclassifiable*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 83/M [redacted] Dose 2 Recovering/Resolving 5-7 Days	Polymyalgia rheumatica Aortic aneurysm / Hyperlipidaemia / Hypertension / Intra-thoracic aortic aneurysm repair Atorvastatin / metoprolol fumarate	Pt received dose 2 on an unspecified date in March 2021. The patient presented with pelvis and shoulder myalgia, difficulty standing from a sitting position and difficulty in raising hands, 5-7 days after the second dose of vaccine. The patient's laboratory tests included anaemia (Hct 37%), ESR 61 and CRP 8. There was great improvement after 2 days of cortisone (Medrol 24mg). The outcome of the event was recovering. *The case is possibly related with vaccine administration.* *WHO-UMC Causality Assessment: Possible*
[redacted] 59/F [redacted] Dose 1 Unknown 10-13 Days	Polymyalgia rheumatica, Arthralgia, Discomfort Not Reported Not Reported	Pt received dose 1 on 06 May 2021. Pt experienced joint pain on 17 May 2021 About 10-13 days after dose 1, she had proximal joint pain and constant discomfort. ESR was 50 and CRP was 72 on the 14 June 2021 (CRP dropped to 51 on the 18 June 2021). Treatment with Prednisolone 15 mg once daily was received for all events. The outcome of the event joint pain was not recovered and for all other events was unknown. *The patient's presentation could be consistent with PMR but the lack of detail provided to rule out other diagnoses (e.g. infection) was limited given that lab analyses were performed a month after the onset of the symptoms.* *WHO-UMC Causality Assessment: Unclassifiable*

Table 6. 16 AE Reports with ESR and CRP

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 78/M [redacted] Dose 2 Recovered/Resolved 7 Days	Polymyalgia rheumatica, Arthritis, Arthralgia, Myalgia, Pyrexia, Rheumatoid arthritis Chronic kidney disease / Hyperlipidaemia / Hypertension / Hyperuricaemia Not Reported	Pt received dose 2 on 05 June 2021 and 7 days after vaccination, pt was reported to have PMR) and arthritis, right shoulder pain, and low-grade fever. On 16 June 2021, due to generalized myalgia, pt was hospitalized. The patient received treatment with antibiotics which were ineffective. On 23 June 2021, ESR was 82 mm/hr. On 24 June 2021, left knee MRI was performed and severe oedema around the joint was found. On 23 June 2021, rheumatoid factor (RF) was 16 IU/mL. From 25 June 2021 pt was started on corticosteroid and symptoms improved. The outcome of the event polymyalgia rheumatica was recovered. *Details presented indicate the possibility of other (or >1) musculoskeletal diagnoses in this patient. Specifically, a unilateral knee effusion, unilateral shoulder pain and elevated RF are not consistent with the diagnosis of PMR.* *WHO-UMC Causality Assessment: Unlikely*

CASE PROVIDING C-REACTIVE PROTEIN AND NO SEDIMENTATION RATE VALUES

Of the 204 reports, 26 provided CRP values only. These are described in more detail in Table 7 below.

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 73/M [redacted] Not reported Recovering/Resolving 4 Days	Polymyalgia rheumatica Not Reported Allopurinol, amlodipine, HCTZ, irbesartan	A 73-year-old man with no medical history reported but taking medication for Gout and 3 antihypertensives, received BNT162B2 (dose # unspecified) and 4 days later was reported to have PMR with a CRP of 96 (units unspecified). He began treatment for a month with glucocorticoids (both Celeston and Medrol were mentioned) and PMR was resolving. *This case describes a man with elevated CRP but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*
[redacted] 57/M [redacted] Dose 1 Unknown Not reported	Polymyalgia rheumatica, Inflammation Not Reported Not Reported	A 57-year-old male patient with no medical history and concomitant medicatons reported, received BNT162b2 (dose 1) 07 May 2021. The patient experienced polymyalgia rheumatica on May 2021 with a CRP value of 52mg/l. He began treatment with corticosteroids (Cortancyl 20 mg) and had a good response. He is currently still under corticosteroid therapy. The outcome of the event was unknown. *This case describes a man with elevated CRP but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 76/F [redacted]	Polymyalgia rheumatica, Movement disorder, Pain, Insomnia, Myalgia, Basophil count increased, C-reactive protein increased, Platelet count increased, Inappropriate schedule of product administration Knee arthroplasty Not reported	A 76-year-old female patient with a medical history of a knee prosthesis (implanted 18 years ago) and with no concomitant medications reported, received BNT162b2 (dose 2) in July 2021 (unspecified date). Pt received dose 1 in April 2021 and experienced alpha globulin increased, blood cholesterol increased, blood iron decreased, blood potassium increased, uric acid increased, C-reactive protein increased, LDL increased, platelet count increased, and transferrin increased. One week after dose 2, she had severe pain in arms and legs which caused insomnia for 4 weeks. Myalgia was most prominent in the arms, bilaterally, reaching to the shoulders with no morning stiffness in the fingers. Symptoms started suddenly after vaccination. There was suspected polymyalgia rheumatica. The patient underwent laboratory tests and procedures which included: alpha 1 globulin (normal range: 2.9% - 4.9%): 6.5% on 22 June 2021; alpha 2 globulin (normal range: 7.1% - 11.8%): 15.8 [unit unspecified] on 22 June 2021; basophil count (normal range: 10/nL - 70/nL): 110/nL on 22 June 2021, 100/nL on 12 July 2021; blood cholesterol (upper normal limit: 200 mg/dL): 277 mg/dl on 22 June 2021; blood iron (normal range: 49 ug/dL - 151 ug/dL): 40 ug/dl on 22 June 2021, unknown result on 12 July 2021; blood potassium (normal range: 3.5 mmol/L - 5.5 mmol/L): 5.7 mmol/l on 22 June 2021; blood uric acid (upper normal limit: 6.0 mg/dl): 6.8 mg/dl on 22 June 2021; C-reactive protein (upper normal limit: 0.5 mg/dl): 6.4 mg/dl on 22 June 2021, 7.4 mg/dl on 25 June 2021, and 9.2 mg/dl on 02 July 2021; low density lipoprotein (normal upper limit: 160): 171 [unit unspecified] on 22 June 2021; platelet count (normal range: 140/nL - 400/nL: 593/nL on 22 June 2021, 600/nL on 25 June 2021, 566/nL on 02 July 2021, and 608/nL on 12 July 2021; and transferrin (normal range: 16 mg/dL - 45 mg/dL): 174 mg/dL on 22 June 2021. The outcome of the events 'movement disorder', 'pain', and 'myalgia' was recovering, while the outcome of the remining events was unknown. *This case describes a woman with elevated CRP and shoulder myalgia with no morning stiffness (one of the typical clinical manifestation of PMR). More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 50/M [redacted]	Polymyalgia rheumatica, Groin pain, Lymphadenopathy Not Reported Not Reported	50-year-old male with no medical history and concomitant medications reported, received BNT162B2 (dose unspecified) on 05 May 2021. On 31 May 2021, he had polymyalgia rheumatica with pain in the left groin that started in early May 2021 and then worsened. Lab data performed on 16 June 2021 showed: lymphadenopathy, CRP 44 (unspecified unit), cyclic citrullinated peptide antibody 0.7 (unspecified unit), human leukocyte antigen 27 negative. Pt started treatment with Prednisolon 20 mg and symptoms improved. This case describes a man with elevated CRP but no other clinical description of PMR. More data would be needed for a proper assessment. WHO-UMC Causality Assessment: Unclassifiable.
[redacted] 73/F [redacted] Dose 2 Recovering/Resolving 18 Days	Polymyalgia rheumatica, Arthralgia, Chills, Pain, Pyrexia Not Reported Not Reported	73-year-old female patient with no medical history and concomitant medications reported, received BNT162B2 (dose 2) on 28 March 2021. Pt received dose 1 on 08 March 2021. On 29 March 2021, pt had fever and chills (remission after Novalgin administration) and few days later, she had severe pain in the shoulder girdle and hip joints limiting faster movement. The patient underwent lab tests and procedures on 11 June 2021 which included IgG: 17.2% and CRP: 21.3 mg/l. On 18 June 2021, it was concluded it was polymyalgia rheumatica. Pt is still under treatment with corticosteroids and is recovering from the events (only mild remission of the symptoms). *This case describes a woman with elevated CRP and severe pain in the shoulder girdle and hip joints. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 82/F [redacted] Dose 2 Recovered/Resolved 19 Days	Polymyalgia rheumatica Not Reported Not Reported	82-year-old female patient with no medical history and concomitant medications reported, received BNT162B2 (dose 2) on 30 April 2021. Pt received dose 1 on 30 March 2021. On 19 May 2021, pt had shoulder pain with "morning derusting" which extended to pelvic girdle pain. Lab data included anti-CCP, antinuclear negative, CRP: 30 mg/l. Pt was diagnosed with rhizomelic pseudopolyarthritis and started corticosteroid therapy with prednisone at 15 mg/day and symptoms improved. *This case describes a woman with elevated CRP and shoulder pain that improved after corticosteroids therapy. The reported TTO is plausible. The lack of information about the medical history and the concomitant medications hampers a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 84/F [redacted] Dose 2 Recovering/Resolving Not Reported	Polymyalgia rheumatica, Pain, Mobility decreased, Inflammation, Vaccination site pain, Malaise, Myalgia, Arthralgia Hyperlipidaemia / Hypertension Ascorbic acid, calcium pantothenate / benidipine hydrochloride / candesartan cilexetil / pitavastatin calcium	84-year-old female patient with ongoing hypertension and hyperlipidaemia treated with pitavastatin calcium, benidipine hydrochloride, candesartan cilexetil, ascorbic acid and calcium pantothenate. Pt received BNT162B2 (dose 1) on 19 May 2021 and after 4-5 days, she had pain around back and shoulder blades and had myalgia at night. On 09 June 2021, she received BNT162B2 (dose 2) and had vaccination site pain (improved with acetaminophen). After few days, she had general malaise and arthralgia. Six days after the vaccination, she also experienced myalgia. On 23 June 2021, no abnormality on ECG were found and CRP was 2.9 (also 5.232 on unknown date), and pain continued. On 02 July 2021, the patient had white blood cell count (WBC) of 9740/uL, (normal range: 3300-8600), Haemoglobin (Hb) of 10.6g/dL (normal range: 11.6-14.8); and soluble IL-2 receptor (IL-2R) was 1082 U/ml (normal range: 122 -496). A diagnosis of polymyalgia rheumatica was suspected. The outcome of events was recovering. *This case describes a woman with elevated CRP, elevated soluble IL-2 receptor and shoulder pain. No information about the treatment is reported. Leukocytosis is also present, suggesting a possible infective process or an alternative aetiology for the disease* *WHO-UMC Causality Assessment: Unlikely.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 52/M [redacted] Dose 1 Recovering/Resolving 7 Days	Gait disturbance, Arthropathy, Muscular weakness, Polymyalgia rheumatica, Myalgia, Limb discomfort Hypometabolism Levothyroxine sodium	52-year-old male patient with a medical history of hypometabolism treated with levothyroxine sodium from 04 April 2018, received BNT162B2 (dose 1) on 29 May 2021 and BNT162B2 (dose 2) on 04 June 2021. The same day, he experienced difficulty in walking, arthropathy and the day after, he also had muscular weakness and polymyalgia rheumatica, myalgia, heaviness in thigh musculature, limb discomfort. Lab data included CRP: 15-20 (unspecified value) on 2021, PET: verified polymyalgia rheumatica diagnose on 07Oct2021 with arthritis in both knees, hypergammaglobulinemia, IG-G 20 g/l on 2021. Unspecified therapeutic measures were taken as a result of the events. *This case describes a man with elevated CRP and other symptoms including muscle weakness (not a clinical feature of PMR). Lab data showed also hypergammaglobulinemia of unspecified origin. No other work-up was performed to exclude active infection.* *WHO-UMC Causality Assessment: Unlikely.*
[redacted] 87/M [redacted] Dose 2 Recovered/Resolved 22 Days	Polymyalgia rheumatica, Musculoskeletal stiffness, Fatigue Not Reported Not Reported	A 87-year-old male patient with no medical history and concomitant medications received BNT162B2 (dose 2) on 16 March 2021. He previously took dose 1 on 22 February 2022 and experienced bursitis, pain in arm, shoulder pain and myalgia. In an unspecified date in March 2021, he had severe stiffness in femoral muscles similar to hips bilaterally and pronounced tiredness and on 07 April 2021, he experienced possibly polymyalgia rheumatica with a CRP value of 69 mg/l on 07 April 2021. Pt recovered from the event on April 2021. The outcome of the other events was unknown. *This case describes a man with elevated CRP and musculoskeletal stiffness, 22 days after vaccination. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 71/M [redacted] Dose 1 and 2 Recovering/Resolving 14 Days	Polymyalgia rheumatica Atrial fibrillation / Obesity / Prosthesis implantation / Vascular graft Not Reported	This literature report describes a 71-year-old man patient with grade 1 obesity, atrial fibrillation, bypass surgery and aortic bioprosthesis that received BNT162B2 (dose 1) on 09 April 2021. On 23 April 2021, he developed a mild pain in his left shoulder. One month later, he got his second dose (on 07 May 2021). Pain was persistent, but CRP was normal (7.5 mg/). Slowly, pain worsened with involvement of both shoulders and morning stiffness lasting at least 2 hours. He also developed thigh, neck and lumbar pain. CRP increased at 55 mg/L (in 2021). Ultrasound showed subdeltoid bursitis and biceps tenosynovitis. Thoraco-abdominal-pelvic computed tomography (TAP-CT) did not show any carcinologic process or large vessel arteritis. The patient met the EULAR 2012 classification criteria of PMR and prednisone was started at 15 mg/day, increased at 20 mg/day after 7 days (54% of improvement of PMR-AS) with good efficiency. CRP was 24 mg/L (in 2021). *This case describes a man with elevated CRP and PMR symptoms confirmed by ultrasound. The time to onset is plausible with a temporal relationship.* *WHO-UMC Causality Assessment: Possible.*
[redacted] 68/M [redacted] Not Reported Not Recovered/Not Resolved 4 Days	Polymyalgia rheumatica, Limb discomfort, Myalgia Not Reported Not Reported	A 68-year-old male patient with no medical history and concomitant medications, received BNT162b2 (dose unspecified) on 04 May 2021. On 08 May 2021, he experienced polymyalgia rheumatica, limb discomfort and myalgia. The patient underwent laboratory tests and procedures which included: bronchoscopy: 44, notes: unit: min/1h; CRP: 37 mg/l; platelet count: 409/nl. The outcome of all events was not recovered. *This case describes a man with elevated CRP but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 71/M [redacted] Dose 1 Recovering/Resolving 14 Days	Polymyalgia rheumatica Not Reported Not Reported	A 71-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 1) on an unspecified date. After 14 days, he experienced inflammatory shoulder pain with 2-hour morning stiffness. After two months of progressive worsening and the appearance of pelvic girdle pain, the diagnosis of Pseudo-rheumatoid arthritis (PRA) was made. CT did not show vasculitis; CRP was 55 mg/l; ultrasound scan revealed tenosynovitis of the long biceps and bilateral subacromial deltoid bursitis. Prednisone was started and the clinical improvement was rapid. *This case describes a man with elevated CRP and PMR symptoms confirmed by ultrasound. The time to onset is plausible with a temporal relationship. More information about medical history and concomitant medications is needed for a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*
[redacted] 65/F [redacted] Dose 2 Unknown Not Reported	Polymyalgia rheumatica, Blood iron decreased Not Reported Not Reported	A 65-year-old female patient with no medical history and concomitant medications, received BNT162B2 (dose 2), on 23 September 2021 and BNT162B2 (dose 1) on 12 August 2021 and experienced headache, influenza like illness, injection site pain, lethargy, musculoskeletal pain, polymyalgia rheumatica. Overall body and muscles aches started and continued in both arms, legs and hips. She also had sleep difficulty. Then, after dose 2, the pain worsened. CRP was 64 (unspecified values) and iron levels were low (unspecified values). She was diagnosed with polymyalgia rheumatica and started prednisone. *This case describes a woman with elevated CRP and other symptoms such as headache and influenza-like illness. Time to onset is unspecified and more data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 60/M [redacted] Dose 2 Unknown 26 Days	Polyarthritis, Polymyalgia rheumatica, Rheumatoid arthritis, Arthritis reactive, Arthritis, Pyrexia, Arthralgia, C-reactive protein increased, Pain, Headache, Malaise, Periarthritis Not Reported Not Reported	A 60-year-old male patient with no medical history and concomitant medications reported received BNT162B2 (dose 2) on 20 August 2021 and BNT162B2 (dose 1) on 30 July 2021. On 20 August 2021, he had pain from the right shoulder joint to the upper arm and pain in the left hip joint, headache, general malaise and pyrexia (39 degrees centigrade). On 27 August 2021, arthralgia was also occurred and on 10 September 2021, he was diagnosed with periarthritis scapulohumeralis. On 11 September 2021, blood test showed WBC count of 12200 and CRP level of 11.85 mg/dl. On 14 September 2021, the patient visited the emergency room and polyarthritis of unknown cause was diagnosed. CRP was 11.86 mg/dl. Treatement with analgesic drugs was started. Polymyalgia rheumatica was suspected and was treated with prednisolone 15 mg for 1 day but there was no improvement. Rheumatoid arthritis was diagnosed and pt started treatment with Etanercept and Methotrexate. *This case describes a man with elevated CRP that was diagnosed with rheumatoid arthritis.* *WHO-UMC Causality Assessment: Unlikely.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 74/F [redacted] Not Reported Recovering/Resolving 27 Days	Polymyalgia rheumatica, Inflammatory pain, Headache, C-reactive protein increased, Red blood cell sedimentation rate increased Not Reported Not Reported	A 74-year-old female patient with no medical history and concomitant medications reported, received BNT162B2 (dose 2) on 05 May 2021. On 01 June 2021, she experienced polymyalgia rheumatica, inflammatory pain of the cervical spine, shoulders and hips, headache, CRP increased (36 mg/ml), red blood cell sedimentation rate increased (45, unspecified values). Lab data included: CRP was 36 mg/l (09 September 2021). On 22 September 2021, upon investigation, almost normal, temporal and facial arteries were noted. No abnormalities noted during PET and X-ray tests. Pt started prednisone 40mg/d for 10 days and improvement of symptoms without complete regression was observed. Corticosteroid therapy was increased at 50 mg/day with complete regression of symptoms. No recurrence observed after gradual reduction of corticosteroid treatment (25mg/day on 04 November 2021). *Symptoms reported, lab data and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 76/F [redacted] Dose 3 Recovering/Resolving 24 Days	Immunisation, Polymyalgia rheumatica, Inflammation Not Reported Not Reported	A 76-year-old female patient received with no medical history and concomitant medications reported, received BNT162B2 (dose 3) on 20 October 2021. On 13 November 2021, she experienced polymyalgia rheumatica/pseudopolyarthritis rhizomelica/sudden morning onset of right and left shoulder and right and left thigh flexor pain and inflammation with a CRP of 131 (unspecified unit) in an unspecified date in 2021. CRP levels improved in one week following analgesics and diclofenac treatment. Cortisone treatment (30mg of prednisolone) resulted in regression of inflammatory signs and a clear clinical improvement of the symptoms. *Symptoms reported, lab data and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 79/F [redacted] Dose 1 Recovering/Resolving 7 Days	Polymyalgia rheumatica Bronchitis bacterial / Tobacco user / Varicose vein / Varicose vein operation Not Reported	A 79-year-old female patient, long- term smoker with chornic mucopurulnet bronchitis and with a varicose vein operation in an unspecified date. The patient's concomitant medications were not reported. She received BNT162B2 (dose 1) on 25 March 2021 and one week after, she experienced rheumatic polymyalgia. Around 01 April 2021, she had pain in her left shoulder and in both hips. She began to wake up at night due to pain and in the mornings, she felt stiff for at least 30 minutes. There was no oedema, no headache or fever. Elevated inflammatory parameter was identified: s-CRP (12 April 2021): 108.9 mg/l on 12 April 2021. On 14 April 2021, the diagnose of polymyalgia rheumatica was confirmed and Medrol 16 mg was started, and pain began to abate. Supportive therapy with Oleovit, Actonel and Calcium was added. The outcome of the event was recovering. *Symptoms reported, lab data, time to onset and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR. Of note, concomitant meds were not reported.* *WHO-UMC Causality Assessment: Possible.*
[redacted] 78/M [redacted] Dose 2 Not Recovered/Not Resolved Not Reported	Polymyalgia rheumatica Not Reported Not Reported	A 78-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 2) on 16 April 2021. The patient experienced pseudo rhizomelic arthritis on an unspecified date in April 2021, occurring a few days after the second injection. The patient had CRP of 90 (unspecified units) on an unknown date. The event required specialist advice and treatment with cortisone. The outcome of the event was not recovered. *This case describes a man with elevated CRP but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 87/F [redacted] Dose 1 Not Recovered/Not Resolved 15 Days	Polymyalgia rheumatica, Neck pain, Pain in extremity Cardiac disorder / Chronic obstructive pulmonary disease / Diuretic therapy / Hypertension / Local anaesthesia / Mineral supplementation / Muscle relaxant therapy / Pain / Respiratory disorder / Thrombosis prophylaxis Amlodipine mesilate / bendroflumethiazide, potassium chloride / bendroflumethiazide, potassium chloride / bisoprolol fumarate / calcium, colecalciferol / chlorzoxazone / lidocaine hydrochloride / paracetamol / paracetamol / salbutamol sulfate / tramadol / umeclidinium bromide, vilanterol trifenatate / warfarin sodium	A 87-year-old female patient received BNT162b2 (dose 1), on 27 December 2020. Medical history included hypertension, chronic obstructive pulmonary disease, heart disorder, respiratory disorder, pain, muscle relaxant therapy, thrombosis prophylaxis, diuretic therapy, local anaesthetic and calcium supplementation all from an unknown date and unknown if ongoing. There was no information regarding past medication. Multiple concomitant medications were reported. On 11 January 2021, the patient experienced polymyalgia rheumatica, neck pain and pain in upper extremities with a CRP value of 118 mg/l on an unspecified date. The patient was vaccinated with the second dose on 23 January 2021 and no additional events were reported. The patient was treated with prednisolone. The outcome of all the events was not recovered. *This case describes a woman with elevated CRP and multiple co-morbities and concomitant medications which confound the assessment* *WHO-UMC Causality Assessment: Unlikely.*
[redacted] 82/F [redacted] Dose 2 Recovered/Resolved 16 Days	Polymyalgia rheumatica Hypertension Lercanidipine / valsartan	A 82-year-old female patient with a medical history on hypertension treated with valsartan and lercanidipine, received BNT162b2 (dose 2) on 15 March 2021. On 31 March 2021, she experienced pseudopolyarthritis (myalgias and arthralgias mainly in the hips and shoulders) with a CRP: >100 mg/l on an unspecified date. Treatment with Cortancyl between 20 and 40 mg/day resulted in disappearance of pain on 26 May 2021. *Symptoms reported, lab data, time to onset and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR.* *WHO-UMC Causality Assessment: Possible.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 50/M [redacted] Dose 1 Recovering/Resolving 7 Days	Polymyalgia rheumatica, Chills, Weight decreased Not Reported Not Reported	A 50-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 1) on 08 January 2021. On 15 January 2021, he showed polyarthralgia affecting the pelvic and shoulder girdles as well as neck pain associated with some chills. Subsequently, his overall condition changed by losing 7 kilos. Later, he had arthromyalgia affecting mainly the girdle that was relieved by the non-steroidal anti-inflammatory drugs. He never had talalgia. He had pain when mobilising the shoulders, the pelvis and when pressing the muscles of the roots of the limbs suggestive of rhizomelic pseudopolyarthritis. Lab work-up on January 2021 showed: haemoglobin level at 118 g/l, platelets 420 giga/l (x10 9/l), inflammatory syndrome with fibrinogen at 6.8 g/l, CRP at 21 (unspecified values), ferritinemia at 730 (unspecified values), normal thyroid workup, serum protein electrophoresis in favour of an inflammatory syndrome, anti-neutrophil cytoplasm antibody negative, anti-neutrophil cytoplasm antibodies positive, anti-cyclic citrullinated peptide negative. Positron emission tomography (PET) scan showed intense hyperfixation of the shoulders, hips, right costo-vertebral joints of T1, bilateral acromioclavicular in favour of progressive rhizomelic pseudopolyarthritis. Systemic corticosteroid therapy was started. The patient was recovering from polymyalgia rheumatica, while outcome of the remaining events was unknown. *Symptoms reported, lab data and improvement of the symptoms after corticosteroids therapy support the diagnosis of PMR. Nevertheless, lack on information about medical history and concomitant meds precludes a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary *MAH Comment*
[redacted] 84/M [redacted] Dose 2 Recovered/Resolved 7 Days	Polymyalgia rheumatica, Inflammation, Muscular weakness, Oedema peripheral, Myalgia Hypertension / Tachycardia Not Reported	A 84-year-old male patient with a medical history of hypertension and tachycardia, received BNT162b2 (dose 2) on 15 April 2021. Concomitant medications were not reported. He received dose 1 on an unknown date with no adverse effect reported. On 22 April 2021, the patient experienced edema of extremities, inflammation, muscular weakness, polymyalgia, and polymyalgia rheumatica with CRP: 22 mg/l. The outcome of the events edema of extremities, inflammation, muscular weakness, polymyalgia, and polymyalgia rheumatica was recovered in June 2021. *Muscular weakness and edema of extremities are not typical symptoms of PMR which may suggest an alternative aetiology of the disease.* *WHO-UMC Causality Assessment: Unlikely.*
[redacted] 81/M [redacted] Dose 2 Recovering/Resolving 4 Days	Polymyalgia rheumatica, C-reactive protein increased, Arthralgia, Myalgia, White blood cell count increased Not Reported Not Reported	A 81-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 2) on 18 May 2021. On 27 April 2021, the patient previously received dose 1. On 21 May 2021 and 22 May 2021, he experienced polymyalgia rheumatica-like pain (felt pain in the proximal muscles of both upper and lower limbs) and had arthralgia in fingers of both hands and both shoulders. He also had myalgia the same day. Corticosteroid treatment (Predonine 10 mg) was started and after that, the patient was gradually recovering. Lab data included CRP increased to 5.20 mg/dl and WBC increased to 9.6 10*3/ul on 15 June 2021. *Lab data provided were performed a month after the onset of the symptoms. Even though the subject reported a positive response to corticosteroids therapy, more data are needed to perform a meaningful assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 67/F [redacted] Dose 1 Recovering/Resolving 8 Days	Polymyalgia rheumatica, Malaise, Pain, C-reactive protein increased, Hypoaesthesia, Inflammation Not Reported Not Reported	A 67-year-old female patient with no medical history and concomitant medications not reported, received BNT162b2 (dose 1) on 28 May 2021. A week after vaccination, the patient experienced neck, shoulder, legs pain. The symptoms slightly subsided in approximately five days. On 12 June 2021, the patient visited the hospital and WBC was 8780 (unspecified units), CRP increased to 16.41 (unspecified units), albumin 3.1 g/dl. On 15 June 2021, the patient was hospitalized, and steroid (Predonine 15g) was administered supposing it was polymyalgia rheumatica. Treatment led to improvement of the symptoms and albumin decreased to 2.6 (unspecified units) on an unspecified date. On 24 July 2021, symptoms improved, and steroid was ended. The outcome of the event 'PMR' was recovering. *This case describes a man with elevated CRP and neck, shoulder, legs pain. Although the reported time to onset is plausible with a temporal relationship, more data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*
[redacted] 63/M [redacted] Not Reported Recovered/Recovering 7 Days	Polymyalgia rheumatica Not Reported Not Reported	A 63-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose unknown). He had polymyalgia rheumatica with CRP =57 mg/l on an unspecified date. Ultrasound scan showed left sub acromial-deltoid bursitis and right hip synovitis. Prednisone was started and the symptoms disappeared in 48 hours. *This case describes a man with elevated CRP and PMR. Although patient responded to corticosteroids therapy, more data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 6. 26 AE Reports with CRP only

AER # **Age/Sex** **Country** **Dose** **Event Outcome** **Latency**	**PTs** **Relevant Medical History** **Concomitant medication**	**Summary** ***MAH Comment***
[redacted] 79/Unknown [redacted] Not Reported Unknown 14 Days	Polymyalgia rheumatica Not Reported Not Reported	A 79-year-old patient with no medical history and concomitant medications reported, received BNT162b2 (dose unspecified) on an unspecified date. Patient experienced shoulder pain with a one-hour morning rollover and CRP=40 mg/l, 14 days after vaccination. *This case describes a patient with elevated CRP and shoulder pain 14 days after vaccination. The lack of information about treatment, medical history and concomitant medications precludes a final assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

CASES PROVIDING SEDIMENTATION RATE AND NO C-REACTIVE PROTEIN VALUES

Of the 204 reports, 6 provided ESR values (no CRP values provided). They are described in more detail in Table 8.

Table 8. 6 AE Reports with ESR only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 79/F [redacted] Dose 2 Recovering/Resolving 7 Days	Polymyalgia rheumatica Not Reported Not Reported	A 79-year-old female patient with no medical history and concomitant medications reported, received BNT162b2 (dose 2) on 03 May 2021. The patient previously received dose 1 on 29 March 2021 and had no adverse reaction. On10 May 2021, she experienced polymyalgia rheumatica and was treated with Prednisone. Lab data included erythrocyte sedimentation rate (ESR) 109 mm/h on unknown date. The outcome of the event was recovering. *This case describes a woman with elevated ESR but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*
[redacted] 71/M [redacted] Dose 2 Not Recovered/Not Resolved 25 Days	Polymyalgia rheumatica Not Reported Not Reported	A 71-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 2) on 21 May 2021 and BNT162b2 (dose 1) on 15 April 2021. On 15 June 2021, he had polymyalgia rheumatica with pain in the hip that later extended to the arms and neck/shoulders. On an unspecified date, ESR = 44 (unspecified units). Treatment included analgesics and corticosteroids. *This case describes a woman with elevated ESR but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*
[redacted] Unknown/F [redacted] Not Reported Not Recovered/Not Resolved 14 Days	Polymyalgia rheumatica Not Reported Not Reported	A female patient with no medical history and concomitant medications reported, received BNT162b2 (unspecified dose), on 03 August 2021. On 17 August 2021, she had severe pain of the shoulder, more than the pelvic girdle (polymyalgia rheumatica) and ESR=150 u.w in the first hour. *This case describes a woman with elevated ESR but no other clinical description of PMR. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 8. 6 AE Reports with ESR only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 83/M [redacted] Dose 2 Unknown 27 Days	Polymyalgia rheumatica, Red blood cell sedimentation rate increased, General physical health deterioration, Arthralgia Not Reported Not Reported	A 83-year-old male patient with no medical history and concomitant medications reported, received BNT162b2 (dose 2) on 14 March 2021 and BNT162b2 (dose 1) on 21 February 2021. He experienced polymyalgia rheumatica, elevated erythrocyte sedimentation rate (30/70 mm Westergren method), increasing deterioration of the patient's general condition, pain especially in the shoulder area (arthralgia). Lab data included: antinuclear antibody: 1:100; red blood cell sedimentation rate: 30/70 mm elevated on an unspecified date. Treatment with 25 mg of prednisolone resulted in immediate improvement of the symptoms. *This case describes a man with elevated ESR but minimal pain in the vaccinated area. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable*
[redacted] 69/F [redacted] Dose 1 Unknown Not Reported	Polymyalgia rheumatica, Arthralgia, Pelvic pain, Erythema Not Reported Not Reported	A 69-year-old female patient with no medical history and concomitant medications reported, received BNT162b2 (dose 1) on 12 July 2021. She experienced polymyalgia rheumatica, arthralgia, pelvic pain and erythema. Lab data included ESR= 150 in the first hour. *This case describes a woman reporting elevated ESR and PMR symptoms with unknown time to onset. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

Table 8. 6 AE Reports with ESR only

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 84/F [redacted] Dose 2 Not Recovered/Not Resolved Not Reported	Polymyalgia rheumatica, Pain in extremity, Arthralgia, Musculoskeletal pain, Mobility decreased, Gait disturbance, Weight increased, Fluid retention Not Reported Not Reported	A 84-year-old female patient with no medical history and concomitant medications, received BNT162b2 (dose 2) on 28 January 2021 and BNT162b2 (dose 1) on 05 January 2021 and experienced mild limb and joint pain. At the beginning of February 2021 (about one week after the second vaccination), she had pain under the buttock. The pain worsened during the month and her mobility was severely impaired in February 2021, walking became increasingly difficult. At the beginning of March 2021 the pain was so intense that walking was almost impossible. Additionally, there was a massive weight gain from fluid retention in March 2021. The condition worsened. Blood sedimentation of 6.9 (unspecified units) was detected. On 18 March 2021, she was hospitalized and polymyalgia rheumatica was diagnosed and treated with cortisone. *This case describes a woman reporting elevated ESR and PMR symptoms with unknown time to onset. More data would be needed for a proper assessment.* *WHO-UMC Causality Assessment: Unclassifiable.*

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

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

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

Out of the 26 cases reporting only elevated CRP, eighteen cases did not report sufficient information and were considered unclassifiable as per WHO-UMC causality assessment. Five cases were confounded by possible alternative aetiology and were assessed as unlikely, and three cases met the criteria to be considered 'possible' as per WHO-UMC causality.

4. RESULTS – PMR EXACERBATION CASES REPORTED AFTER BNT162B2 VACCINATION

A total of 54 cases, among 565 cases that report PMR in the medical history, report PMR as an adverse event following vaccination, potentially indicating an exacerbation or flare of underlying PMR. Among these 54 cases there are 35 (64.8%) females and 19 (35.2%) males. Age was reported as ranging from 51 to 88 years (mean: 70.9; N: 51). The majority of cases were reported from the United Kingdom (50%), followed by France (13%), Netherland (11.1%) and Germany (7.4%).

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

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

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

- 10 reported corticosteroid therapy (2 of which started 4 and 6 months after vaccination).
- 11 reported an increase in corticosteroid dose.
- 1 reported analgesic.
- 1 reported acupuncture.
- 2 reported that no treatment was needed.

Among the 54 cases, 3 subjects reported it in the context of giant cell arteritis (GCA: known to be often present as concomitant disease with PM), 1 in the context of Herpes Zoster, 1 in the context of urinary infection and 1 in the context of tapering down corticosteroid to have a better immune response to vaccination. Time to onset was reported as shown in Table 7.

Table 7. Time to onset

Time to onset	Number of cases	Percentage (%)
Same day	9	16.6
1-3 days	16	29.6
4-10 days	8	15
11-30 days	10	18.4
>30 days	4	7.4
Unknown	7	13

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

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

Table 8. AE Reports describing PMR exacerbations after Dose 1 and Dose 2

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 51/F [redacted] Dose 1 and 2 Recovering 7 Days (after each dose)	Polymyalgia Rheumatica Polymyalgia Rheumatica Not Reported	A 51-year-old female patient received bnt162b2 and 7 days after each vaccination the patient had polymyalgia rheumatica complaints. Outcome is reported as recovering. *The subject is under continuous corticosteroid treatment indicating an unstable disease. Is not mentioned whether the treatment was suspended shortly before vaccination or "scaled down". Lack of these crucial information preclude a final diagnosis of relapse.*
[redacted] 72/F [redacted] Dose 1 Unknown 15 days and reported as pain and stiffness worsened after the 2nd vaccine dose without a specific timing reported.	Polymyalgia rheumatica, Disease recurrence, Musculoskeletal stiffness, Myalgia, Pain Polymyalgia rheumatica Not reported	A 72-year-old female patient received and about 2 weeks after first vaccination the patient started to experience stiffness and muscle soreness. After the second dose these symptoms worsened. He was diagnosed with polymyalgia rheumatica and started corticosteroids. *The information is confusing as it was reported as polymyalgia rheumatica in the medical history, but the subject now refers to it as a new disease. Lack of information on medical history and concomitant medication preclude a final diagnosis of relapse.*

Table 8. AE Reports describing PMR exacerbations after Dose 1 and Dose 2

AER # Age/Sex Country Dose Event Outcome Latency	PTs Relevant Medical History Concomitant medication	Summary MAH Comment
[redacted] 74/M [redacted] Dose 2 Recovering Unknown	Polymyalgia rheumatica, Arthralgia, Mobility decreased, Abdominal pain upper, Insomnia, Inappropriate schedule of product administration Polymyalgia rheumatica, Immunodeficiency, heart attack, B12 deficiency anemia, Esophageal acid reflux, autoimmune disorder Acetylsalicylic acid / atorvastatin calcium / diastase, magnesium carbonate, sodium bicarbonate / hydroxocobalamin / omeprazole / prednisolone / sacubitril, valsartan.	A 74-year-old male patient received BNT162B2 and after unknown time experienced polymyalgia rheumatica, extreme pains in shoulder, wrists and knees, lack of mobility, sleep disturbances and diabetes. After the second dose, on unknown date, the patient experienced the same symptoms. He performed blood exams, but the results were not reported. Outcome is reported as recovering. *The subject is under continuous corticosteroid treatment indicating an unstable disease. It is not mentioned whether the treatment was suspended shortly before vaccination or scale down. Lack of these crucial information preclude a final diagnosis of relapse. Time to onset of flare is not reported.*

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

5. CLINICAL TRIAL DATA

There were no reports of PMR in the pivotal Phase 2/3 Study C4591001 of individuals 16 years of age (21926 vaccine/21921 placebo) and older from Dose 1 to 1 month after Dose 2 that was placebo-controlled (data 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.

6. LITERATURE DATA

A literature search was conducted using Database: Database: OVID MEDLINE(R) 1946-present, OVID MEDLINE(R) In-Process & Epub Ahead of Print, Embase <1974 to 2022 January 21> for vaccination and Polymyalgia Rheumatica. Search strategy:

1. polymyalgia rheumatica.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, bo, bt, tn, dm, mf, dv, dq] (10383).
2. vaccination.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, bo, bt, tn, dm, mf, dv, dq] (616225).

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

A potential link between vaccination and new onset or relapse of PMR/giant cell arteritis was previously described with influenza vaccine. The role of the adjuvant was suspected to induce

inflammatory cytokine production such as interleukin-6 or tumor necrosis factor- α leading to a flare of the disease.[11]

Yang et al.[12] described a prospective observational study (70 patients) examining the immunogenicity and safety profile of the SARS-CoV-2 vaccine in patients with immune-mediated diseases taking immunomodulatory medications. Adults with an immune-mediated disease scheduled to receive either a Pfizer or Moderna SARS-COV-2 vaccine were enrolled in this study. The authors concluded that patients with autoimmune and inflammatory disease experience adverse events following SARS-CoV-2 vaccination as fever, fatigue and arthralgias mimicking flares with both frequency and severity appearing slightly greater than that of the reported results from the vaccine clinical trials.

Spinelli et al.[13] reported a study including 126 patients with rheumatic Musculo-skeletal diseases (RMD) (all under therapy). Overall, 5 cases reported a flare of the disease (0.007 person/month) After excluding other possible causes, and confirming the temporal relationship with the vaccination, only 3 out of the 126 evaluated patients showed a mild disease flare probably attributable to the vaccination. All disease reactivations consisted in mild articular flares lasting 7 days on average and requiring just symptomatic treatment. The authors conclude that the low incidence rate of disease reactivation and the similar adverse event following vaccination occurrence compared to controls reassure on mRNA vaccine safety in RMD patients.

Bixio et al.[14] performed a study focusing on COVID-19 vaccines safety and immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs), they have estimated an incidence of between 5% and 17% for RMD flares after COVID-19 vaccination. The results showed a low flare rate after the BNT162b2 COVID 19 vaccine in patients with RA in remission (7.8% of which 83% after the 2nd dose and all resolved within 2 weeks). Of note, 83% of the patients with flares withdrew or delayed anti-rheumatic therapies in the proximity of vaccination according to ACR guidelines. The data were consistent with previous findings about Varicella-zoster virus (6.7%) and Hepatitis B virus (2.2%) vaccinations.

---

[11] Ottaviani S, Juge PA, Forien M, Ebstein E, Palazzo E, Dieude P. Polymyalgia rheumatica following COVID-19 vaccination: A case-series of ten patients. Joint Bone Spine. Dec 22 2021;89(2):105334.

[12] M. Yang PK, D. Paez, A. Carvidi, M. Matloubian, M. Nakamura, L. S. Gensler. Reactogenicity of sars-cov-2 vaccines in patients with autoimmune and inflammatory disease. *Ann Rheum Dis*. May 2021 2021.

[13] Spinelli FR, Favalli EG, Garufi C, et al. Low frequency of disease flare in patients with rheumatic musculoskeletal diseases who received SARS-CoV-2 mRNA vaccine. *Arthritis Res Ther*. Jan 11 2022;24(1):21.

[14]Bixio R, Bertelle D, Masia M, Pistillo F, Carletto A, Rossini M. Incidence of Disease Flare After BNT162b2 Coronavirus Disease 2019 Vaccination in Patients With Rheumatoid Arthritis in Remission. *ACR Open Rheumatol*. Dec 2021;3(12):832-833.

Watad A et al.[15] evaluated immune-mediated diseases (IMDs) flares or new disease onset within 28-days of SARS-CoV-2 vaccination at five large tertiary centers in countries with early vaccination adoption, three in Israel, one in UK, and one in USA. Of the relapsed cases, 75% were mild to moderate in severity and over 80% of cases had excellent resolution of inflammatory features, mostly with the use of corticosteroid therapy. They concluded that, despite the high population exposure in the regions served by these centers, IMDs flares or onset temporally associated with SARS-CoV-2 vaccination appear rare.

Boekel L et al.[16] describe the results of a questionnaire that assessed adverse events following COVID-19 vaccinations in patients with autoimmune diseases and healthy controls. The questionnaire was sent to patients with systemic autoimmune diseases who were enrolled in two ongoing prospective cohort studies (Netherlands Trial Register, trial ID NL8513 and NCT04498286). Between April 26, 2020 and March 1, 2021, all adult patients with systemic autoimmune diseases from the Amsterdam Rheumatology and Immunology Center (Amsterdam, Netherlands), and all adult patients with multiple sclerosis from the Amsterdam Multiple Sclerosis Center of Amsterdam UMC (Amsterdam, Netherlands) were invited to participate. Patients enrolled in the first study were asked (but not obliged) to recruit their own healthy control participant who was of the same sex and of comparable age (age difference <5 years). Data were collected via online questionnaires distributed via email. Analysis of the results of our questionnaire demonstrate that adverse events of COVID-19 vaccinations in patients with autoimmune diseases are comparable with controls, independent of the type of vaccine. Subjects were requested to send all adverse events reported within the first 7 days after vaccination, in addition patients with rheumatic diseases and healthy controls were asked whether they experienced an increased number of joint complaints in the first 2 months after vaccination. The observed adverse events consisted of expected transient local or systemic reactions that were mostly self-limiting. The frequency of participants who reported adverse events was lower than that reported in clinical trials, but similar to a nationwide observational study on adverse events of COVID-19 vaccinations in the general population done in the UK. The data were consistent with previous studies that reported higher frequencies of adverse events in women and younger people. The authors conclude that COVID-19 vaccinations do not seem to trigger autoimmune disease flares, which is in accordance with data from previous small studies that assessed consequences of mRNA vaccines in patients with autoimmune diseases.

Many published studies showed reassuring results after COVID-19 vaccination with no increase of autoimmune diseases nor flares in subjects with underlying autoimmune

[15] Watad A, De Marco G, Mahajna H, et al. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. *Vaccines* (Basel). Apr 29 2021;9(5).

[16] Boekel L, Kummer LY, van Dam KPJ, et al. Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. *The Lancet Rheumatology*. 2021;3(8):e542-e545.

diseases.[12,14,15,16,17,18] Interestingly, Yang et al.[12] suggest that patients with autoimmune and inflammatory disease experience adverse events following SARS-CoV-2 vaccination as fever, fatigue and arthralgias that mimicking flares. When the time to onset of flare is reported in the literature article is reported as a mean of 4 days after vaccination which suggest the possibility of a reactogenicity event from the vaccine instead of a real flare of the underlying disease.

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

A French rheumatology service at the University of Paris Hospital described as series of 10 patients fulfilling ACR/EULAR criteria for PMR following COVID-19 vaccination (7 were new-onset and 3 were relapses). Nine of the patients were vaccinated with BNT162b2 and one with mRNA-1273. The median time to symptoms was 10 days, 70% of the patients were women and the median patient age was 74.5 years. All patients were PCR negative for SARS-CoV-2 and had elevated C-reactive protein levels (median 26 mg/l) and PET scans indicative of inflammation in the PMR-related joint sites. All responded favorable to treatment with systemic (n=9) or local (n=1) glucocorticoids (+/- methotrexate [n=3] or tocilizumab [n=1]). The authors also describe that during the period of May to October 2021, 12 patients were diagnosed with PMR while from May to October in previous years (2020) and (2018 and 2019), PMR diagnoses were lower at 3 and 6, respectively. While the authors postulate a causal association, they concede that this data cannot exclude the possibility that these patients would have developed PMR without vaccination.[11]

---

[17] Barbhaiya M LJ, Bykerk VP, et al. Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City. *Ann Rheum Dis*. 2021;80:1352-1354.

[18] Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. *The Lancet Rheumatology*. 2021;3(7):e469-e470.

[19] Mettler C, Jonville-Bera AP, Grandvuillemin A, Treluyer JM, Terrier B, Chouchana L. Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study. Rheumatology (Oxford). Oct 9 2021.

Several additional articles have been published describing polymyalgia flare or new onset of polymyalgia rheumatica after COVID-19 vaccination (including BNT162b2, ChAdOx1 and mRNA1273 COVID-19 vaccination).[11,20,21,22,23,24]

[20] Izuka S, Komai T, Natsumoto B, Shoda H, Fujio K. Self-limited Polymyalgia Rheumatica-like Syndrome Following mRNA-1273 SARS-CoV-2 Vaccination. *Intern Med.* Dec 28 2021.

[21] COVID-19 vaccine shot as a trigger? Comment on: "Can SARS-CoV-2 trigger relapse of polymyalgia rheumatica?" by Manzo et al. Joint Bone Spine 2021;88:105150. Joint Bone Spine. Jan 2022;89(1):105282.

[22] Manzo C, Natale M, Castagna A. Polymyalgia rheumatica as uncommon adverse event following immunization with COVID-19 vaccine: A case report and review of literature. *Aging Med (Milton).* Aug 15 2021.

[23] Osada A, Sakuragi C, Toya C, Mitsuo A. New-onset Polymyalgia Rheumatica Following the Administration of the Pfizer-BioNTech COVID-19 *Vaccine. Intern Med.* Dec 11 2021.

[24] Chan JEZ, Irimpen A. Severe but Self-Limiting Polyarthralgia with Functional Impairment Following ChAdOx1 nCov-19 Vaccination in an Elderly Recipient. *Vaccines* (Basel). Oct 21 2021;9(11).

7. OBSERVED VERSUS EXPECTED ANALYSIS OF SPONTANEOUSLY REPORTED EVENTS

The MAH conducted unadjusted observed to expected ratio (O/E) analyses for the 628 new onset cases of polymyalgia rheumatica reported through 18 December 2021.

O/E analyses using 21- and 42-day risk windows are provided in Table 9 overall and by gender for all cases reported globally, and by age for the United States (US) and European Economic Area (EEA) countries only because these regions make detailed information about vaccine administration publicly available.

Expected polymyalgia rheumatica cases for the O/E analyses were derived using background incidence rates from a study in the United Kingdom that extracted anonymized electronic medical records from general practices for patients over the age of 40 years from the Clinical Practice Research Datalink in the period of 1990 – 2016 [i] This study reported an overall polymyalgia rheumatica incidence rate of 95.9 cases per 100,000 person-years, with rates higher for females and increasing with age. Based on age-specific background rates from this study, all O/E ratios and upper limits of the 95% confidence intervals (CI) across all stratifications were below 1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.

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

Events	Observed Cases	Person-Years[a]	Background Rate Per 100,000 Person-Years[b]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
Global – all ages							
21 day risk period	460	88,917,877.7	95.90	85,272.2	0.005	0.005	0.006
42 day risk period	507	132,927,707.4	95.90	127,477.7	0.004	0.004	0.004
By Age – EEA and US							
<=11 years							
21 day risk period	0	785,983.1	0.00	0.0	NA	NA	NA
42 day risk period	0	1,113,755.0	0.00	0.0	NA	NA	NA
12-17 years							
21 day risk period	0	2,558,968.5	0.00	0.0	NA	NA	NA
42 day risk period	0	3,737,127.5	0.00	0.0	NA	NA	NA
18-24 years							
21 day risk period	0	3,601,697.5	0.00	0.0	NA	NA	NA
42 day risk period	0	5,262,763.4	0.00	0.0	NA	NA	NA
25-49 years							
21 day risk period	12	15,484,028.8	3.20	495.5	0.024	0.013	0.042
42 day risk period	13	22,700,554.0	3.20	726.4	0.018	0.010	0.031
50-59 years							
21 day risk period	42	7,236,785.4	27.60	1,997.4	0.021	0.015	0.028
42 day risk period	44	10,620,266.2	27.60	2,931.2	0.015	0.011	0.020

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

Events	Observed Cases	Person-Years[a]	Background Rate Per 100,000 Person-Years[b]	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
60-69 years							
21 day risk period	95	6,262,999.7	105.70	6,620.0	0.014	0.012	0.018
42 day risk period	107	9,165,352.6	105.70	9,687.8	0.011	0.009	0.013
70+ years							
21 day risk period	196	9,337,505.6	293.50	27,405.6	0.007	0.006	0.008
42 day risk period	220	13,961,488.5	293.50	40,977.0	0.005	0.005	0.006
By Gender – EEA and US							
Females							
21 day risk period	192	23,992,023.4	125.20	30,038.0	0.006	0.006	0.007
42 day risk period	216	35,277,492.8	125.20	44,167.4	0.005	0.004	0.006
Males							
21 day risk period	153	21,275,945.3	64.40	13,701.7	0.011	0.009	0.013
42 day risk period	168	31,283,814.4	64.40	20,146.8	0.008	0.007	0.010

a. European Centre for Disease Prevention and Control. Data on COVID-19 vaccination in the EU/EEA. Available from: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea; Our World in Data. COVID-19 Dataset. Available from: https://github.com/owid/covid-19-data; Centers for Disease Control and Prevention. Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic.

b. Partington, R. J., Muller, S., Helliwell, T., Mallen, C. D., & Abdul Sultan, A. (2018). Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Annals of the rheumatic diseases, 77(12), 1750–1756.[25]

[25] Partington RJ, Muller S, Helliwell T, Mallen CD, Abdul Sultan A. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. *Ann Rheum Dis*. Dec 2018;77(12):1750-1756.

For the person-year calculations in each risk window, vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine when available. For countries where the Pfizer BioNTech COVID-19 vaccine is authorized but manufacturer stratified data were not available, the doses administered were assumed to be divided equally by the number of brands of vaccines authorized during that period. The estimate of administered doses does not reflect exposure in persons vaccinated in countries that did not publicly report.

There are several limitations to observed to expected analyses for signal detection. The observed case counts are likely to be underestimated due to underreporting that occurs with spontaneous report surveillance. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous surveillance systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition. Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association.

With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Thus, the exposure is underestimated. The expected count also assumes that the incidence rate in the vaccinated population is the same as that in the population used to calculate the background rate. The background rates used in these analyses are from the UK; a large proportion of exposure data derive from the US and other areas of Europe. 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 expected in the vaccinated population.

8. CONCLUSION

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

Out of the remaining 204 cases, only 16 co-reported elevated CRP and ESR levels, while 26 cases report only elevated CRP and 6 reported only elevated ESR. Most of the reports (30 cases) did not report sufficient information to confirm the PMR diagnosis or reported it in the context of alternative diseases that could cause elevation of CRP or ESR (11 cases). Seven reports described possible PMR cases after vaccination.

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

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

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

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

APPENDIX 6A.4 GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AKI	Acute kidney injury
CD	cluster of differentiation
CI	confidence interval
CM	clinical modification
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
EBV	Epstein-Barr virus
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
GN	glomerulonephritis
HLT	high level term
ICD	International classification of diseases
IFN	interferon
IgAN	immunoglobulin A nephropathy
IL	interleukin
MA	marketing authorization
MAH	marketing authorization holder
MCD	minimal change disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NS	nephrotic syndrome
NSAID	nonsteroidal anti-inflammatory drug
O/E	observed to expected
OWD	our world data
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	preferred term
PY	person-years
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
US	United States

1. INTRODUCTION

Reference is made to the Signal Assessment Report dated 30 September 2021, in which the Pharmacovigilance Risk Assessment Committee (PRAC) requested the Marketing Authorization Holder (MAH) to provide the following:

"Having considered the available evidence from cumulative review submitted by the MA, 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 to product information accordingly and without delay."

Response

2. METHODOLOGY

As a previously submitted COVID-19 Vaccine - Response to PRAC - Safety Signal of Glomerulonephritis and Nephrotic Syndrome covering a reporting period through 03 August 2021 cumulative review contained all available information from a pivotal clinical trial, no additional information is available for clinical trial data.

Literature Search

As a comprehensive cumulative review of the literature was provided in the previous response to PRAC, an interval search was conducted for information on COVID vaccine and terms relevant to Glomerulonephritis and Nephrotic syndrome by using the following names for the vaccine (PF-07302048 or PF07302048 or "PF 07302048" or PF-7302048 or PF7302048 or PF 7302048 or BNT162B2 or BNT 162B2 or BNT162$ or BNT 162$ or tozinameran or comirnaty) in the following databases: OVID MEDLINE(R) 1946-present, OVID MEDLINE(R) In-Process & Epub Ahead of Print, Embase <1974 to 2021 December 28>.

Cases from Pfizer's Safety Database

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality.

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

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

3. RESULTS

3.1.1. Literature Data

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

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

of nephrotic syndrome cannot be proven on basis of observation of nephrotic syndrome after vaccination alone.

The second article, Izzedine et al[2], was a commentary and case series on development of nephrotic syndrome and vasculitis following SARS-CoV-2 Vaccine. The authors provided a summary of reported cases from literature sources following COVID-19 vaccination and discuss proposed mechanisms or explanations for the observed events, in form of part publications of the same events with other vaccinations (notably influenza), or suspected trigger role of the immune response to vaccination. However, authors recognize that such mechanisms remain to be elucidated, stating that 'it is also possible that these phenomena are completely circumstantial and unrelated'. The discussion on potential role of environmental factors, such as infections, is relevant and based on temporal and spatial clustering of cases. The authors also noted that reported cases of GN do not provide evidence of exclusion of COVID-19 infection, and thus, whether the reported cases could be attributed to SARS-COV-2 warrants investigation.

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

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

The fifth article, Mancianti et al[5], was a case report of a 39-year-old Caucasian male with a history of biopsy-proven minimal change disease with nephrotic syndrome 38 years before (at age on 1, who remained on been on regular follow-up for 37 years) and who developed MCD and AKI 3 days after first dose of the BNT162b1. The patient recovered after standard

treatment (prednisolone). Similar to earlier publications, this article also presents a suspicion of association with the vaccine due to temporal relationship and includes a presentation of the role of immune response to vaccination in inducing T-cell mediated response based on theoretical and animal model consideration, also proposing that dosing is not continued in patients who experience such events.

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

Literature summary:

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

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

3.2. Cases from Pfizer's Safety Database

A total of 226 cases were retrieved from the global safety database using the search strategy mentioned above. Some cases were coded with more than one of the relevant events in the HLT. Table 1 below lists relevant PTs reported in this dataset and a respective number of cases.

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

PT	Number of Cases
Nephrotic syndrome	138
Glomerulonephritis	27

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

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

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

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

Table 2. Reported Age in 226 Cases

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

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

Table 3. Reporting Country in 226 Cases

Country	Number of Cases	% of Total Cases
Japan	47	20.80
France	42	18.60
Germany	27	11.90
Spain	13	5.80
United States	13	5.80

Table 3. Reporting Country in 226 Cases

Country	Number of Cases	% of Total Cases
Italy	12	5.30
United Kingdom	9	4.00
Australia	8	3.50
Netherlands	5	2.20
New Zealand	5	2.20
Japan	47	20.80
France	42	18.60

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

Out of the 226 cases, 102 cases described a pre-existing medical condition and/or use of co-suspect/concomitant medication representing a reasonable alternative cause of the relevant events; some examples of conditions are autoimmune disorders, immunodeficiencies, infections, diabetes, and some examples of medications are NSAIDs, immunosuppressants, cephalosporins. Six (6) out of these 102 cases reported COVID-19 or Suspected COVID-19. Out of these 102 cases, 61 cases reported a pre-existing glomerulonephritis, nephrotic syndrome related events and/or acute kidney injury, renal impairment, renal transplant, chronic kidney disease, renal cancer. These 61 cases reported a total of 69 relevant events from HLT Glomerulonephritis and nephrotic syndrome. When dose sequence was provided in these 61 cases, it was following Dose 1 for 25 relevant events, Dose 2 for 39 events and Dose 3 for 4 events. The outcome of the relevant events at the time of reporting was resolved/resolving for 35 events; not resolved for 12 events; resolved with sequelae for 3 events, and unknown for 19 events. The time to onset (latency) from time of the vaccination until the development of the relevant event was reported as: from within the same day of vaccination to 3 days post vaccination for 15 relevant events, from day 5 to day 10 for 13 events, from day 13 to day 24 for 9 events, and post day 24 for 10 events.

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

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

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

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

of 120 cases. Out of 120 cases, renal failures was reported in 2 cases.

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

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

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

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

O/E Analysis

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

O/E using 14-day, 21-day, and 42-day risk windows are provided in Table 4 overall for all processed cases and backlog cases reported globally, by gender for all processed cases reported globally, as well as by dose and age for the United States (US) and European Economic Area (EEA) countries only because these regions make detailed information about vaccine administration publicly available.

Expected glomerulonephritis and nephrotic syndrome cases for the O/E analyses were derived using background incidence rates from a retrospective cohort study using two large US administrative claims-based datasets.[7] Primary cases of glomerulonephritis thought to originate in and be primarily confined to the kidney were identified using an algorithm based on ICD-9-CM codes. Based on these background rates, all O/E ratios and upper limits of the 95% confidence intervals (CI) across all stratifications and risk windows were below 1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.

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

Stratification	Observed Cases	Person-Years (PY)[a]	Background Rate Per 100,000 PY[b]	Expected Cases	O/E Ratio	95% CI Lower Limit	95% CI Upper Limit
Global – all ages							
Overall processed cases							
14 day risk window	143	46,278,258.0	38.50	17,817.1	0.008	0.007	0.009
21 day risk period	172	61,214,970.0	38.50	23,567.8	0.007	0.006	0.008
42 day risk period	197	89,749,700.0	38.50	34,553.6	0.006	0.005	0.007
Overall processed + backlog cases (Note 0 cases in the backlog)							
14 day risk window	143	46,278,258.0	38.50	17,817.1	0.008	0.007	0.009
21 day risk period	172	61,214,970.0	38.50	23,567.8	0.007	0.006	0.008
42 day risk period	197	89,749,700.0	38.50	34,553.6	0.006	0.005	0.007
By dose - EEA and US							
All ages Dose 1							
14 day risk window	33	3,247,087.0	38.50	1,250.1	0.026	0.018	0.037
21 day risk period	43	4,982,393.6	38.50	1,918.2	0.022	0.016	0.030
42 day risk period	49	4,982,393.6	38.50	1,918.2	0.026	0.019	0.034
All ages Dose 2							
14 day risk window	46	4,184,495.0	38.50	1,611.0	0.029	0.021	0.038
21 day risk period	56	6,551,217.7	38.50	2,522.2	0.022	0.017	0.029
42 day risk period	69	14,798,341.0	38.50	5,697.4	0.012	0.009	0.015
All ages Dose 3							
14 day risk window	6	3,655,235.5	38.50	1,407.3	0.004	0.002	0.009
21 day risk period	6	5,008,070.3	38.50	1,928.1	0.003	0.001	0.007
42 day risk period	6	7,615,135.2	38.50	2,931.8	0.002	0.001	0.004

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

Stratification	Observed Cases	Person-Years (PY)[a]	Background Rate Per 100,000 PY[b]	Expected Cases	O/E Ratio	95% CI Lower Limit	95% CI Upper Limit
By Age – EEA and US							
<=11 years							
14 day risk window	0	494,578.3	20.00	98.9	0.000	-	-
21 day risk period	1	734,938.9	20.00	147.0	0.007	0.000	0.038
42 day risk period	1	1,054,139.0	20.00	210.8	0.005	0.000	0.026
12-17 years							
14 day risk window	12	1,111,690.7	20.00	222.3	0.054	0.028	0.094
21 day risk period	14	1,669,840.0	20.00	334.0	0.042	0.023	0.070
42 day risk period	16	2,561,798.6	20.00	512.4	0.031	0.018	0.051
18-24 years							
14 day risk window	8	1,172,457.5	20.00	234.5	0.034	0.015	0.067
21 day risk period	10	1,776,857.7	20.00	355.4	0.028	0.013	0.052
42 day risk period	13	2,875,980.0	20.00	575.2	0.023	0.012	0.039
25-49 years							
14 day risk window	31	3,964,417.9	20.00	792.9	0.039	0.027	0.055
21 day risk period	39	6,042,786.8	20.00	1,208.6	0.032	0.023	0.044
42 day risk period	42	10,347,398.0	20.00	2,069.5	0.020	0.015	0.027
50-59 years							
14 day risk window	8	1,313,630.2	20.00	262.7	0.030	0.013	0.060
21 day risk period	9	1,955,385.1	20.00	391.1	0.023	0.011	0.044
42 day risk period	14	3,475,172.8	20.00	695.0	0.020	0.011	0.034

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

Stratification	Observed Cases	Person-Years (PY)[a]	Background Rate Per 100,000 PY[b]	Expected Cases	O/E Ratio	95% CI Lower Limit	95% CI Upper Limit
60-69 years							
14 day risk window	5	1,219,547.6	57.00	695.1	0.007	0.002	0.017
21 day risk period	11	1,749,620.6	57.00	997.3	0.011	0.006	0.020
42 day risk period	12	2,829,307.6	57.00	1,612.7	0.007	0.004	0.013
70+ years							
14 day risk window	21	1,810,495.3	57.00	1,032.0	0.020	0.013	0.031
21 day risk period	21	2,612,252.5	57.00	1,489.0	0.014	0.009	0.022
42 day risk period	26	4,252,073.7	57.00	2,423.7	0.011	0.007	0.016
By Gender - Global							
Females							
14 day risk window	46	5,876,013.2	32.50	1,909.7	0.024	0.018	0.032
21 day risk period	58	8,767,091.2	32.50	2,849.3	0.020	0.015	0.026
42 day risk period	65	14,519,811.0	32.50	4,718.9	0.014	0.011	0.018
Males							
14 day risk window	39	5,210,804.2	46.50	2,423.0	0.016	0.011	0.022
21 day risk period	47	7,774,590.3	46.50	3,615.2	0.013	0.010	0.017
42 day risk period	59	12,876,059.0	46.50	5,987.4	0.010	0.008	0.013

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

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

For the person-year calculations in each risk window, vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine when available.[8,9,10] For countries where the Pfizer BioNTech COVID-19 vaccine is authorized but manufacturer stratified data were not available, the doses administered were assumed to be divided equally by the number of brands of vaccines authorized during that period. The estimate of administered doses does not reflect exposure in persons vaccinated in countries that did not publicly report.

There are several limitations to observed to expected analyses for signal detection. The observed case counts are likely to be underestimated due to underreporting that occurs with spontaneous report surveillance. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous surveillance systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition. Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association.

With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Thus, the exposure is underestimated. The expected count also assumes that the incidence rate in the vaccinated population is the same as that in the population used to calculate the background rate. The background rates used in these analyses are from the US; a large proportion of exposure data derive from Europe. 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 expected in the vaccinated population.

4. CONCLUSION

Based on the nephrology related literature, William G, et al[11], the current evidence suggests that infections may initiate many of the autoimmune or other reactions in genetically susceptible individuals, which lead to glomerular disease through numerous simultaneous and/or sequential pathways that begin with activation of the innate immune response. These pathways vary depending on the nature of the infectious pathogen and the genetically regulated immune response of the host. These mechanisms include immune dysregulation, adjuvant or bystander effects, epitope spreading, molecular mimicry, epitope conformational changes, and antigen complementarity. Infections may also have direct effects on podocytes and other glomerular cells, either due to direct infection or the induction of innate immune responses. Continued efforts are essential to clarify the genetic basis for susceptibility to GN, as are efforts to improve therapy.[11]"

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

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

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

REFERENCES

1 Nakazawa E, Uchimura T, Hirai Y, Togashi H, Oyama Y, Inaba A et al. New-onset pediatric nephrotic syndrome following Pfizer-BioNTech SARS-CoV-2 vaccination: a case report and literature review. CEN Case Rep. 2021: 1–5.

2 Izzedine H, Bonilla M, Jhaveri KD. Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial? Nephrology Dialysis Transplantation. 2021; 36(9):1565-1569.

3 Abdulgayoom M, Albuni MK, Abdelmahmuod E, Murshed K, Eldeeb Y. Minimal change nephrotic syndrome four days after the administration of Pfizer-BioNTech COVID-19 vaccine-a new side effect or coincidence? Clinical Case Reports. 2021; 9(10): e05003.

4 Davidovic T, Schimpf J, Sprenger-Mahr H, Abbassi-Nik A, Soleiman A, Zitt E et al. De Novo and Relapsing Glomerulonephritis following SARS-CoV-2 mRNA Vaccination in Microscopic Polyangiitis. Case Reports in Nephrology. 2021; 2021: 8400842.

5 Mancianti N, Guarnieri A. Tripodi S. Salvo DP, Garosi G. Minimal change disease following vaccination for SARS-CoV-2. Journal of Nephrology. 2021; 34(4): 1039-1040.

6 Hanna C., Herrera Hernandez LP, Bu L, Kizilbash S, Najera L, Rheault MN et al. IgA nephropathy presenting as macroscopic hematuria in 2 pediatric patients after receiving the Pfizer COVID-19 vaccine. Kidney International. 2021; 100(3): 705-706.

7 Wetmore JB, Guo H, Liu J, et al. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney Int. 2016 Oct;90(4):853-60. doi: 10.1016/j.kint.2016.04.026. Epub 2016 Jul 15. PMID: 27425855.

8 European Centre for Disease Prevention and Control. Data on COVID-19 vaccination in the EU/EEA. Available from: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed June 2021.

9 Our World in Data. COVID-19 Dataset. Available from: https://github.com/owid/covid-19-data. Accessed June 2021

[10] Centers for Disease Control and Prevention. Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic.

[11] William G, et al. The etiology of glomerulonephritis: roles of infection and autoimmunity. International Society of Nephrology *Kidney International* (2014) 86, 905–914.

APPENDIX 6A.5 MULTISYSTEM INFLAMMATORY SYNDROME

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AER	adverse event report
BC	Brighton Collaboration
BNP	B-type natriuretic peptide
BP	blood pressure
COVID-19	coronavirus disease 2019
CT	computed tomography
CRP	C-reactive protein
DLP	data lock point
EMA	European Medicines Agency
IL	interleukin
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MIS	multisystem inflammatory syndrome
MRI	magnetic resonance imaging
MSSR	monthly summary safety report
PCR	polymerase chain reaction
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	(MedDRA) preferred term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

In August 2021, the EMA issued a signal assessment report on MIS-C with SARS-CoV-2 vaccination and requested all MAH of these vaccines perform cumulative review of MIS- C and MIS-A.

A cumulative review of cases reported within Pfizer's global safety database was performed with a DLP of 02 September 2021. Analysis of these cases, in conjunction with observed to expected analysis did not support a causal relationship between Comirnaty and MIS-C/A.

In concordance with Pfizer's assessment the PRAC agreed that the signal be closed and that no update to the product information is currently warranted.

PRAC requested the MAH continue to closely monitor MIS-C/A and report on new cases in the MSSR and PSUR. Cases were requested to be assessed using the BC case definition[1] with MIS-C defined as patients age < 21 years and MIS-A those age ≥ 21 years.

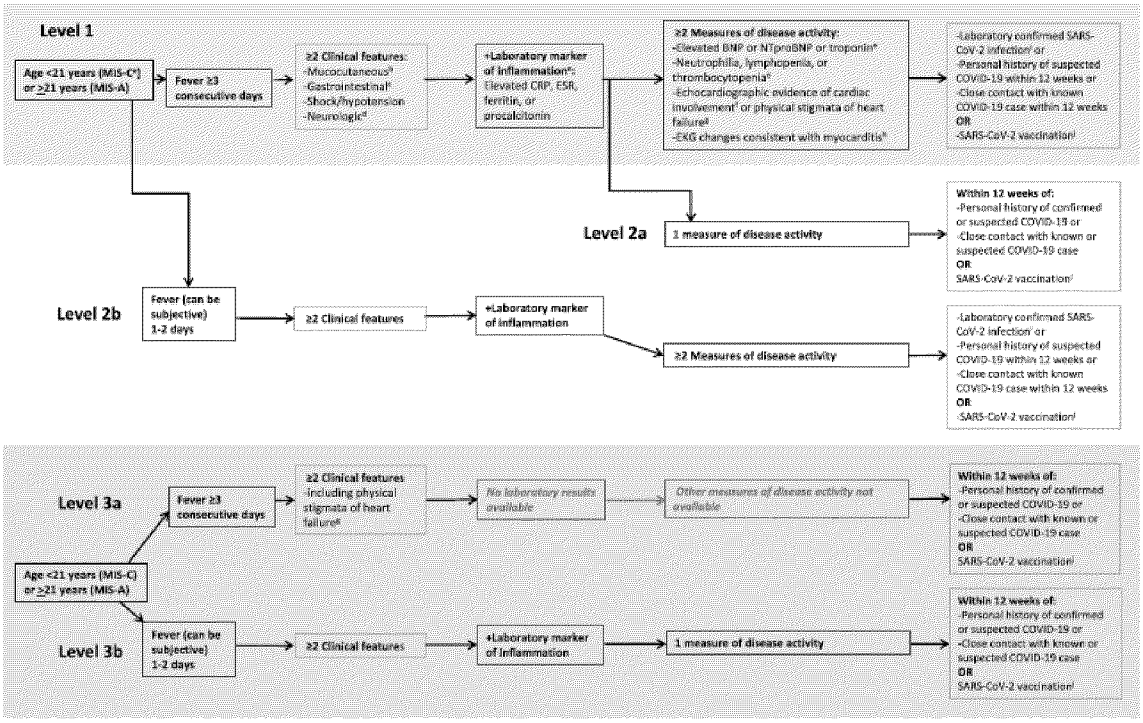
Interval cases have subsequently been analyzed and discussed in the 11th MSSR (interval 03 September 2021 through 26 October 2021) and 1st bimonthly safety report (interval 27 October 2021 through 15 December 2021).

2. CASE DEFINITION

The BC MIS-C Working Group developed the case definition of ''Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A)" to be utilized in the evaluation of AEs following immunization as shown in Figure 1.[1] Per the PRAC request, this algorithm was utilized during the review of cases retrieved from the Pfizer safety database as described in this report.

The application of such criteria on post-marketing data is limited in cases where minimal clinical detail has been reported. This is particularly true of BC Level 5 "*sufficient clinical and laboratory evidence exists to ascertain that a case is NOT MIS-C/A. An alternative diagnosis has been ascertained.*"[1] In the MAH search of the database for potential reports of MIS-C/A that are not specifically reported as such, it should be noted that some cases with insufficient clinical detail cannot be categorized as BC level 5 because they also lack sufficient information to ascertain an alternative diagnosis. Such cases have been classified as having 'insufficient information'.

Figure 1. Brighton Collaboration Multi-system Inflammatory Syndrome Case Definition algorithm [1]



Level 4 of Diagnostic Certainty – Insufficient Evidence
Reported MIS-C/A with insufficient evidence to meet Level 1–3 in the case definition.
Example:
2 clinical features and history of COVID-19 within 12 weeks, but laboratory results and measures of disease activity are not available, and the fever criteria is not met.
Level 5 of Diagnostic Certainty – Not a case of MIS-C/A
Sufficient clinical and laboratory evidence exists to ascertain that a case is **NOT** MIS-C/A.
An alternative diagnosis has been ascertained.

Note: Minimal to mild respiratory symptoms may be present and does not exclude a case of MIS-C/A, however a case must be excluded if there is concern for COVID-19-related pulmonary disease. One of the critical components of the case definition is that it is only applied when there is no clear alternative diagnosis for the reported event.

a: MIS-C=multisystem inflammatory syndrome in children, MIS-A=multisystem inflammatory syndrome in adults, CRP=C reactive protein (detected by any measure), ESR=erythrocyte sedimentation rate, BNP=brain natriuretic protein, NT-proBNP=N terminal pro-BNP, EKG=electrocardiogram, SARS-CoV-2=severe acute respiratory syndrome coronavirus-2, COVID-19=coronavirus disease 2019; **b:** rash, erythema or cracking of the lips/mouth/ pharynx, bilateral nonexudative conjunctivitis, erythema or edema of the hands or feet; **c:** abdominal pain, vomiting, diarrhea; **d:** altered mental status, headache, weakness, paresthesias, lethargy; **e:** laboratory values are defined as low or high based on local laboratory norms; **f:** echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echo brightness, lack of distal tapering), valvular regurgitation, pericardial effusion, evidence of abnormal left ventricular strain; **g:** physical stigmata of heart failure: gallop (IF diagnosed by expert) or rales, lower extremity edema, jugular venous distension, hepatosplenomegaly; **h:** EKG changes consistent with myocarditis or myo-pericarditis: abnormal ST segments and/or arrhythmia and/or pathologic Q waves and/or AV conduction delay and/or PR segment depression and/or low voltage QRS; **i:** laboratory evidence of SARS-CoV-2 infection: serologic evidence of SARS-CoV-2 infection OR SARS-CoV-2.

3. MIS CASES IN THE PSUR INTERVAL PERIOD

Pfizer's safety database was searched for all cases reporting the following MedDRA preferred terms, as delineated in the PRAC request.

> Multisystem inflammatory syndrome in children, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, Kawasaki's disease, toxic shock syndrome, distributive shock, hypotensive crisis, vaccine associated enhanced disease, vaccine associated enhanced respiratory disease, cytokine release syndrome, cytokine storm, haemophagocytic lymphohistiocytosis, macrophage activation, macrophages increased, septic shock, autoinflammatory disease, multisystem inflammatory syndrome in adults, multisystem inflammatory syndrome

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

3.1. MIS-C

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

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

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

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

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

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

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

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

The patient had no medical history and reported no other vaccines within four weeks prior to Dose 1 nor any concomitant medications in the two weeks before event onset.

Dose 1 was received 13 November 2021. It is reported that the patient developed pyrexia approximately 3 weeks later and was described to have an inflammatory reaction which persisted despite antibiotics. Additional symptoms reported include diarrhea, headache and altered consciousness (described as "febrile delirium") and mucocutaneous involvement including ocular hyperemia, redness of the lips and palmar-plantar redness.

The patient was hospitalized on 30 November 2021 for 11 days. He was found to be hypotensive (BP 94/52 mmHg). Normal brain imaging on CT and MRI.

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

30 November 2021: White blood cells 6300 (lymphocytes 8.2%, neutrophils 86.7%), hemoglobin 13.2 g/dL, platelets 93000, fibrinogen 595, BNP 66.9, CRP 17.63. Echocardiography: "increased brightness around the coronary arteries".

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

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

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

3.2. MIS-A

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

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

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

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

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

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

3.3. Cases reported with "unspecified age"

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

4. CUMULATIVE ANALYSIS OF MIS

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

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

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

5. SUMMARY AND CONCLUSION

In summary, for the interval PSUR period covering 19 June through 18 December 2021, 440 cases were retrieved for the search strategy to identify potential cases of MIS-C/A. There are no cases identified as BC level 1-3 in this period which have not previously been presented in the original PRAC signal response, MSSR #11 or 1st Summary bimonthly safety report.

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

Recent publications on MIS-C/A and COVID-19 mRNA vaccination provide some real-world insights which merit consideration when considering the benefit-risk of Comirnaty. Although limited by small numbers Levy *et al*[2], suggested a lower incidence of MIS-C in vaccinated than unvaccinated adolescents in France. A case-control study in the United States identified that 95% of patients age 12-18 years hospitalized with MIS-C were

unvaccinated; 39% of those unvaccinated MIS-C patients required respiratory or cardiovascular life support compared with 0% of vaccinated patients with MIS-C[3].

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

REFERENCES

1 Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P, Giovannini-Chami L, Wood N, Chandler RE, Klein NP, Schlaudecker EP, Poli MC, Muscal E, Munoz FM. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021 May 21;39(22):3037-3049. doi: 10.1016/j.vaccine.2021.01.054.

2 Levy M, Recher M, Hubert H, et al. Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. *JAMA*. Published online December 20, 2021. doi:10.1001/jama.2021.23262

3 Zambrano LD, Newhams MM, Olson SM, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021. MMWR Morb Mortal Wkly Rep 2022;71:52–58.
DOI: http://dx.doi.org/10.15585/mmwr.mm7102e1

APPENDIX 6B. OBSERVED VERSUS EXPECTED ANALYSES FOR ADVERSE EVENTS OF SPECIAL INTEREST

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

As part of ongoing signal detection activities, MAH is conducting observed versus expected (O/E) analyses to determine whether the reported counts of spontaneously reported adverse events of special interest (AESI) are higher than expected based on the "natural" background rates of the AESI in the absence of vaccine exposure, as outlined in the "Considerations on core requirements for RMP's of COVID-19 vaccines: coreRMP19 guidance,"[1] the "Considerations on core requirements for PSURs of COVID-19 vaccines," [2] the "Guide on Methodological Standards in Pharmacoepidemiology (Revision 8)," [3] and by Mahaux et al.[4] Analyses are reported cumulatively based on recent guidance from the European Medicines Agency[2] for the period since the vaccine was first granted emergency use authorization. The methodology applied to the O/E analyses in this report includes spontaneously reported cases from the safety database in the numerator, and is in alignment with monthly, now bimonthly, summary safety reports that are part of ongoing signal detection activities. The reporting period for cases and vaccination exposure in the O/E analyses is 01 December 2020 through 15 December 2021, which aligns with the most recent Summary Bimonthly Safety Report (SBSR 1). In addition, sensitivity analyses incorporate backlog cases to further aid in signal detection.

2. METHODS

2.1. Overall analyses

2.1.1. Variables

The AESI list included in the overall analyses is informed by recommendations from expert groups such as Brighton Collaboration (SPEAC), ACCESS/VAC4EU and various regulatory authorities.

2.1.2. Observed cases

In primary analyses, observed case counts reflect reported processed post-authorisation cases that have a complete workflow cycle in the safety database (meaning that they went to Distribution or Closed workflow status at least once) through 15 December 2021. The pre-defined MedDRA preferred term (PT) search criteria for the cases are provided in Table 1.

In addition to the primary analyses, as requested by regulators, sensitivity analyses were conducted using different observed case counts that included backlog of cases[a] to address potential undercounting of cases. Additional sensitivity analysis modified observed case counts for ADEM by including observed cases of acute disseminated encephalomyelitis (ADEM) identified using a narrow definition (only the PT ADEM), and a broad definition using the PTs ADEM, Encephalitis, and Encephalopathy.

The risk window for observed cases was aligned with the corresponding risk window for expected cases, i.e., observed case counts included only cases with time to onset occuring within a 21-day or 42-day risk window from vaccine exposure for each respective analysis.

[a] Those retrieved considering Product family = BNT162B2 OR Generic Name Suspect beginning with the word BNT162.

Cases with time to onset outside of the risk windows were excluded from the analyses. Time to onset was imputed for cases with missing values based on distribution of cases with known time to onset. For the death analysis, all cases were included in both the 21-day and 42-day risk windows regardless of time ot onset to take the most conservative approach due to timing to process the fatal case data in time for this report.

Unless otherwise noted, reported events have not undergone adjudication, which is considered appropriate in a setting where the goal of observed versus expected analyses is signal detection.[4]

Table 1. Preferred Terms (PT) Used to Identify Spontaneously Reported Adverse Events of Special Interest (AESI)

AESI	PTs
Acute disseminated encephalomyelitis (ADEM), narrow definition	Acute disseminated encephalomyelitis
ADEM and encephalitis, broad definition	Acute disseminated encephalomyelitis, Encephalitis, Encephalopathy
Acute kidney injury/renal failure	Acute kidney injury, Renal failure
Acute liver injury/liver injury	Liver injury
Acute myocardial infarction/myocardial infarction	Acute myocardial infarction, Myocardial infarction
Acute respiratory distress syndrome (ARDS)	Acute respiratory distress syndrome
Ageusia/anosmia	Ageusia, Anosmia
Appendicitis[a]	Appendicitis
Arrhythmia	Arrhythmia
Autoimmune thyroiditis	Autoimmune thyroiditis, Thyroiditis subacute
Behcet's syndrome	Behcet's syndrome
Bell's palsy	Bell's palsy, Facial paralysis, Facial paresis, Oculofacial paralysis
Chillblains	Chillblains
Chronic fatigue syndrome/ME/PVFS	Chronic fatigue syndrome, Post viral fatigue syndrome
Coronary artery disease	Coronary artery disease
Cutaneous vasculitis	Cutaneous vasculitis, Urticarial vasculitis, Vasculitic rash
Death	Fatal clinical outcome
Deep vein thrombosis	Deep vein thrombosis
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Erythema multiforme	Erythema multiforme
Fibromyalgia	Fibromyalgia
Giant cell arteritis	Giant cell arteritis
Guillain-Barré syndrome	Guillain-Barre syndrome
Haemorrhage	Haemorrhage
Haemorrhagic stroke	Brain stem haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke, Intracranial haematoma, Subarachnoid haemorrhage
Heart failure	Cardiac failure, Cardiac failure acute

Table 1. Preferred Terms (PT) Used to Identify Spontaneously Reported Adverse Events of Special Interest (AESI)

AESI	PTs
Herpes zoster	Genital herpes zoster, Herpes zoster, Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster meningoradiculitis, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Herpes zoster pharyngitis, Herpes zoster reactivation, Ophthalmic herpes zoster
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	Immune thrombocytopenia, Thrombocytopenia, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura
Ischemic stroke	Basal ganglia infarction, Basal ganglia stroke, Basilar artery thrombosis, Brain stem stroke, Cerebral infarction, Cerebral thrombosis, Cerebral venous sinus thrombosis, Cerebrovascular accident, Ischaemic stroke, Lacunar infarction, Pituitary infarction, Thrombotic stroke
Limb ischemia	Peripheral ischaemia
Meningitis	Meningitis, Meningitis aseptic
Multiple sclerosis (MS)	Multiple sclerosis, Multiple sclerosis relapse, Optic neuritis
Multisystem inflammatory syndrome	Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Systemic inflammatory response syndrome
Myasthenia gravis	Myasthenia gravis
Myocarditis	Myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Autoimmune myocarditis, Immune-mediated myocarditis
Myocarditis/pericarditis	Myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Autoimmune myocarditis, Immune-mediated myocarditis, Pericarditis, Autoimmune pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pleuropericarditis
Narcolepsy	Cataplexy, Narcolepsy
Pericarditis	Pericarditis, Autoimmune pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pleuropericarditis
Polyneuropathy	Neuropathy peripheral, Polyneuropathy
Postural orthostatic tachycardia syndrome	Postural orthostatic tachycardia syndrome
Pulmonary embolus	Pulmonary embolism
Rhabdomyolysis	Rhabdomyolysis
Rheumatoid arthritis, polyarthritis	Polyarthritis, Rheumatoid arthritis
Seizures/convulsions/seizure disorders (including febrile)	Febrile convulsion, Generalised tonic-clonic seizure, Partial seizures, Seizure
Stress cardiomyopathy	Stress cardiomyopathy
Sudden hearing loss[a]	Deafness, Deafness bilateral, Deafness neurosensory, Deafness transitory, Deafness unilateral, Sudden hearing loss, Deafness permanent
Thrombotic thrombocytopenia syndrome	Thrombosis with thrombocytopenia syndrome
Transverse myelitis	Myelitis transverse
Type 1 diabetes	Type 1 diabetes mellitus

Table 1. Preferred Terms (PT) Used to Identify Spontaneously Reported Adverse Events of Special Interest (AESI)

AESI	PTs
Vasculitis	Polymyalgia rheumatica, Vasculitis

a. Appendicitis and sudden hearing loss are additional PTs under monitoring

2.1.3. Expected cases

Expected case counts were determined cumulatively by multiplying estimated background incidence rates by the duration of post-vaccination exposure time. Duration of exposure time was estimated for the cumulative period using 21-day and 42-day risk windows.

2.1.3.1. Background incidence rates

Background incidence rates were obtained from the vACcine Covid-19 monitoring readinESS (ACCESS) project where available, as recommended by guidance from European Medicines Agency[2] ACCESS includes a consortium of 10 data sources from 7 European countries (Denmark, Germany, France, Italy, Netherlands, Spain, United Kingdom). These data sources include health insurance data (GePaRD, SNDS), hospitalisation record linkage data (PHARMO, Danish registries (DCE-AU), SIDIAP, ARS), or data from general practitioners (CPRD, PEDIANET, BIFAP, FISABIO). For each event, a rate from a single data provider was selected for each AESI based on the range of observed values, type of care typically sought for the AESI (e.g. hospital or general practitioner), and relevant characteristics of the databases, as described in the ACCESS User Guide[5]. In general, a data provider with a mid-range rate within these criteria was chosen for the primary overall analyses. Data providers with low- and high- range rates were chosen for the sensitivity analyses. Incidence rates were then averaged for the most recent three years of data available, excluding 2020, within each data access provider.

For AESIs not available through the ACCESS project, incidence rates were identified in the literature and analyses conducted within electronic health records. If a plausible range of background rates was identified across multiple data sources, a single rate from the low end of the range was selected. This conservative approach is more likely to identify a signal than an approach using a higher background rate.

Sources of background incidence rates for all AESIs are referenced in Table 3.

2.1.3.2. Post-vaccination exposure time

Estimated exposure time was derived from three publicly available sources, the European Centre for Disease Prevention and Control (ECDC) data on COVID-19 vaccination in the European Union (EU)/ European Economic Area (EEA), the Our World in Data (OWD) COVID-19 data, and the Centers for Disease Control and Prevention (CDC) COVID-19 vaccination data.[6,7,8] For countries represented in both the ECDC and OWD data sources, the ECDC data was prioritized over the OWD data. Within the OWD data, the dataset with information on manufacturer was prioritized over global administration data. When available, vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine. For

countries where the Pfizer-BioNTech COVID-19 vaccine is authorized but manufacturer stratified data were not available, the doses administered were assumed to be divided equally by the number of brands of vaccines authorized during that period. The ECDC and OWD data sources use official numbers from governments and health ministries worldwide; the estimate of administered doses does not reflect exposure in persons vaccinated in countries that did not publicly report.

Exposure time was calculated using a 21-day and 42-day risk window. For the cumulative period, estimated exposure time was calculated through 15 December 2021.

2.2. Age-stratified analyses—United States and European Economic Area

2.2.1. Variables

Age-stratified analyses were performed on a subset of the AESIs included in the overall analyses. The subset of AESIs was selected based on those with available age-specific background rates from the ACCESS project, those prioritized by Pfizer Safety for age-stratified analyses, and those requested by regulatory authorities.

2.2.2. Observed cases

As with the overall analyses, reported processed case counts for age-stratified analyses include post-authorisation cases that have a complete workflow cycle in the safety database (meaning that they went to Distribution or Closed workflow status at least once), via the pre-defined MedDRA preferred term search criteria provided in Table 1. Unless otherwise noted, events have not undergone adjudication, which is considered appropriate in a setting where the goal of observed versus expected analyses is signal detection.[4]

Observed cases for each age-group were limited to those with time to onset occuring within a 21-day and 42-day risk window for each respective analysis. The methods for cases that fell outside the risk windows, had missing time to onset, or were fatal cases were the same as the methods used for the overall analyses.

For age-stratified analyses, cases were limited to those occurring in EEA countries and the United States as these regions make publicly available information about vaccine administration. Cases were then grouped by age; those with unknown age were proportionally allocated across age groups based on the distribution of known age-groups at the event level.

2.2.3. Expected cases

Expected case counts were determined cumulatively by multiplying estimated background incidence rates by the duration of post-vaccination exposure time. Duration of exposure time was estimated for the cumulative period using 21-day and 42-day risk windows.

2.2.3.1. Background incidence rates

Age-specific background rates for most AESIs were obtained from the ACCESS project. A rate from a single data provider was selected for each AESI based on the range of observed values, type of care typically sought for the AESI (e.g. hospital or general practitioner), and

relevant characteristics of the databases, as described in the ACCESS User Guide.[5] In general, a data provider with a mid-range rate within these criteria was chosen for the primary age-stratified analyses. Data providers with low- and high- range rates were chosen for the sensitivity analyses. To align with the age groups available for post-vaccination exposure time, the background rate for the ACCESS age group of 0-19 years was used for the ≤11 years and 12-17 years age groups, the background rate for the ACCESS age group of 20-29 years was used for the 18-24 years age group, the average of the background rates for the ACCESS age groups 20-29 years, 30-39 years, and 40-49 years was used for the 25-49 years age group, and the background rate for the ACCESS age group of 70-79 years was used for the 70+ years age group.

For AESIs not available through the ACCESS project, age-stratified incidence rates were identified in the literature. If age-stratified rates were not available in the literature, a constant overall rate was used across all age groups. The background rates selected for each AESI are provided in Table 8.

2.2.3.2. Post-vaccination exposure time

Age-stratified exposure time estimates were derived from the ECDC data on COVID-19 vaccination in the EU/EEA[6] and OWD[7] data and CDC data[8] in the US. Vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine. Since authorization of the Pfizer-BioNTech COVID-19 vaccine in children ≤17 years differs by country, those countries not reporting vaccine administration data in children ≤17 years were assumed to not be contributing person time to the exposure estimate for the ≤11 and 12-17 year age groups. Exposure time was calculated using 21-day and 42-day risk windows. For the cumulative period, estimated exposure time was calculated through 15 December 2021.

2.3. Evaluation of O/E results

For purposes of signal detection in the overall analyses for processed cases and sensitivity analyses including the backlog,[b] the MAH considers events for which the upper level of the 95% CI exceeds 1 for at least one of the risk windows (21 days, 42 days). While typically the lower level of the 95% CI would be the criterion for evaluating a difference from expectation,[4] in this setting, given the generally substantial gap between the lower limit and 1, an upper limit in excess of 1 increases the sensitivity of detecting an excess risk in vaccinees.

For the the age-stratified analyses, the MAH considers events for which the O/E ratio exceeds 1 given the small numbers of cases in some age groups and wide confidence intervals. This method is in line with the usual interpretation of O/E, which is that there is a signal of risk when the O/E is greater than 1[4].

[b] Those retrieved considering Product family = BNT162B2 OR Generic Name Suspect beginning with the word BNT162.

3. RESULTS

3.1. Overall analysis

Table 2. Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI), Cumulative Period

AESI	Processed Cases				All Cases[a]			
	21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.223	0.182, 0.271	0.159	0.130, 0.192	0.228	0.186, 0.276	0.163	0.134, 0.197
ADEM and encephalitis, broad definition	0.076	0.069, 0.085	0.057	0.051, 0.062	0.078	0.070, 0.087	0.058	0.052, 0.064
Acute kidney injury/renal failure	0.003	0.003, 0.003	0.002	0.002, 0.002	0.003	0.003, 0.003	0.002	0.002, 0.002
Acute liver injury/liver injury	0.002	0.002, 0.003	0.002	0.001, 0.002	0.002	0.002, 0.003	0.002	0.001, 0.002
Acute myocardial infarction/myocardial infarction	0.012	0.011, 0.012	0.009	0.008, 0.009	0.012	0.012, 0.013	0.009	0.009, 0.009
Acute respiratory distress syndrome (ARDS)	0.004	0.003, 0.005	0.003	0.003, 0.004	0.004	0.003, 0.005	0.003	0.003, 0.004
Ageusia/anosmia	0.182	0.176, 0.188	0.127	0.123, 0.131	0.197	0.190, 0.203	0.137	0.133, 0.142
Appendicitis	0.004	0.004, 0.004	0.003	0.003, 0.003	0.004	0.004, 0.005	0.003	0.003, 0.003
Arrhythmia	0.004	0.004, 0.004	0.003	0.003, 0.003	0.004	0.004, 0.004	0.003	0.003, 0.003
Autoimmune thyroiditis	0.038	0.033, 0.044	0.031	0.027, 0.035	0.041	0.036, 0.047	0.033	0.029, 0.038
Behcet's syndrome	0.052	0.035, 0.076	0.035	0.023, 0.051	0.058	0.039, 0.082	0.039	0.026, 0.055
Bell's palsy	0.278	0.270, 0.285	0.210	0.205, 0.216	0.288	0.281, 0.295	0.218	0.213, 0.223
Chillblains	0.019	0.016, 0.021	0.013	0.011, 0.015	0.019	0.017, 0.022	0.013	0.012, 0.015
Chronic fatigue syndrome/ME/PVFS	0.023	0.021, 0.026	0.016	0.014, 0.018	0.024	0.022, 0.028	0.017	0.015, 0.019
Coronary artery disease	0.001	0.001, 0.001	0.000	0.000, 0.001	0.001	0.001, 0.001	0.001	0.000, 0.001
Cutaneous vasculitis	0.037	0.032, 0.042	0.027	0.023, 0.030	0.038	0.033, 0.044	0.028	0.024, 0.032
Death	0.010	0.010, 0.010	0.007	0.007, 0.007	0.010	0.010, 0.011	0.007	0.007, 0.007
Deep vein thrombosis	0.059	0.057, 0.061	0.046	0.045, 0.048	0.061	0.059, 0.063	0.048	0.046, 0.050
Disseminated intravascular coagulation	0.119	0.093, 0.150	0.085	0.067, 0.106	0.119	0.093, 0.150	0.085	0.067, 0.106
Erythema multiforme	0.042	0.037, 0.047	0.030	0.026, 0.033	0.043	0.038, 0.049	0.031	0.027, 0.034
Fibromyalgia	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001

Table 2. Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI), Cumulative Period

	Processed Cases				All Cases[a]			
	21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Giant cell arteritis	0.084	0.069, 0.101	0.064	0.054, 0.076	0.092	0.077, 0.109	0.069	0.058, 0.081
Guillain-Barré syndrome	0.328	0.305, 0.352	0.264	0.247, 0.281	0.342	0.319, 0.366	0.274	0.257, 0.292
Haemorrhage	0.085	0.081, 0.089	0.062	0.059, 0.064	0.088	0.084, 0.092	0.064	0.061, 0.067
Haemorrhagic stroke	0.030	0.028, 0.031	0.022	0.021, 0.023	0.030	0.029, 0.032	0.022	0.021, 0.024
Heart failure	0.002	0.002, 0.002	0.002	0.002, 0.002	0.002	0.002, 0.002	0.002	0.002, 0.002
Herpes zoster	0.025	0.024, 0.025	0.020	0.019, 0.020	0.026	0.026, 0.027	0.020	0.020, 0.021
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	0.041	0.039, 0.043	0.033	0.032, 0.034	0.042	0.040, 0.044	0.034	0.032, 0.035
Ischemic stroke	0.023	0.022, 0.023	0.017	0.017, 0.018	0.024	0.023, 0.024	0.018	0.017, 0.018
Limb ischemia	0.000	0.000, 0.001	0.000	0.000, 0.000	0.000	0.000, 0.001	0.000	0.000, 0.000
Meningitis	0.015	0.013, 0.017	0.012	0.010, 0.013	0.015	0.013, 0.018	0.012	0.010, 0.014
Multiple sclerosis (MS)	0.068	0.063, 0.073	0.052	0.048, 0.055	0.071	0.066, 0.076	0.054	0.050, 0.057
Multisystem inflammatory syndrome	0.298	0.263, 0.337	0.241	0.215, 0.269	0.305	0.270, 0.344	0.246	0.220, 0.275
Myasthenia gravis	0.081	0.067, 0.098	0.060	0.050, 0.072	0.083	0.068, 0.100	0.061	0.051, 0.073
Myocarditis, low	**4.634**	**4.512, 4.759**	**3.449**	**3.362, 3.537**	**4.984**	**4.858, 5.113**	**3.718**	**3.628, 3.809**
Myocarditis, mid	**1.411**	**1.374, 1.449**	**1.050**	**1.024, 1.077**	**1.518**	**1.479, 1.557**	**1.132**	**1.105, 1.160**
Myocarditis, high	**0.990**	**0.964, 1.017**	0.737	0.719, 0.756	**1.065**	**1.038, 1.093**	0.795	0.775, 0.814
Myocarditis/ pericarditis	0.549	0.538, 0.561	0.415	0.407, 0.423	0.597	0.586, 0.609	0.452	0.444, 0.461
Narcolepsy	0.054	0.041, 0.070	0.039	0.030, 0.051	0.055	0.042, 0.071	0.040	0.031, 0.052
Pericarditis	0.263	0.255, 0.272	0.204	0.199, 0.210	0.287	0.279, 0.296	0.224	0.218, 0.230
Polyneuropathy	0.592	0.560, 0.625	0.419	0.397, 0.441	0.611	0.578, 0.644	0.432	0.410, 0.455
Postural orthostatic tachycardia syndrome	0.012	0.010, 0.015	0.009	0.007, 0.011	0.014	0.012, 0.017	0.010	0.009, 0.012
Pulmonary embolus	0.141	0.137, 0.146	0.115	0.112, 0.119	0.146	0.141, 0.151	0.119	0.116, 0.123
Rhabdomyolysis	0.017	0.015, 0.020	0.012	0.010, 0.014	0.017	0.015, 0.020	0.012	0.010, 0.014
Rheumatoid arthritis, polyarthritis	0.016	0.015, 0.017	0.012	0.011, 0.012	0.017	0.015, 0.018	0.012	0.011, 0.013

Table 2. Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI), Cumulative Period

	Processed Cases				All Cases[a]			
	21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Seizures/convulsions/seizure disorders (including febrile)	0.044	0.043, 0.045	0.031	0.030, 0.032	0.046	0.044, 0.047	0.032	0.031, 0.033
Stress cardiomyopathy	0.048	0.037, 0.062	0.035	0.027, 0.044	0.050	0.038, 0.064	0.036	0.028, 0.045
Sudden hearing loss	0.076	0.072, 0.079	0.055	0.053, 0.058	0.079	0.075, 0.083	0.058	0.055, 0.060
Thrombotic thrombocytopenia syndrome	0.020	0.014, 0.027	0.015	0.011, 0.020	0.020	0.014, 0.027	0.015	0.011, 0.020
Transverse myelitis	0.106	0.088, 0.128	0.079	0.066, 0.094	0.114	0.095, 0.136	0.084	0.071, 0.100
Type 1 diabetes	0.002	0.002, 0.003	0.002	0.002, 0.003	0.003	0.002, 0.004	0.003	0.002, 0.003
Vasculitis	0.077	0.072, 0.083	0.059	0.055, 0.063	0.082	0.076, 0.087	0.062	0.058, 0.066

a. All cases includes processed cases plus backlog cases retrieved considering Product family = BNT162B2 OR Generic Name Suspect beginning with the word BNT162

Table 3. Observed versus Expected Analyses of Spontaneously Reported Adverse Events of Special Interest (AESI) Inputs, Cumulative Period

AESI	Background Rate per 100,000 Person Years (PY)	Processed Cases				All Cases[c]			
		21-Day Risk Window[a]		42-Day Risk Window[b]		21-Day Risk Window[a]		42-Day Risk Window[b]	
		Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
ADEM, narrow definition	0.51[9]	100	448.0	106	668.5	102	448.0	109	668.5
ADEM and encephalitis, broad definition	5.30[10]	355	4,655.7	393	6,947.6	364	4,655.7	403	6,947.6
Acute kidney injury/renal failure	314.15[11]	773	275,960.1	878	411,812.0	790	275,960.1	899	411,812.0
Acute liver injury/liver injury	29.84[11]	61	26,212.5	63	39,116.6	62	26,212.5	64	39,116.6
Acute myocardial infarction/myocardial infarction	201.80[12]	2,110	177,268.0	2,300	264,535.0	2,181	177,268.0	2,378	264,535.0
Acute respiratory distress syndrome (ARDS)	30.79[11]	103	27,047.0	123	40,361.9	106	27,047.0	126	40,361.9
Ageusia/anosmia	20.90[13]	3,337	18,359.3	3,476	27,397.3	3,614	18,359.3	3,760	27,397.3
Appendicitis	96.50[14]	340	84,768.9	377	126,499.6	357	84,768.9	396	126,499.6
Arrhythmia	1,048.50[11]	3,537	921,038.3	3,728	1,374,454.4	3,761	921,038.3	3,960	1,374,454.4
Autoimmune thyroiditis	6.20[12]	209	5,446.3	253	8,127.4	223	5,446.3	271	8,127.4
Behcet's syndrome	0.61[15]	28	535.8	28	799.6	31	535.8	31	799.6
Bell's palsy	23.84[10]	5,813	20,941.9	6,575	31,251.3	6,031	20,941.9	6,816	31,251.3
Chillblains	11.90[16]	195	10,453.4	203	15,599.4	200	10,453.4	208	15,599.4
Chronic fatigue syndrome/ME/PVFS	13.16[17]	271	11,560.2	281	17,251.1	283	11,560.2	293	17,251.1
Coronary artery disease	175.95[9]	96	154,560.5	115	230,648.8	103	154,560.5	122	230,648.8
Cutaneous vasculitis	6.18[18]	199	5,428.7	216	8,101.2	207	5,428.7	224	8,101.2
Death	1,117.43[19]	10,029	981,584.3	10,029	1,464,806.6	10,270	981,584.3	10,270	1,464,806.6
Deep vein thrombosis	50.00[20]	2,590	43,921.7	3,033	65,543.8	2,675	43,921.7	3,133	65,543.8
Disseminated intravascular coagulation	0.69[21]	72	606.1	77	904.5	72	606.1	77	904.5
Erythema multiforme	7.62[22]	280	6,693.7	296	9,988.9	290	6,693.7	306	9,988.9
Fibromyalgia	430.00[23]	401	377,726.7	422	563,677.1	421	377,726.7	445	563,677.1
Giant cell arteritis	1.60[12]	118	1,405.5	134	2,097.4	129	1,405.5	145	2,097.4
Guillain-Barré syndrome	2.70[24]	778	2,371.8	933	3,539.4	811	2,371.8	969	3,539.4
Haemorrhage	22.30[12]	1,662	19,589.1	1,800	29,232.6	1,726	19,589.1	1,868	29,232.6
Haemorrhagic stroke	44.72[25]	1,165	39,283.6	1,290	58,622.4	1,189	39,283.6	1,317	58,622.4

Table 3. Observed versus Expected Analyses of Spontaneously Reported Adverse Events of Special Interest (AESI) Inputs, Cumulative Period

AESI	Background Rate per 100,000 Person Years (PY)	Processed Cases				All Cases[c]			
		21-Day Risk Window[a]		42-Day Risk Window[b]		21-Day Risk Window[a]		42-Day Risk Window[b]	
		Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
Heart failure	633.30[11]	1,242	556,312.4	1,352	830,178.3	1,276	556,312.4	1,390	830,178.3
Herpes zoster	459.00[26]	10,055	403,201.3	11,767	601,692.5	10,513	403,201.3	12,321	601,692.5
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	44.55[18]	1,612	39,134.2	1,926	58,399.6	1,658	39,134.2	1,983	58,399.6
Ischemic stroke	237.40[11]	4,750	208,540.3	5,327	311,202.2	4,906	208,540.3	5,498	311,202.2
Limb ischemia	260.00[27]	99	228,392.9	114	340,828.0	102	228,392.9	117	340,828.0
Meningitis	13.47[28]	176	11,832.5	207	17,657.5	180	11,832.5	211	17,657.5
Multiple sclerosis (MS)	11.60[12]	692	10,189.8	784	15,206.2	722	10,189.8	816	15,206.2
Multisystem inflammatory syndrome	1.00[9,24,d]	262	878.4	316	1,310.9	268	878.4	323	1,310.9
Myasthenia gravis	1.47[29]	105	1,291.3	116	1,927.0	107	1,291.3	118	1,927.0
Myocarditis, low	1.34[21]	5,455	1,177.1	6,058	1,756.6	5,867	1,177.1	6,531	1,756.6
Myocarditis, mid	4.40[30]	5,455	3,865.1	6,058	5,767.9	5,867	3,865.1	6,531	5,767.9
Myocarditis, high	6.27[11]	5,455	5,507.8	6,058	8,219.2	5,867	5,507.8	6,531	8,219.2
Myocarditis/ pericarditis	18.68[22]	9,013	16,409.2	10,154	24,487.2	9,802	16,409.2	11,080	24,487.2
Narcolepsy	1.16[13]	55	1,019.0	60	1,520.6	56	1,019.0	61	1,520.6
Pericarditis	18.00[30]	4,165	15,811.8	4,821	23,595.8	4,542	15,811.8	5,274	23,595.8
Polyneuropathy	2.50[12]	1,300	2,196.1	1,372	3,277.2	1,341	2,196.1	1,415	3,277.2
Postural orthostatic tachycardia syndrome	10.10[31]	109	8,872.2	119	13,239.9	126	8,872.2	136	13,239.9
Pulmonary embolus	30.00[20]	3,717	26,353.0	4,536	39,326.3	3,849	26,353.0	4,697	39,326.3
Rhabdomyolysis	12.78[32]	192	11,226.4	197	16,753.0	196	11,226.4	201	16,753.0
Rheumatoid arthritis, polyarthritis	64.70[12]	902	56,834.7	981	84,813.7	940	56,834.7	1,024	84,813.7
Seizures/convulsions/seizure disorders (including febrile)	91.14[22]	3,521	80,060.5	3,659	119,473.3	3,648	80,060.5	3,791	119,473.3
Stress cardiomyopathy	1.39[22]	59	1,221.0	63	1,822.1	61	1,221.0	65	1,822.1
Sudden hearing loss	27.00[33]	1,797	23,717.7	1,960	35,393.7	1,873	23,717.7	2,048	35,393.7

Table 3. Observed versus Expected Analyses of Spontaneously Reported Adverse Events of Special Interest (AESI) Inputs, Cumulative Period

AESI	Background Rate per 100,000 Person Years (PY)	Processed Cases				All Cases[c]			
		21-Day Risk Window[a]		42-Day Risk Window[b]		21-Day Risk Window[a]		42-Day Risk Window[b]	
		Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
Thrombotic thrombocytopenia syndrome	2.39[11]	42	2,099.5	47	3,133.0	42	2,099.5	47	3,133.0
Transverse myelitis	1.22[11]	114	1,071.7	127	1,599.3	122	1,071.7	135	1,599.3
Type 1 diabetes	23.60[13]	50	20,731.0	75	30,936.7	58	20,731.0	83	30,936.7
Vasculitis	11.43[34]	773	10,040.5	877	14,983.3	820	10,040.5	928	14,983.3

a. 87,843,419 PY
b. 131,087,686 PY
c. All cases includes processed cases plus backlog cases retrieved considering Product family = BNT162B2 OR Generic Name Suspect beginning with the word BNT162
d. Average of age-specific rates from ACCESS DK_DCE_AU and ACCESS ES_FISABIO as described in Table 8

3.1.1. Summary of overall analyses

For the primary analysis, only myocarditis using the low, mid, and high background rates meet the signal criteria with the upper limit of the O/E 95% CI >1. Myocarditis is further detailed in Section 5.

For all other AESIs, the upper limit of the 95% CI is less than 1.

3.2. Age-stratified analysis

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Acute kidney injury/renal failure	0.000	-	0.061	0.033, 0.103	0.073	0.043, 0.115	0.026	0.020, 0.033	0.009	0.007, 0.012	0.007	0.005, 0.008	0.007	0.006, 0.008
Acute liver injury/liver injury	0.000	-	0.000	-	0.000	-	0.004	0.002, 0.008	0.002	0.000, 0.005	0.002	0.001, 0.006	0.002	0.001, 0.004
Acute respiratory distress syndrome (ARDS)	0.000	-	0.000	-	0.042	0.012, 0.109	0.011	0.005, 0.020	0.005	0.002, 0.010	0.005	0.002, 0.008	0.006	0.004, 0.007
Ageusia/anosmia	0.000	-	0.407	0.299, 0.542	0.228	0.190, 0.272	0.347	0.326, 0.368	0.183	0.167, 0.200	0.117	0.105, 0.131	0.074	0.065, 0.083
Appendicitis	0.000	-	0.009	0.006, 0.013	0.007	0.005, 0.011	0.008	0.007, 0.010	0.005	0.004, 0.007	0.004	0.002, 0.006	0.002	0.001, 0.003
Arrhythmia	0.000	-	0.015	0.010, 0.022	0.045	0.038, 0.053	0.066	0.063, 0.070	0.021	0.019, 0.023	0.008	0.007, 0.008	0.003	0.003, 0.003
Chillblains	0.000	-	0.000	-	0.013	0.004, 0.031	0.026	0.018, 0.035	0.034	0.020, 0.054	0.015	0.008, 0.025	0.013	0.008, 0.019
Chronic fatigue syndrome/ME/PVFS	0.000	-	0.003	0.000, 0.017	0.006	0.001, 0.019	0.025	0.019, 0.033	0.017	0.010, 0.028	0.006	0.002, 0.014	0.007	0.003, 0.013
Coronary artery disease	0.000	-	0.000	-	0.000	-	0.002	0.001, 0.004	0.001	0.001, 0.002	0.001	0.000, 0.001	0.001	0.000, 0.001
Cutaneous vasculitis	0.000	-	0.007	0.001, 0.024	0.081	0.032, 0.166	0.097	0.068, 0.135	0.090	0.059, 0.132	0.073	0.047, 0.108	0.053	0.038, 0.072
Death	0.031	0.006, 0.089	0.051	0.036, 0.069	0.012	0.008, 0.016	0.013	0.012, 0.015	0.010	0.009, 0.011	0.010	0.009, 0.010	0.013	0.013, 0.013
Disseminated intravascular coagulation	0.000	-	0.130	0.016, 0.471	0.067	0.002, 0.372	0.081	0.026, 0.190	0.161	0.065, 0.331	0.096	0.038, 0.197	0.067	0.031, 0.127
Erythema multiforme	0.000	-	0.021	0.010, 0.038	0.039	0.017, 0.077	0.065	0.049, 0.085	0.074	0.048, 0.108	0.074	0.046, 0.113	0.056	0.038, 0.079
Guillain-Barré syndrome	0.000	-	0.434	0.208, 0.799	0.292	0.170, 0.468	0.555	0.474, 0.646	0.258	0.205, 0.320	0.224	0.176, 0.282	0.212	0.173, 0.256
Haemorrhagic stroke	0.000	-	0.084	0.017, 0.245	0.082	0.030, 0.179	0.069	0.055, 0.085	0.039	0.031, 0.048	0.026	0.021, 0.032	0.029	0.026, 0.032

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Heart failure	0.000	-	0.014	0.002, 0.051	0.094	0.054, 0.153	0.023	0.017, 0.029	0.008	0.007, 0.011	0.003	0.002, 0.004	0.006	0.006, 0.007
Herpes zoster	0.000	-	0.025	0.021, 0.029	0.024	0.021, 0.027	0.052	0.050, 0.055	0.034	0.032, 0.036	0.026	0.025, 0.028	0.024	0.023, 0.025
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	0.000	-	0.197	0.151, 0.253	0.080	0.061, 0.103	0.075	0.066, 0.084	0.053	0.044, 0.062	0.040	0.034, 0.047	0.043	0.039, 0.048
Ischemic stroke	0.000	-	0.365	0.216, 0.576	0.271	0.202, 0.357	0.160	0.146, 0.175	0.076	0.069, 0.084	0.047	0.043, 0.050	0.039	0.037, 0.041
Multisystem inflammatory syndrome	0.000	-	0.323	0.197, 0.499	**1.868**	**0.896, 3.436**	0.259	0.181, 0.361	0.297	0.173, 0.476	0.510	0.315, 0.779	0.880	0.704, 1.087
Myasthenia gravis	0.000	-	0.185	0.022, 0.668	0.000	-	0.086	0.049, 0.140	0.144	0.085, 0.227	0.044	0.019, 0.086	0.112	0.075, 0.160
Myocarditis, low	**1.428**	**0.295, 4.174**	**64.778**	**59.017, 70.949**	**12.082**	**11.223, 12.990**	**4.923**	**4.641, 5.219**	**3.177**	**2.825, 3.561**	**1.175**	**0.987, 1.388**	0.871	0.731, 1.029
Myocarditis, mid	0.091	0.019, 0.266	**4.122**	**3.756, 4.515**	**4.668**	**4.336, 5.019**	**1.678**	**1.582, 1.779**	0.939	0.835, 1.052	0.510	0.428, 0.602	0.340	0.286, 0.402
Myocarditis, high	0.087	0.018, 0.255	**3.960**	**3.608, 4.338**	**1.971**	**1.831, 2.119**	0.898	0.847, 0.952	0.793	0.705, 0.889	0.500	0.420, 0.590	0.356	0.299, 0.420
Myocarditis/pericarditis	0.043	0.009, 0.126	**2.323**	**2.133, 2.525**	0.832	0.779, 0.888	0.483	0.462, 0.505	0.421	0.387, 0.459	0.212	0.187, 0.240	0.173	0.153, 0.193
Narcolepsy	0.000	-	0.063	0.002, 0.351	0.021	0.001, 0.117	0.062	0.033, 0.106	0.244	0.137, 0.403	0.012	0.000, 0.064	0.143	0.068, 0.263
Rhabdomyolysis	0.000	-	0.040	0.021, 0.068	0.024	0.012, 0.043	0.022	0.016, 0.030	0.008	0.003, 0.016	0.014	0.007, 0.025	0.025	0.016, 0.035
Seizures/convulsions/seizure disorders (including febrile)	0.005	0.002, 0.010	0.042	0.037, 0.049	0.103	0.089, 0.120	0.094	0.087, 0.101	0.060	0.053, 0.068	0.039	0.033, 0.046	0.028	0.025, 0.032
Stress cardiomyopathy	NA	NA	NA	NA	NA	NA	0.217	0.071, 0.507	0.049	0.016, 0.114	0.042	0.018, 0.082	0.029	0.015, 0.051
Thrombotic thrombocytopenia syndrome	0.000	-	0.000	-	0.000	-	0.000	-	0.000	-	0.000	-	0.000	-

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Transverse myelitis	0.000	-	0.000	-	0.056	0.007, 0.202	0.250	0.175, 0.346	0.083	0.036, 0.163	0.020	0.002, 0.073	0.087	0.040, 0.166
Type 1 diabetes	0.000	-	0.013	0.005, 0.025	0.003	0.000, 0.009	0.003	0.002, 0.006	NA	NA	NA	NA	NA	NA
Venous thromboembolism (includes deep vein thrombosis and pulmonary embolism)	0.000	-	0.172	0.109, 0.258	0.139	0.114, 0.168	0.130	0.122, 0.138	0.082	0.076, 0.088	0.053	0.049, 0.057	0.045	0.043, 0.047

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Acute kidney injury/renal failure	0.000	-	0.042	0.023, 0.070	0.067	0.043, 0.099	0.021	0.016, 0.026	0.007	0.005, 0.009	0.005	0.004, 0.006	0.005	0.005, 0.006
Acute liver injury/liver injury	0.000	-	0.000	-	0.002	0.000, 0.011	0.003	0.001, 0.005	0.001	0.000, 0.003	0.002	0.001, 0.004	0.001	0.001, 0.003
Acute respiratory distress syndrome (ARDS)	0.000	-	0.000	-	0.036	0.012, 0.085	0.007	0.003, 0.013	0.004	0.002, 0.008	0.004	0.002, 0.006	0.005	0.004, 0.006
Ageusia/anosmia	0.000	-	0.291	0.215, 0.385	0.160	0.134, 0.190	0.249	0.234, 0.264	0.130	0.119, 0.142	0.083	0.075, 0.093	0.054	0.047, 0.060
Appendicitis	0.000	-	0.007	0.005, 0.010	0.006	0.004, 0.008	0.006	0.005, 0.007	0.004	0.003, 0.005	0.003	0.002, 0.004	0.001	0.001, 0.002
Arrhythmia	0.000	-	0.011	0.007, 0.016	0.032	0.027, 0.038	0.047	0.045, 0.050	0.015	0.014, 0.016	0.005	0.005, 0.006	0.002	0.002, 0.002
Chillblains	0.000	-	0.000	-	0.011	0.004, 0.024	0.018	0.013, 0.024	0.024	0.014, 0.038	0.010	0.005, 0.017	0.008	0.005, 0.013
Chronic fatigue syndrome/ME/PVFS	0.000	-	0.002	0.000, 0.011	0.004	0.001, 0.013	0.018	0.013, 0.023	0.012	0.007, 0.020	0.004	0.001, 0.010	0.004	0.002, 0.009
Coronary artery disease	0.000	-	0.000	-	0.000	-	0.002	0.001, 0.004	0.001	0.001, 0.002	0.001	0.000, 0.001	0.000	0.000, 0.001
Cutaneous vasculitis	0.000	-	0.005	0.001, 0.017	0.063	0.027, 0.124	0.070	0.050, 0.096	0.066	0.044, 0.096	0.052	0.034, 0.076	0.040	0.029, 0.054
Death	0.021	0.004, 0.063	0.035	0.025, 0.048	0.008	0.006, 0.011	0.009	0.008, 0.010	0.007	0.006, 0.008	0.007	0.006, 0.007	0.009	0.009, 0.009
Disseminated intravascular coagulation	0.000	-	0.089	0.011, 0.323	0.046	0.001, 0.254	0.056	0.018, 0.130	0.125	0.054, 0.246	0.065	0.026, 0.135	0.045	0.021, 0.085
Erythema multiforme	0.000	-	0.018	0.010, 0.031	0.027	0.011, 0.052	0.046	0.035, 0.060	0.054	0.036, 0.078	0.055	0.035, 0.083	0.038	0.026, 0.053
Guillain-Barré syndrome	0.000	-	0.417	0.228, 0.699	0.259	0.162, 0.392	0.442	0.382, 0.509	0.229	0.188, 0.277	0.193	0.156, 0.236	0.180	0.151, 0.213
Haemorrhagic stroke	0.000	-	0.096	0.031, 0.223	0.065	0.026, 0.135	0.055	0.044, 0.067	0.029	0.024, 0.036	0.020	0.016, 0.024	0.022	0.020, 0.024
Heart failure	0.000	-	0.010	0.001, 0.035	0.068	0.040, 0.109	0.017	0.013, 0.021	0.007	0.005, 0.008	0.002	0.002, 0.003	0.004	0.004, 0.005

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Herpes zoster	0.000	-	0.020	0.017, 0.023	0.019	0.016, 0.021	0.042	0.041, 0.044	0.027	0.026, 0.028	0.021	0.020, 0.022	0.019	0.018, 0.020
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	0.000	-	0.144	0.111, 0.184	0.061	0.047, 0.077	0.062	0.055, 0.069	0.041	0.035, 0.048	0.033	0.029, 0.038	0.035	0.032, 0.038
Ischemic stroke	0.000	-	0.291	0.180, 0.446	0.211	0.160, 0.273	0.130	0.120, 0.141	0.060	0.055, 0.065	0.036	0.034, 0.039	0.029	0.028, 0.030
Multisystem inflammatory syndrome	0.000	-	0.288	0.188, 0.422	**1.790**	**0.979, 3.004**	0.187	0.132, 0.258	0.238	0.146, 0.368	0.398	0.255, 0.592	0.756	0.621, 0.911
Myasthenia gravis	0.000	-	0.127	0.015, 0.458	0.000	-	0.059	0.034, 0.096	0.098	0.058, 0.155	0.037	0.018, 0.068	0.088	0.061, 0.122
Myocarditis, low	**1.338**	**0.364, 3.425**	**47.836**	**43.734, 52.219**	**9.071**	**8.455, 9.721**	**3.806**	**3.601, 4.020**	**2.561**	**2.299, 2.844**	0.995	0.851, 1.156	0.724	0.620, 0.841
Myocarditis, mid	0.085	0.023, 0.218	**3.044**	**2.783, 3.323**	**3.505**	**3.267, 3.756**	**1.298**	**1.228, 1.371**	0.757	0.679, 0.840	0.432	0.370, 0.502	0.283	0.242, 0.329
Myocarditis, high	0.082	0.022, 0.209	**2.924**	**2.674, 3.192**	**1.480**	**1.379, 1.586**	0.695	0.657, 0.734	0.639	0.574, 0.710	0.423	0.362, 0.492	0.296	0.253, 0.344
Myocarditis/pericarditis	0.040	0.011, 0.103	**1.724**	**1.589, 1.868**	0.628	0.590, 0.668	0.377	0.361, 0.393	0.351	0.325, 0.379	0.189	0.169, 0.210	0.140	0.126, 0.156
Narcolepsy	0.000	-	0.043	0.001, 0.241	0.014	0.000, 0.080	0.049	0.027, 0.080	0.166	0.093, 0.274	0.016	0.002, 0.057	0.105	0.053, 0.189
Rhabdomyolysis	0.000	-	0.029	0.016, 0.049	0.017	0.008, 0.030	0.016	0.012, 0.021	0.005	0.002, 0.011	0.010	0.005, 0.018	0.017	0.011, 0.024
Seizures/convulsions/seizure disorders (including febrile)	0.004	0.001, 0.007	0.030	0.026, 0.034	0.074	0.064, 0.086	0.067	0.062, 0.073	0.042	0.037, 0.048	0.027	0.023, 0.032	0.020	0.018, 0.022
Stress cardiomyopathy	NA	NA	NA	NA	NA	NA	0.178	0.065, 0.387	0.040	0.015, 0.087	0.029	0.012, 0.056	0.021	0.011, 0.036
Thrombotic thrombocytopenia syndrome	0.000	-	0.000	-	0.077	0.002, 0.427	0.000	-	0.000	-	0.000	-	0.000	-
Transverse myelitis	0.000	-	0.000	-	0.038	0.005, 0.139	0.184	0.131, 0.252	0.057	0.024, 0.111	0.021	0.004, 0.061	0.078	0.040, 0.136

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
Type 1 diabetes	0.000	-	0.015	0.008, 0.025	0.003	0.001, 0.008	0.003	0.002, 0.005	NA	NA	NA	NA	NA	NA
Venous thromboembolism (includes deep vein thrombosis and pulmonary embolism)	0.000	-	0.143	0.095, 0.207	0.118	0.099, 0.139	0.108	0.102, 0.114	0.067	0.062, 0.071	0.043	0.040, 0.046	0.036	0.034, 0.037

Table 6. Age-Stratified Observed (Obs) to Expected (Exp) Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States Inputs, 21-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	Obs cases	Exp cases[a]	Obs cases	Exp cases[b]	Obs cases	Exp cases[c]	Obs cases	Exp cases[d]	Obs cases	Exp cases[e]	Obs cases	Exp cases[f]	Obs cases	Exp cases[g]
Acute kidney injury/renal failure	0	67.1	14	229.0	18	246.6	67	2,592.8	48	5,432.2	86	12,549.5	368	54,105.4
Acute liver injury/liver injury	0	41.9	0	143.0	0	354.0	8	2,008.2	3	1,919.3	5	2,101.5	10	4,616.2
Acute respiratory distress syndrome (ARDS)	0	84.9	0	289.6	4	94.2	10	937.4	8	1,637.9	14	3,107.1	48	8,523.7
Ageusia/anosmia	0	33.8	47	115.4	127	556.4	1,039	2,997.8	483	2,644.3	307	2,613.8	256	3,467.9
Appendicitis	0	844.7	25	2,880.5	25	3,443.8	118	14,804.9	36	6,892.9	22	5,934.9	17	8,893.3
Arrhythmia	0	484.4	25	1,651.8	140	3,091.2	1,312	19,858.5	541	26,027.5	397	52,557.8	575	202,362.7
Chillblains	0	73.7	0	251.2	5	377.6	39	1,523.4	17	505.0	12	825.4	22	1,759.3
Chronic fatigue syndrome/ME/PVFS	0	98.7	1	336.7	3	469.6	51	2,019.0	16	940.0	5	809.4	8	1,212.8
Coronary artery disease	0	4.7	0	16.1	0	110.3	11	4,624.0	20	15,008.0	14	23,199.2	28	52,133.2
Cutaneous vasculitis	0	87.9	2	299.8	7	86.7	36	369.7	26	288.6	25	342.6	41	768.6
Death	3	98.3	40	785.4	37	3,111.9	376	28,597.2	446	44,186.2	787	82,203.6	5,184	395,019.3
Disseminated intravascular coagulation	0	4.5	2	15.3	1	15.0	5	61.4	7	43.6	7	73.2	9	134.6
Erythema multiforme	0	142.9	10	487.3	8	205.9	53	811.6	26	352.9	21	284.1	31	553.9
Guillain-Barré syndrome	0	6.8	10	23.0	17	58.2	166	299.2	82	317.9	74	329.7	105	495.8
Haemorrhagic stroke	0	10.5	3	35.8	6	73.2	84	1,221.2	89	2,269.3	100	3,832.8	379	12,923.4
Heart failure	0	41.9	2	143.0	16	170.2	65	2,882.7	74	8,775.1	66	23,455.7	620	103,061.9
Herpes zoster	0	1,680.4	147	5,954.2	204	8,618.3	2,164	41,269.5	1,550	45,429.1	1,456	55,321.1	2,234	93,057.1
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	0	90.7	61	309.3	60	752.3	272	3,643.7	139	2,645.0	159	3,952.1	402	9,311.7
Ischemic stroke	0	14.5	18	49.4	51	188.1	465	2,908.8	446	5,847.2	575	12,361.9	1,728	44,473.9
Multisystem inflammatory syndrome	0	18.2	20	61.9	10	5.4	35	135.0	17	57.1	21	41.2	86	97.7
Myasthenia gravis	0	1.2	2	10.8	0	24.5	16	185.5	18	125.3	8	183.9	30	268.4
Myocarditis, low	3	2.1	464	7.2	733	60.7	1,133	230.1	295	92.9	138	117.5	138	158.5

Table 6. Age-Stratified Observed (Obs) to Expected (Exp) Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States Inputs, 21-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	Obs cases	Exp cases[a]	Obs cases	Exp cases[b]	Obs cases	Exp cases[c]	Obs cases	Exp cases[d]	Obs cases	Exp cases[e]	Obs cases	Exp cases[f]	Obs cases	Exp cases[g]
Myocarditis, mid	3	33.0	464	112.6	733	157.0	1,133	675.0	295	314.3	138	270.6	138	405.5
Myocarditis, high	3	34.4	464	117.2	733	371.9	1,133	1,261.1	295	372.1	138	276.1	138	388.0
Myocarditis/pericarditis	3	69.7	552	237.7	910	1,093.8	1,892	3,916.8	535	1,269.3	260	1,223.9	295	1,709.5
Narcolepsy	0	4.7	1	15.9	1	47.8	13	210.2	15	61.4	1	86.7	10	70.0
Rhabdomyolysis	0	95.9	13	326.9	11	456.1	44	1,960.7	7	912.9	11	786.0	29	1,177.8
Seizures/convulsions/seizure disorders (including febrile)	7	1,373.7	199	4,684.3	172	1,662.3	647	6,886.9	247	4,095.8	159	4,063.4	288	10,125.5
Stress cardiomyopathy	0	0.0	0	0.0	1	0.0	5	23.0	5	102.1	8	191.3	12	409.2
Thrombotic thrombocytopenia syndrome	0	0.5	0	1.8	0	8.9	0	70.6	0	115.7	0	193.1	0	465.4
Transverse myelitis	0	2.7	0	9.2	2	35.7	36	144.2	8	96.4	2	99.0	9	103.2
Type 1 diabetes	0	187.5	8	639.5	2	765.8	11	3,441.2	4	0.0	2	0.0	3	0.0
Venous thromboembolism (includes deep vein thrombosis and pulmonary embolism)	0	39.2	23	133.8	111	798.0	977	7,528.2	751	9,171.5	752	14,207.0	1,852	40,832.7

a. 750,190 PY
b. 2,558,185 PY
c. 3,568,669 PY
d. 15,341,822 PY
e. 7,142,942 PY
f. 6,150,205 PY
g. 9,215,858 PY

Table 7. Age-Stratified Observed (Obs) to Expected (Exp) Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States Inputs, 42-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	Obs cases	Exp cases[a]	Obs cases	Exp cases[b]	Obs cases	Exp cases[c]	Obs cases	Exp cases[d]	Obs cases	Exp cases[e]	Obs cases	Exp cases[f]	Obs cases	Exp cases[g]
Acute kidney injury/renal failure	0	95.6	14	334.1	24	360.3	79	3,800.6	55	7,973.4	95	18,361.7	416	80,594.5
Acute liver injury/liver injury	0	59.7	0	208.7	1	517.2	8	2,943.8	3	2,817.2	5	3,074.8	10	6,876.3
Acute respiratory distress syndrome (ARDS)	0	120.9	0	422.6	5	137.6	10	1,374.1	10	2,404.1	18	4,546.1	60	12,696.8
Ageusia/anosmia	0	48.2	49	168.4	130	812.8	1,094	4,394.4	504	3,881.3	319	3,824.4	277	5,165.8
Appendicitis	0	1,202.6	31	4,203.4	28	5,031.2	132	21,701.9	38	10,117.4	25	8,683.7	17	13,247.3
Arrhythmia	0	689.6	27	2,410.4	144	4,516.1	1,372	29,109.8	568	38,203.1	422	76,899.6	626	301,436.3
Chillblains	0	104.9	0	366.6	6	551.6	40	2,233.2	18	741.2	12	1,207.6	22	2,620.6
Chronic fatigue syndrome/ME/PVFS	0	140.6	1	491.3	3	686.1	52	2,959.6	17	1,379.7	5	1,184.2	8	1,806.6
Coronary artery disease	0	6.7	0	23.5	0	161.1	15	6,778.2	24	22,028.8	17	33,943.7	33	77,656.8
Cutaneous vasculitis	0	125.2	2	437.5	8	126.7	38	542.0	28	423.6	26	501.2	46	1,144.9
Death	3	139.9	40	1,146.0	37	4,546.3	376	41,919.6	446	64,856.5	787	120,275.6	5,184	588,414.4
Disseminated intravascular coagulation	0	6.4	2	22.4	1	21.9	5	90.0	8	64.0	7	107.1	9	200.4
Erythema multiforme	0	203.5	13	711.1	8	300.8	55	1,189.7	28	517.9	23	415.7	31	825.0
Guillain-Barré syndrome	0	9.6	14	33.6	22	85.0	194	438.5	107	466.6	93	482.3	133	738.6
Haemorrhagic stroke	0	15.0	5	52.3	7	106.9	98	1,790.1	98	3,330.9	111	5,607.9	428	19,250.5
Heart failure	0	59.7	2	208.7	17	248.7	72	4,225.7	84	12,880.1	75	34,319.0	680	153,519.3
Herpes zoster	0	2,392.4	172	8,688.5	233	12,591.0	2,551	60,495.5	1,801	66,680.8	1,716	80,942.6	2,634	138,616.4
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia	0	129.1	65	451.3	67	1,099.0	331	5,341.1	159	3,882.4	193	5,782.5	488	13,870.6
Ischemic stroke	0	20.6	21	72.0	58	274.8	555	4,263.9	512	8,582.5	660	18,087.2	1,913	66,247.6
Multisystem inflammatory syndrome	0	25.8	26	90.3	14	7.8	37	197.9	20	83.9	24	60.3	110	145.5
Myasthenia gravis	0	1.7	2	15.8	0	35.8	16	271.9	18	183.8	10	269.1	35	399.8
Myocarditis, low	4	3.0	500	10.5	804	88.6	1,284	337.3	349	136.3	171	171.9	171	236.1

Table 7. Age-Stratified Observed (Obs) to Expected (Exp) Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States Inputs, 42-Day Risk Window, Cumulative Period

	≤11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	Obs cases	Exp cases[a]	Obs cases	Exp cases[b]	Obs cases	Exp cases[c]	Obs cases	Exp cases[d]	Obs cases	Exp cases[e]	Obs cases	Exp cases[f]	Obs cases	Exp cases[g]
Myocarditis, mid	4	47.0	500	164.3	804	229.4	1,284	989.5	349	461.3	171	395.9	171	604.0
Myocarditis, high	4	48.9	500	171.0	804	543.3	1,284	1,848.6	349	546.2	171	404.0	171	577.9
Myocarditis/pericarditis	4	99.2	598	346.8	1,004	1,598.0	2,165	5,741.5	654	1,863.1	338	1,790.7	357	2,546.5
Narcolepsy	0	6.6	1	23.1	1	69.9	15	308.1	15	90.2	2	126.9	11	104.3
Rhabdomyolysis	0	136.5	14	477.1	11	666.3	46	2,874.1	7	1,339.9	12	1,150.0	29	1,754.4
Seizures/convulsions/seizure disorders (including febrile)	7	1,955.7	205	6,835.5	180	2,428.5	680	10,095.3	254	6,011.8	163	5,945.4	303	15,082.7
Stress cardiomyopathy	0	0.0	0	0.0	1	0.0	6	33.7	6	149.9	8	279.9	13	609.5
Thrombotic thrombocytopenia syndrome	0	0.7	0	2.6	1	13.0	0	103.4	0	169.8	0	282.6	0	693.3
Transverse myelitis	0	3.8	0	13.4	2	52.1	39	211.4	8	141.5	3	144.9	12	153.8
Type 1 diabetes	0	267.0	14	933.2	3	1,118.8	15	5,044.3	6	0.0	3	0.0	5	0.0
Venous thromboembolism (includes deep vein thrombosis and pulmonary embolism)	0	55.9	28	195.2	137	1,165.8	1,191	11,035.4	898	13,462.0	898	20,786.8	2,170	60,823.7

a. 1,068,029 PY
b. 3,732,996 PY
c. 5,213,644 PY
d. 22,489,043 PY
e. 10,484,399 PY
f. 8,998,625 PY
g. 13,727,794 PY

Table 8. Age-Stratified Observed to Expected Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) Background Rates per 100,000 Person Years

AESI	≤11 years	12-17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years
Acute kidney injury/renal failure[11]	8.95	8.95	6.91	16.90	76.05	204.05	587.09
Acute liver injury/liver injury[11]	5.59	5.59	9.92	13.09	26.87	34.17	50.09
Acute respiratory distress syndrome (ARDS)[11]	11.32	11.32	2.64	6.11	22.93	50.52	92.49
Ageusia/anosmia[13]	4.51	4.51	15.59	19.54	37.02	42.50	37.63
Appendicitis[14]	112.60	112.60	96.50	96.50	96.50	96.50	96.50
Arrhythmia[11]	64.57	64.57	86.62	129.44	364.38	854.57	2,195.81
Chillblains[16]	9.82	9.82	10.58	9.93	7.07	13.42	19.09
Chronic fatigue syndrome/ME/PVFS[17]	13.16	13.16	13.16	13.16	13.16	13.16	13.16
Coronary artery disease[9]	0.63	0.63	3.09	30.14	210.11	377.21	565.69
Cutaneous vasculitis[18]	11.72	11.72	2.43	2.41	4.04	5.57	8.34
Death[35]	13.10	30.70	87.20	186.40	618.60	1336.6	4286.3
Disseminated intravascular coagulation[21]	0.60	0.60	0.42	0.40	0.61	1.19	1.46
Erythema multiforme[22]	19.05	19.05	5.77	5.29	4.94	4.62	6.01
Guillain-Barré syndrome[24]	0.90	0.90	1.63	1.95	4.45	5.36	5.38
Haemorrhagic stroke[25]	1.40	1.40	2.05	7.96	31.77	62.32	140.23
Heart failure[11]	5.59	5.59	4.77	18.79	122.85	381.38	1,118.31
Herpes zoster[26]	224.00	232.75	241.50	269.00	636.00	899.50	1,009.75
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia[18]	12.09	12.09	21.08	23.75	37.03	64.26	101.04
Ischemic stroke[11]	1.93	1.93	5.27	18.96	81.86	201.00	482.58
Multisystem inflammatory syndrome[24,9,a]	2.42	2.42	0.15	0.88	0.80	0.67	1.06
Myasthenia gravis[29]	0.16	0.42	0.69	1.21	1.75	2.99	2.91
Myocarditis, low[21]	0.28	0.28	1.70	1.50	1.30	1.91	1.72
Myocarditis, mid[30]	4.40	4.40	4.40	4.40	4.40	4.40	4.40
Myocarditis, high[11]	4.58	4.58	10.42	8.22	5.21	4.49	4.21
Myocarditis/pericarditis[22]	9.29	9.29	30.65	25.53	17.77	19.90	18.55
Narcolepsy[13]	0.62	0.62	1.34	1.37	0.86	1.41	0.76
Rhabdomyolysis[32]	12.78	12.78	12.78	12.78	12.78	12.78	12.78

Table 8. Age-Stratified Observed to Expected Analysis of Spontaneously Reported Adverse Events of Special Interest (AESI) Background Rates per 100,000 Person Years

AESI	≤11 years	12-17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years
Seizures/convulsions/seizure disorders (including febrile)[22]	183.11	183.11	46.58	44.89	57.34	66.07	109.87
Stress cardiomyopathy[22]	-	-	-	0.15	1.43	3.11	4.44
Thrombotic thrombocytopenia syndrome[11]	0.07	0.07	0.25	0.46	1.62	3.14	5.05
Transverse myelitis[11]	0.36	0.36	1.00	0.94	1.35	1.61	1.12
Type 1 diabetes[13]	25.00	25.00	21.46	22.43	-	-	-
Venous thromboembolism (includes deep vein thrombosis and pulmonary embolism) [11]	5.23	5.23	22.36	49.07	128.40	231.00	443.07

a. ACCESS DK_DCE_AU background rates used for 5-11 years, 12-17 years, and 18-24 years age groups and ACCESS ES_FISABIO background rates for all other age groups

3.2.1. Summary of age-stratified analyses

For this analysis, MIS, myocarditis, and myocarditis/pericarditis are noted to have O/E > 1. MIS is further discussed below; myocarditis and myocarditis/pericarditis are further discussed in Section 5.

For all other AESIs, the upper limit of the 95% CI is less than 1.

4. DISCUSSION

4.1. Cardiogenic shock and hypertension

Although requested by regulatory authorities, cardiogenic shock, and hypertension are not included in this analysis because relevant background rates were not able to be identified due to the fact that these endpoints are sequelae of clinically heterogeneous primary causes.

4.2. Age stratified analyses, multisystem inflammatory syndrome

In the age stratified analyses, the O/E ratio exceeds 1 for MIS for both the 21-day and 42-day risk windows in the 18-24 years age group.

Low exposure estimates, underestimated age specific background rates, and methods used to distribute cases with missing age into the age categories could be contributing to the variability in O/E across age groups seen in these stratified analyses.

MIS is a condition known to be associated with COVID-19. The MAH's COVID-19 vaccine requires two doses spaced 21 days apart before achieving maximum effectiveness. It is possible that COVID-19 may occur within the 21-day window between doses. Additionally, general awareness of MIS is currently increased because of COVID-19, leading to possible stimulated reporting. The MAH will continue to monitor MIS.

4.3. Limitations

There are several limitations to observed to expected analyses for signal detection. The observed case counts are likely to be underestimated due to underreporting that occurs with spontaneous reporting. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous surveillance systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition. Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association.

With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Thus, the exposure is underestimated, leading to underestimation of the expected cases.

The expected count also assumes that the expected incidence rate in the vaccinated population is the same as that in the population used to calculate the background rate. The background rates used in these analyses are primarily derived from EU health care systems; a large proportion of exposure data are derived from the US. It is possible that the delivery of health care, population demographics, and underlying health status of the populations used for the background rate estimates differ from those expected in the vaccinated population.

5. OBSERVED VERSUS EXPECTED ANALYSES FOR MYOCARDITIS AND MYOCARDITIS/PERICARDITIS

As requested by regulators, the MAH conducted analyses for myocarditis and pericarditis stratified by age, sex, and dose. Dose stratified analyses include dose 3 for both the US and EEA countries. Since background incidence rates stratified by age and sex were not available for pericarditis alone, analyses are provided for a combined myocarditis/pericarditis.

5.1. Methods

Spontaneously reported cases of myocarditis and myocarditis/pericarditis identified using the search criteria in Table 1 were limited to those occurring in EEA countries or the United States. Cases were also limited to those with time to onsets occurring within the 14-day or 21-day risk windows to increase the sensitivity for signal detection for these events. Time to onset was imputed for cases with missing values based on cases with known time to onset. Cases were then grouped by age and sex and by dose; those with unknown values were proportionally allocated across groups. Expected case counts were determined cumulatively by multiplying estimated background incidence rates by the duration of post-vaccination exposure time. Duration of exposure time was estimated for the cumulative period using 14-day and 21-day risk windows. Three background rates were used for myocarditis: a low, mid, and high rate.

Age and sex stratified and dose stratified estimated exposure time was derived from the ECDC data on COVID-19 vaccination in the EU/EEA and OWD and CDC data in the US.[6,7],[8] Vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine. In the US, dose 3 estimates were taken into consideration starting on 22 Sep 2021, the earliest date data were available. Exposure time was calculated using 14-day and 21-day risk windows for the cumulative period.

5.2. Results

Table 9. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	**Person Years**	**Obs Cases**	**Bkgd rate[a,21]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,30]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,11]**	**Exp Cases**	**O/E Ratio**	**95% CI**
Males ≤11 years	112,005	1	0.48	0.5	**1.860**	**0.047, 10.363**	4.40	4.9	0.203	0.005, 1.131	8.26	9.3	0.108	0.003, 0.602
Males 12-17 years	477,070	328	0.48	2.3	**143.235**	**128.152, 159.60**	4.40	21.0	**15.626**	**13.980, 17.412**	8.26	39.4	**8.324**	**7.447, 9.275**
Males 18-24 years	676,746	534	2.77	18.7	**28.486**	**26.121, 31.008**	4.40	29.8	**17.933**	**16.444, 19.521**	20.20	136.7	**3.906**	**3.582, 4.252**
Males 25-49 years	3,096,523	634	2.48	76.8	**8.256**	**7.626, 8.924**	4.40	136.2	**4.653**	**4.298, 5.030**	14.97	463.5	**1.368**	**1.263, 1.478**
Males 50-59 years	1,476,280	133	1.66	24.5	**5.427**	**4.544, 6.432**	4.40	65.0	**2.048**	**1.714, 2.427**	8.48	125.2	**1.062**	**0.890, 1.259**
Males 60-69 years	1,223,383	63	2.37	29.0	**2.173**	**1.670, 2.780**	4.40	53.8	**1.170**	**0.899, 1.497**	4.80	58.7	**1.073**	**0.824, 1.373**
Males 70+ years	2,119,011	48	2.58	54.7	0.878	0.647, 1.164	4.40	93.2	0.515	0.380, 0.683	3.82	80.9	0.593	0.437, 0.786
Females ≤11 years	126,304	0	0.08	0.1	0.000	-	4.40	5.6	0.000	-	1.42	1.8	0.000	-
Females 12-17 years	537,973	58	0.08	0.4	**134.765**	**102.333, 174.21**	4.40	23.7	**2.450**	**1.861, 3.168**	1.42	7.6	**7.592**	**5.765, 9.815**
Females 18-24 years	763,139	90	0.74	5.6	**15.937**	**12.815, 19.589**	4.40	33.6	**2.680**	**2.155, 3.295**	4.55	34.7	**2.592**	**2.084, 3.186**
Females 25-49 years	3,491,824	294	0.72	25.1	**11.694**	**10.395, 13.110**	4.40	153.6	**1.914**	**1.701, 2.145**	3.97	138.6	**2.121**	**1.885, 2.378**
Females 50-59 years	1,664,741	102	0.97	16.1	**6.317**	**5.150, 7.668**	4.40	73.2	**1.393**	**1.135, 1.690**	3.46	57.6	**1.771**	**1.444, 2.150**
Females 60-69 years	1,379,560	39	1.48	20.4	**1.910**	**1.358, 2.611**	4.40	60.7	0.642	0.457, 0.878	4.20	57.9	0.673	0.479, 0.920
Females 70+ years	2,389,523	49	0.96	22.9	**2.136**	**1.580, 2.824**	4.40	105.1	0.466	0.345, 0.616	4.83	115.4	0.425	0.314, 0.561
Overall, dose 1	8,807,322	774	1.34	118.0	**6.558**	**6.104, 7.037**	4.40	387.5	**1.997**	**1.859, 2.143**	6.27	552.2	**1.402**	**1.305, 1.504**

Table 9. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	**Person Years**	**Obs Cases**	**Bkgd rate[a,21]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,30]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,11]**	**Exp Cases**	**O/E Ratio**	**95% CI**
Overall, dose 2	8,455,538	1,553	1.34	113.3	**13.706**	**13.033, 14.406**	4.40	372.0	**4.174**	**3.969, 4.387**	6.27	530.2	**2.929**	**2.785, 3.079**
Overall, dose 3	2,271,482	46	1.34	30.4	**1.511**	**1.106, 2.016**	4.40	99.9	0.460	0.337, 0.614	6.27	142.4	0.323	0.236, 0.431

a. Background rate per 100,000 person years

Table 10. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	**Person Years**	**Obs Cases**	**Bkgd rate[a,21]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,30]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,11]**	**Exp Cases**	**O/E Ratio**	**95% CI**
Males ≤11 years	125,778	1	0.48	0.6	**1.656**	**0.042, 9.229**	4.40	5.5	0.181	0.005, 1.007	8.26	10.4	0.096	0.002, 0.536
Males 12-17 years	332,053	47	0.48	1.6	**29.488**	**21.667, 39.213**	4.40	14.6	**3.217**	**2.364, 4.278**	8.26	27.4	**1.714**	**1.259, 2.279**
Males 18-24 years	452,799	53	2.77	12.5	**4.226**	**3.165, 5.527**	4.40	19.9	**2.660**	**1.993, 3.480**	20.20	91.5	0.579	0.434, 0.758
Males 25-49 years	1,765,916	50	2.48	43.8	**1.142**	**0.847, 1.505**	4.40	77.7	0.643	0.478, 0.848	14.97	264.4	0.189	0.140, 0.249
Males 50-59 years	794,914	11	1.66	13.2	0.834	0.416, 1.492	4.40	35.0	0.314	0.157, 0.563	8.48	67.4	0.163	0.081, 0.292
Males 60-69 years	744,603	5	2.37	17.6	0.283	0.092, 0.661	4.40	32.8	0.153	0.050, 0.356	4.80	35.7	0.140	0.045, 0.326
Males 70+ years	820,069	12	2.58	21.2	0.567	0.293, 0.991	4.40	36.1	0.333	0.172, 0.581	3.82	31.3	0.383	0.198, 0.669
Females ≤11 years	141,834	1	0.08	0.1	**8.813**	**0.223, 49.103**	4.40	6.2	0.160	0.004, 0.893	1.42	2.0	0.497	0.013, 2.766
Females 12-17 years	374,442	4	0.08	0.3	**13.353**	**3.638, 34.189**	4.40	16.5	0.243	0.066, 0.622	1.42	5.3	0.752	0.205, 1.926
Females 18-24 years	510,603	8	0.74	3.8	**2.117**	**0.914, 4.172**	4.40	22.5	0.356	0.154, 0.702	4.55	23.2	0.344	0.149, 0.678
Females 25-49 years	1,991,352	37	0.72	14.3	**2.581**	**1.817, 3.557**	4.40	87.6	0.422	0.297, 0.582	3.97	79.1	0.468	0.330, 0.645
Females 50-59 years	896,392	9	0.97	8.7	**1.035**	**0.473, 1.965**	4.40	39.4	0.228	0.104, 0.433	3.46	31.0	0.290	0.133, 0.551
Females 60-69 years	839,659	10	1.48	12.4	0.805	0.386, 1.480	4.40	36.9	0.271	0.130, 0.498	4.20	35.3	0.284	0.136, 0.521
Females 70+ years	924,759	7	0.96	8.9	0.788	0.317, 1.625	4.40	40.7	0.172	0.069, 0.354	4.83	44.7	0.157	0.063, 0.323
Overall, dose 1	5,253,313	81	1.34	70.4	**1.151**	**0.914, 1.430**	4.40	231.1	0.350	0.278, 0.436	6.27	329.4	0.246	0.195, 0.306
Overall, dose 2	4,351,891	168	1.34	58.3	**2.881**	**2.462, 3.351**	4.40	191.5	0.877	0.750, 1.021	6.27	272.9	0.616	0.526, 0.716

Table 10. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a,21]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,30]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,11]	Exp Cases	O/E Ratio	95% CI
Overall, dose 3	1,109,971	6	1.34	14.9	0.403	0.148, 0.878	4.40	48.8	0.123	0.045, 0.267	6.27	69.6	0.086	0.032, 0.188

a. Background rate per 100,000 person years

Table 11. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a,21]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,30]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,11]	Exp Cases	O/E Ratio	95% CI
Males ≤11 years	166,363	1	0.48	0.8	**1.252**	**0.032, 6.977**	4.40	7.3	0.137	0.003, 0.761	8.26	13.7	0.073	0.002, 0.405
Males 12-17 years	710,709	347	0.48	3.4	**101.718**	**91.296, 113.004**	4.40	31.3	**11.096**	**9.960, 12.328**	8.26	58.7	**5.911**	**5.305, 6.567**
Males 18-24 years	1,006,859	564	2.77	27.9	**20.222**	**18.588, 21.962**	4.40	44.3	**12.731**	**11.702, 13.826**	20.20	203.4	**2.773**	**2.549, 3.012**
Males 25-49 years	4,596,035	716	2.48	114.0	**6.282**	**5.830, 6.759**	4.40	202.2	**3.541**	**3.286, 3.810**	14.97	688.0	**1.041**	**0.966, 1.120**
Males 50-59 years	2,180,231	152	1.66	36.2	**4.200**	**3.559, 4.923**	4.40	95.9	**1.584**	**1.343, 1.857**	8.48	184.9	0.822	0.697, 0.964
Males 60-69 years	1,788,135	75	2.37	42.4	**1.770**	**1.392, 2.218**	4.40	78.7	0.953	0.750, 1.195	4.80	85.8	0.874	0.687, 1.095
Males 70+ years	3,117,256	60	2.58	80.4	0.746	0.569, 0.960	4.40	137.2	0.437	0.334, 0.563	3.82	119.1	0.504	0.385, 0.649
Females ≤11 years	187,601	0	0.08	0.2	0.000	-	4.40	8.3	0.000	-	1.42	2.7	0.000	-
Females 12-17 years	801,437	61	0.08	0.6	**95.142**	**72.776, 122.213**	4.40	35.3	**1.730**	**1.323, 2.222**	1.42	11.4	**5.360**	**4.100, 6.885**
Females 18-24 years	1,135,394	101	0.74	8.4	**12.021**	**9.791, 14.607**	4.40	50.0	**2.022**	**1.647, 2.457**	4.55	51.7	**1.955**	**1.592, 2.376**

Table 11. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a,21]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,30]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,11]	Exp Cases	O/E Ratio	95% CI
Females 25-49 years	5,182,763	323	0.72	37.3	**8.656**	**7.737, 9.653**	4.40	228.0	**1.416**	**1.266, 1.580**	3.97	205.8	**1.570**	**1.403, 1.751**
Females 50-59 years	2,458,558	121	0.97	23.8	**5.074**	**4.210, 6.063**	4.40	108.2	**1.119**	**0.928, 1.337**	3.46	85.1	**1.422**	**1.180, 1.700**
Females 60-69 years	2,016,408	47	1.48	29.8	**1.575**	**1.157, 2.094**	4.40	88.7	0.530	0.389, 0.704	4.20	84.7	0.555	0.408, 0.738
Females 70+ years	3,515,204	58	0.96	33.7	**1.719**	**1.305, 2.222**	4.40	154.7	0.375	0.285, 0.485	4.83	169.8	0.342	0.259, 0.442
Overall, dose 1	13,172,888	902	1.34	176.5	**5.110**	**4.782, 5.455**	4.40	579.6	**1.556**	**1.456, 1.661**	6.27	825.9	**1.092**	**1.022, 1.166**
Overall, dose 2	12,637,341	1,667	1.34	169.3	**9.844**	**9.377, 10.328**	4.40	556.0	**2.998**	**2.856, 3.145**	6.27	792.4	**2.104**	**2.004, 2.207**
Overall, dose 3	3,053,053	57	1.34	40.9	**1.393**	**1.055, 1.805**	4.40	134.3	0.424	0.321, 0.550	6.27	191.4	0.298	0.226, 0.386

a. Background rate per 100,000 person years

Table 12. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	**Person Years**	**Obs Cases**	**Bkgd rate[a,21]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,30]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[a,11]**	**Exp Cases**	**O/E Ratio**	**95% CI**
Males ≤11 years	186,227	1	0.48	0.9	**1.119**	**0.028, 6.233**	4.40	8.2	0.122	0.003, 0.680	8.26	15.4	0.065	0.002, 0.362
Males 12-17 years	491,638	50	0.48	2.4	**21.188**	**15.726, 27.933**	4.40	21.6	**2.311**	**1.716, 3.047**	8.26	40.6	**1.231**	**0.914, 1.623**
Males 18-24 years	670,416	59	2.77	18.6	**3.177**	**2.419, 4.098**	4.40	29.5	**2.000**	**1.523, 2.580**	20.20	135.4	0.436	0.332, 0.562
Males 25-49 years	2,614,621	54	2.48	64.8	0.833	0.626, 1.087	4.40	115.0	0.469	0.353, 0.612	14.97	391.4	0.138	0.104, 0.180
Males 50-59 years	1,176,952	11	1.66	19.5	0.563	0.281, 1.007	4.40	51.8	0.212	0.106, 0.380	8.48	99.8	0.110	0.055, 0.197
Males 60-69 years	1,102,461	6	2.37	26.1	0.230	0.084, 0.500	4.40	48.5	0.124	0.045, 0.269	4.80	52.9	0.113	0.042, 0.247
Males 70+ years	1,214,197	13	2.58	31.3	0.415	0.221, 0.710	4.40	53.4	0.243	0.130, 0.416	3.82	46.4	0.280	0.149, 0.479
Females ≤11 years	210,000	1	0.08	0.2	**5.952**	**0.151, 33.165**	4.40	9.2	0.108	0.003, 0.603	1.42	3.0	0.335	0.008, 1.868
Females 12-17 years	554,400	6	0.08	0.4	**13.528**	**4.965, 29.445**	4.40	24.4	0.246	0.090, 0.535	1.42	7.9	0.762	0.280, 1.659
Females 18-24 years	756,001	9	0.74	5.6	**1.609**	**0.736, 3.054**	4.40	33.3	0.271	0.124, 0.514	4.55	34.4	0.262	0.120, 0.497
Females 25-49 years	2,948,402	40	0.72	21.2	**1.884**	**1.346, 2.566**	4.40	129.7	0.308	0.220, 0.420	3.97	117.1	0.342	0.244, 0.465
Females 50-59 years	1,327,201	11	0.97	12.9	0.854	0.427, 1.529	4.40	58.4	0.188	0.094, 0.337	3.46	45.9	0.240	0.120, 0.429
Females 60-69 years	1,243,201	10	1.48	18.4	0.543	0.261, 1.000	4.40	54.7	0.183	0.088, 0.336	4.20	52.2	0.192	0.092, 0.352
Females 70+ years	1,369,201	7	0.96	13.1	0.533	0.214, 1.097	4.40	60.2	0.116	0.047, 0.239	4.83	66.1	0.106	0.043, 0.218
Overall, dose 1	7,828,483	89	1.34	104.9	0.848	0.681, 1.044	4.40	344.5	0.258	0.208, 0.318	6.27	490.8	0.181	0.146, 0.223
Overall, dose 2	6,479,306	182	1.34	86.8	**2.096**	**1.803, 2.424**	4.40	285.1	0.638	0.549, 0.738	6.27	406.3	0.448	0.385, 0.518

Table 12. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 21-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a,21]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,30]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[a,11]	Exp Cases	O/E Ratio	95% CI
Overall, dose 3	1,557,128	7	1.34	20.9	0.335	0.135, 0.691	4.40	68.5	0.102	0.041, 0.211	6.27	97.6	0.072	0.029, 0.148

a. Background rate per 100,000 person years

Table 13. Observed to Expected (O/E) Analysis of Myocarditis/Pericarditis in European Economic Area Countries, Cumulative Period

		14-Day Risk Window					21-Day Risk Window				
Stratification	Bkgd rate[a,22]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	16.77	1	112,005	18.8	0.053	0.001, 0.297	1	166,363	27.9	0.036	0.001, 0.200
Males 12-17 years	16.77	371	477,070	80.0	**4.637**	**4.177, 5.134**	393	710,709	119.2	**3.297**	**2.979, 3.640**
Males 18-24 years	54.88	623	676,746	371.4	**1.677**	**1.548, 1.814**	660	1,006,859	552.6	**1.194**	**1.105, 1.289**
Males 25-49 years	43.53	914	3,096,523	1,347.9	0.678	0.635, 0.724	1,037	4,596,035	2,000.7	0.518	0.487, 0.551
Males 50-59 years	25.25	206	1,476,280	372.8	0.553	0.480, 0.633	244	2,180,231	550.5	0.443	0.389, 0.502
Males 60-69 years	26.50	107	1,223,383	324.2	0.330	0.270, 0.399	128	1,788,135	473.9	0.270	0.225, 0.321
Males 70+ years	24.58	112	2,119,011	520.9	0.215	0.177, 0.259	138	3,117,256	766.2	0.180	0.151, 0.213
Females ≤11 years	1.39	0	126,304	1.8	0.000	-	0	187,601	2.6	0.000	-
Females 12-17 years	1.39	87	537,973	7.5	**11.634**	**9.319, 14.351**	97	801,437	11.1	**8.707**	**7.061, 10.622**
Females 18-24 years	6.42	145	763,139	49.0	**2.960**	**2.497, 3.482**	165	1,135,394	72.9	**2.264**	**1.931, 2.637**
Females 25-49 years	7.61	650	3,491,824	265.7	**2.446**	**2.262, 2.642**	726	5,182,763	394.4	**1.841**	**1.709, 1.980**
Females 50-59 years	10.23	220	1,664,741	170.3	**1.292**	**1.127, 1.474**	254	2,458,558	251.5	**1.010**	**0.890, 1.142**
Females 60-69 years	13.38	86	1,379,560	184.6	0.466	0.373, 0.575	103	2,016,408	269.8	0.382	0.312, 0.463
Females 70+ years	13.26	104	2,389,523	316.9	0.328	0.268, 0.398	126	3,515,204	466.1	0.270	0.225, 0.322
Overall, dose 1	18.68	1,398	8,807,322	1,645.2	0.850	0.806, 0.895	1,624	13,172,888	2,460.7	0.660	0.628, 0.693
Overall, dose 2	18.68	2,150	8,455,538	1,579.5	**1.361**	**1.304, 1.420**	2,355	12,637,341	2,360.7	0.998	0.958, 1.039
Overall, dose 3	18.68	78	2,271,482	424.3	0.184	0.145, 0.229	93	3,053,053	570.3	0.163	0.132, 0.200

a. Background rate per 100,000 person years (PY)

Table 14. Observed to Expected (O/E) Analysis of Myocarditis/Pericarditis in the United States, Cumulative Period

		14-Day Risk Window					21-Day Risk Window				
Stratification	Bkgd rate[a22]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	16.77	1	125,778	21.1	0.047	0.001, 0.264	1	186,227	31.2	0.032	0.001, 0.178
Males 12-17 years	16.77	51	332,053	55.7	0.916	0.682, 1.204	55	491,638	82.4	0.667	0.503, 0.868
Males 18-24 years	54.88	61	452,799	248.5	0.245	0.188, 0.315	67	670,416	367.9	0.182	0.141, 0.231
Males 25-49 years	43.53	63	1,765,916	768.7	0.082	0.063, 0.105	69	2,614,621	1,138.1	0.061	0.047, 0.077
Males 50-59 years	25.25	16	794,914	200.7	0.080	0.046, 0.129	19	1,176,952	297.2	0.064	0.038, 0.100
Males 60-69 years	26.50	6	744,603	197.3	0.030	0.011, 0.066	9	1,102,461	292.2	0.031	0.014, 0.058
Males 70+ years	24.58	15	820,069	201.6	0.074	0.042, 0.123	16	1,214,197	298.4	0.054	0.031, 0.087
Females ≤11 years	1.39	1	141,834	2.0	0.507	0.013, 2.826	1	210,000	2.9	0.343	0.009, 1.909
Females 12-17 years	1.39	5	374,442	5.2	0.961	0.312, 2.242	7	554,400	7.7	0.908	0.365, 1.872
Females 18-24 years	6.42	11	510,603	32.8	0.336	0.168, 0.600	15	756,001	48.5	0.309	0.173, 0.510
Females 25-49 years	7.61	51	1,991,352	151.5	0.337	0.251, 0.442	57	2,948,402	224.4	0.254	0.192, 0.329
Females 50-59 years	10.23	15	896,392	91.7	0.164	0.092, 0.270	17	1,327,201	135.8	0.125	0.073, 0.200
Females 60-69 years	13.38	18	839,659	112.3	0.160	0.095, 0.253	19	1,243,201	166.3	0.114	0.069, 0.178
Females 70+ years	13.26	11	924,759	122.6	0.090	0.045, 0.161	13	1,369,201	181.6	0.072	0.038, 0.122
Overall, dose 1	18.68	118	5,253,313	981.3	0.120	0.100, 0.144	135	7,828,483	1,462.4	0.092	0.077, 0.109
Overall, dose 2	18.68	197	4,351,891	812.9	0.242	0.210, 0.279	219	6,479,306	1,210.3	0.181	0.158, 0.207
Overall, dose 3	18.68	10	1,109,971	207.3	0.048	0.023, 0.089	11	1,557,128	290.9	0.038	0.019, 0.068

a. Background rate per 100,000 person years (PY)

5.3. Discussion - Myocarditis and Pericarditis

For myocarditis in the EEA, almost all O/E ratios were above 1 across age group, gender, and dose, using the low background rate. This was also true for most age groups other than the oldest in both genders, and for dose 1 and dose 2 using the mid and high background rates. For myocarditis in the US, O/E ratios were above 1 for the younger age groups in both males and females and for dose 1 and dose 2 using the low background rate, and for the younger age groups of males using the mid and high background rates. Recent increases in O/E ratios for the younger age groups may have been influenced by increased reporting of cases after the release of a Dear Healthcare Provider letter in late July 2021[36].

For myocarditis/pericarditis, the O/E ratios were above 1 for the <25-year age group in males, females age 12-59 years, and dose 2 in the EEA. All O/E ratios were below 1 for myocarditis/pericariditis in the US.

6. OBSERVED VERSUS EXPECTED ANALYSES FOR THROMBOEMBOLIC EVENTS

As requested by regulators, the MAH performed O/E analyses for thromboembolic events, using the following categories: venous thromboembolism (VTE), broad definition; VTE, narrow definition; cerebral venous sinus thrombosis (CVST); arterial thromboembolism (ATE), broad definition; and ATE, narrow definition. These categories were chosen to align with background rates for thromboembolic events reported by ACCESS.

6.1. Methods

VTE, broad definition includes deep vein thrombosis (DVT), pulmonary embolism (PE), CVST, and other VTE event cases. VTE, narrow definition includes DVT, PE, and CVST cases. ATE, broad definition includes coronary artery disease (CAD), stroke, and other ATE event cases. ATE, narrow definition includes CAD and stroke cases.

Expected case counts were determined cumulatively by multiplying estimated background incidence rates by the duration of post-vaccination exposure time. The ACCESS rate for VTE was used for both the VTE broad and narrow definitions of cases[11]; the ACCESS rate for CVST without thrombocytopenia (TP) was used for CVST cases[25]; and the ACCESS rate for ATE without TP was used for both the ATE broad and narrow definitions of cases[25]. Observed cases were limited to those with time to onsets occurring within the 21-day and 42-day risk windows. Time to onset was imputed for cases with missing values based on cases with known time to onset Duration of exposure time was estimated for the cumulative period using 21-day and 42-day risk windows.

Estimated exposure time was derived from the ECDC data on COVID-19 vaccination in the EU/EEA and OWD and CDC data in the US.[6,7],[8] Vaccine administrations were limited to the Pfizer-BioNTech COVID-19 vaccine. Exposure time was calculated using 21-day and 42-day risk windows for the cumulative period.

6.2. Results

Table 15. Observed to Expected (O/E) Ratios of Thromboembolic Events, Cumulative Period

	Processed Cases				All Cases			
	21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
Thromboembolic Event	O/E ratio	95%CI	O/E ratio	95%CI	O/E ratio	95%CI	O/E ratio	95%CI
Venous thromboembolism, broad	0.056	0.055, 0.057	0.044	0.043, 0.045	0.058	0.057, 0.059	0.046	0.045, 0.047
Venous thromboembolism, narrow	0.038	0.037, 0.039	0.030	0.029, 0.031	0.039	0.038, 0.040	0.031	0.031, 0.032
Cerebral venous sinus thrombosis	0.642	0.581, 0.708	0.519	0.474, 0.567	0.659	0.598, 0.726	0.535	0.489, 0.584
Arterial thromboembolism, broad	0.013	0.013, 0.014	0.010	0.010, 0.011	0.014	0.014, 0.014	0.011	0.011, 0.011
Arterial thromboembolism, narrow	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001

Table 16. Observed versus Expected Analyses of Thromboembolic Events Inputs, Cumulative Period

	Background Rate per 100,000 Person Years (PY)	Processed Cases				All Cases			
		21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
Thromboembolic Event		Obs	Exp[a]	Obs	Exp[b]	Obs	Exp[a]	Obs	Exp[b]
Venous thromboembolism, broad	209.38[11]	10,300	183,926.6	12,145	274,471.4	10,705	183,926.6	12,624	274,471.4
Venous thromboembolism, narrow	209.38[11]	6,975	183,926.6	8,263	274,471.4	7,241	183,926.6	8,576	274,471.4
Cerebral venous sinus thrombosis	0.72[25]	406	632.5	490	943.8	417	632.5	505	943.8
Arterial thromboembolism, broad	323.67[25]	3,837	284,322.8	4,448	424,291.5	3,994	284,322.8	4,626	424,291.5
Arterial thromboembolism, narrow	323.67[25]	376	284,322.8	420	424,291.5	382	284,322.8	427	424,291.5

a. 87,843,419 PY
b. 131,087,686 PY

6.3. Discussion – Thromboembolic Events

The upper level of the 95% CI was below 1 for all thromboembolic events for all risk windows using narrow and broad definitions for the observed cases. These results suggest that the number of reported thromboembolic cases is not higher than expected compared to unvaccinated persons.

7. OBSERVED VERSUS EXPECTED ANALYSES FOR ANAPHYLAXIS (IDENTIFIED RISK)

Since anaphylaxis has already been identified as a risk, the goal of the observed versus expected analysis is risk estimation rather than signal identification. Risk of anaphylaxis is reported per dose administered and compared to rates of anaphylaxis observed for other vaccines rather than rates in an unexposed population.

The MAH has conducted unadjusted observed versus expected analyses for the 7,330 cumulative cases of anaphylaxis reported through 15 December 2021. Anaphylaxis cases were identified using the following PTs: anaphylactic shock, anaphylactic reaction, anaphylactoid shock, and anaphylactoid reaction. A background rate of 1.31 anaphylaxis cases per million vaccine doses was assumed.[37]

An estimated 1,998,199,807 doses of Pfizer-BioNTech COVID-19 vaccine have been administered through 15 December 2021. Approximately 83% of shipped doses of the Pfizer-BioNTech COVID-19 vaccine are administered in the European Union and the United States based on a weighted average between these two areas. This administration estimate was applied to the 2,403,096,715 doses shipped worldwide through 15 December 2021.

Expected counts were determined by multiplying the number of doses administered by the expected rates per dose.

An O/E ratio of 2.800 (95% CI 2.736, 2.865) was observed for BNT162b2 compared to the background rate for anaphylaxis cases observed in the US. This rate has steadily declined each reporting period from the 9.47 (95% CI, 8.61, 10.40) first reported in Summary Monthly Safety Report (SMSR) 2 (through 31 January 2021). The reason for the decline is unknown but could reflect decreased reporting, changes in the accuracy of the exposure estimate, or changes in population being vaccinated.

There are several limitations to consider when interpreting these analyses. The analyses did not adjust for differences in characteristics such as age and comorbidities between persons being administered the vaccine and populations from which the background rate was derived. The spontaneous report system likely underestimates the true number of observed events in vaccinated persons due to incomplete or a lag in reporting.

Conversely, spontaneous report systems are prone to reporting bias whereby events that have been previously identified as potentially related to a vaccine are more likely to be reported than other events, for example, due to increased media attention. With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that 85% of all shipped doses are administered in each

country. The true number of vaccines administered may be higher or lower than this estimate.

Additionally, there are differences in health care delivery, demographics, and underlying health status in the populations used to calculate background rate estimates compared to those in the population administered the vaccine.

---

[1] Consideration on core requirements for RMPs of COVID19 vaccines coreRMP19 guidance EMA/544966/2020

[2] European Medicines Agency. Consideration on core requirements for PSURs of COVID19 vaccines. 8 July 2021. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/consideration-core-requirements-psurs-covid-19-vaccines_en.pdf. Accessed 26 Oct 2021.

[3] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 8). EMA/95098/2010.

[4] Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf. 2016;25(2):215-222. DOI:10.1002/pds.3918

[5] ACCESS background incidence rates of AESIs – User guide. Available from: http://www.encepp.eu/documents/ACCESSbackgroundrates-Userguide_000.pdf. Accessed 6 May 2021.

[6] European Centre for Disease Prevention and Control. Data on COVID-19 vacciantion in the EU/EEA. Available from: https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed June 2021.

[7] Our World in Data. COVID-19 Dataset. Available from: https://github.com/owid/covid-19-data. Accessed June 2021.

[8] Centers for Disease Control and Prevention. Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic.

[9] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES_FISABIO. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[10] Willame C, Dodd C, van der Aa L, et al. Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. Drug Saf. 2021;44(3):383-395. DOI: 10.1007/s40264-020-01031-1.

[11] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, IT_ARS. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[12] Pfizer Internal Data Healthcore, specific PFE_SE_PNG.

[13] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES_SIDIAP_PC. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[14] Coward S, Kareemi H, Clement F, et al. Incidence of Appendicitis over Time: A Comparative Analysis of an Administrative Healthcare Database and a Pathology-Proven Appendicitis Registry. PLoS One. 2016 Nov 7;11(11):e0165161. DOI: 10.1371/journal.pone.0165161.

[15] Thomas T, Chandan JS, Subramanian A, et al. Epidemiology, morbidity and mortality in Behçet's disease: a cohort study using The Health Improvement Network (THIN). Rheumatology (Oxford). 2020;59(10):2785-2795. DOI: 10.1093/rheumatology/keaa010.

[16] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, UK_CPRD. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[17] Vincent A, Brimmer DJ, Whipple MO, et al. Prevalence, incidence, and classification of chronic fatigue syndrome in Olmsted County, Minnesota, as estimated using the Rochester Epidemiology Project. Mayo Clin Proc. 2012;87(12):1145-52. DOI: 10.1016/j.mayocp.2012.08.015.

[18] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES_BIFAP_PC.

Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

19 Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2019 on CDC WONDER Online Database. Available from: http://wonder.cdc.gov/ucd-icd10.html. Accessed 20 Dec 2021.

20 Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74. DOI: 10.1038/nrcardio.2015.83.

21 Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, NL PHARMO HOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

22 Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES_BIFAP_PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

23 Creed F. A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. Pain. 2020;161(6):1169-1176. DOI: 10.1097/j.pain.0000000000001819.

24 Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, DK_DCE_AU. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

25 Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES SIDIAP PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

26 Morant-Talamante N, Diez-Domingo J, Martínez-Úbeda S, et al. Herpes zoster surveillance using electronic databases in the Valencian community (Spain). BMC Infect Dis 2013;13:463.

27 Duff S, Mafilios MS, Bhounsule P, Hasegawa JT. The burden of critical limb ischemia: a review of recent literature. Vasc Health Risk Manag. 2019 Jul 1;15:187-208. doi: 10.2147/VHRM.S209241. PMID: 31308682; PMCID: PMC6617560.

[28] McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. Lancet Infect Dis. 2018;18(9):992-1003. DOI: 10.1016/S1473-3099(18)30245-7.

[29] Incidence of myasthenia gravis in the Emilia-Romagna region: A prospective multicenter study. Neurology. 1998; 51:255-258. DOI: 10.1212/wnl.51.1.255.

[30] Elfström P, Hamsten A, Montgomery SM, et al. Cardiomyopathy, pericarditis and myocarditis in a population-based cohort of inpatients with coeliac disease. J Intern Med. 2007;262(5):545-54. DOI: 10.1111/j.1365-2796.2007.01843.x.

[31] AbdelRazek M, Low P, Rocca W, et al. Epidemiology of Postural Tachycardia Syndrome (S18.005). Neurology. 2019;92(15 Supplement).

[32] HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. Available from: https://hcupnet.ahrq.gov/. Accessed 04 Nov 2021.

[33] Alexander T and Harris J. Incidence of Sudden Sensorineural Hearing Loss. Otol Neurotol. 2013 Dec;34(9):1586-9. doi: 10.1097/MAO.0000000000000222.

[34] Pfizer Internal Study C4591004.

[35] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 2017-2019 on CDC WONDER Online Database. Available from: http://wonder.cdc.gov/ucd-icd10.html. Accessed 07 Jul 2021.

[36] COVID-19 mRNA Vaccines Comirnaty and Spikevax: risk of myocarditis and pericarditis. July 19, 2021. Available at: https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-covid-19-mrna-vaccines-comirnaty-spikevax-risk_en.pdf. Accessed October 12, 2021.

[37] McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137(3):868-78. DOI: 10.1016/j.jaci.2015.07.048.

Summary Tabulation of Fatal Cases and Adverse Events by System Organ Class (SOC) and Preferred Terms (PT) by Age Group

BNT162B2;BNT162B2S01 - ALL

Reporting Period: 19-JUN-2021 Through 18-DEC-2021

Total Number of Cases: 5259 (100%) (ALL) / 5259 (OVERALL)

Total Number of Adverse Events (PT): 19869 (ALL)

MedDRA Version: v.24.1.

CT

Total Number of Cases: 44

Total Number of Adverse Events (PT): 58

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Cardiac disorders					
Number of Cases			1	3	3
Number of Events			1	3	3
Cardiac arrest					1
Cardiogenic shock					1
Cardio-respiratory arrest			1	2	1
Coronary artery disease				1	
Gastrointestinal disorders					
Number of Cases				3	1
Number of Events				3	1
Duodenal perforation					1
Intestinal ischaemia				1	
Large intestine perforation				1	
Pancreatitis				1	
General disorders and administration site conditions					
Number of Cases			3	3	2
Number of Events			3	3	2
Condition aggravated			1		
Death			2	3	2
Hepatobiliary disorders					
Number of Cases				1	
Number of Events				1	
Biliary cyst				1	
Infections and infestations					
Number of Cases		1	4	3	2
Number of Events		2	4	3	2
Acquired immunodeficiency syndrome		1			
COVID-19 pneumonia				1	
Infection					1
Kidney infection					1
Pneumocystis jirovecii pneumonia		1			
Postoperative wound infection			1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Infections and infestations					
Number of Cases		1	4	3	2
Number of Events		2	4	3	2
Sepsis			2	1	
Septic shock				1	
Staphylococcal sepsis			1		
Injury, poisoning and procedural complications					
Number of Cases	1	3			1
Number of Events	1	4			1
Accidental overdose		1			
Gun shot wound	1				
Injury		1			
Road traffic accident		1			1
Toxicity to various agents		1			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Number of Cases				2	2
Number of Events				2	2
Angiosarcoma				1	
Bladder cancer					1
Pancreatic carcinoma metastatic					1
Pancreatic neoplasm				1	
Nervous system disorders					
Number of Cases			2	1	1
Number of Events			2	1	1
Amyotrophic lateral sclerosis			1		
Cerebrovascular accident			1		1
Ischaemic stroke				1	
Psychiatric disorders					
Number of Cases	1	2		1	
Number of Events	1	2		1	
Completed suicide	1	1		1	
Drug abuse		1			
Renal and urinary disorders					
Number of Cases					1
Number of Events					1
Acute kidney injury					1
Respiratory, thoracic and mediastinal disorders					
Number of Cases			1	4	1
Number of Events			1	4	1
Chronic obstructive pulmonary disease				1	
Pulmonary embolism				3	1
Pulmonary fibrosis			1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Vascular disorders					
Number of Cases					2
Number of Events					2
Deep vein thrombosis					1
Shock haemorrhagic					1

*Only post birth cases included

Non CT

Total Number of Cases: 5215

Total Number of Adverse Events (PT): 19811

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Blood and lymphatic system disorders							
Number of Cases	6	2	16	19	34	141	11
Number of Events	11	2	21	22	47	180	11
Acquired haemophilia						1	
Agranulocytosis		1					
Anaemia	2				9	20	1
Anaemia folate deficiency						1	
Anaemia macrocytic						2	
Anaemia megaloblastic						1	
Anaemia vitamin B12 deficiency						1	
Antiphospholipid syndrome						2	
Aplastic anaemia				1	1		
Autoimmune haemolytic anaemia					1	2	
Blood disorder						2	
Blood loss anaemia					1		
Bone marrow failure	1					1	
Coagulation factor deficiency					1		
Coagulopathy	2		4	3		5	1
Cytopenia						1	
Disseminated intravascular coagulation	1		1	2	6	16	
Elephantiasis						1	
Febrile neutropenia				1			
Haemolysis					2		
Haemolytic anaemia					1		
Haemorrhagic diathesis					1		
Hilar lymphadenopathy						1	
Hypercoagulation						3	
Hypereosinophilic syndrome						1	
Hyperleukocytosis					1	2	
Hypocoagulable state						1	
Immune thrombocytopenia			1		2	5	1
Increased tendency to bruise					1		
Iron deficiency anaemia					1		
Leukocytosis				1		9	
Leukopenia					2	3	
Lymphadenitis						2	
Lymphadenopathy			2	2	3	11	2
Lymphadenopathy mediastinal				1			
Lymphocytic infiltration				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Blood and lymphatic system disorders							
Number of Cases	6	2	16	19	34	141	11
Number of Events	11	2	21	22	47	180	11
Lymphopenia						6	
Microcytic anaemia						1	
Monocytosis						1	
Myelosuppression						1	
Neutropenia						2	
Neutrophilia					1	4	
Normochromic anaemia						1	
Normocytic anaemia						4	
Pancytopenia			2		1	6	1
Paratracheal lymphadenopathy						1	
Platelet anisocytosis						1	
Polycythaemia						1	
Red blood cell abnormality	1						
Sickle cell anaemia with crisis			1				
Spleen ischaemia						1	
Splenic artery thrombosis					1		
Splenic infarction						2	
Splenic thrombosis						1	
Splenitis						1	
Splenomegaly				1	1	2	
Spontaneous haematoma					1		
Thrombocytopenia	2	1	7	6	8	34	2
Thrombocytopenic purpura						3	1
Thrombocytosis			1			2	
Thrombosis with thrombocytopenia syndrome			2	1		8	
Thrombotic microangiopathy				1		1	
Thrombotic thrombocytopenic purpura	2			1		2	2
White blood cell disorder					1		
Cardiac disorders							
Number of Cases	25	13	206	162	239	895	73
Number of Events	36	19	328	243	377	1,302	84
Acute coronary syndrome			3	1	2	12	1
Acute left ventricular failure			2	1		1	
Acute myocardial infarction	1		6	16	22	57	4
Angina pectoris			2	2	4	4	
Angina unstable						1	
Aortic valve calcification						1	
Aortic valve disease				1			
Aortic valve incompetence			1			5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	25	13	206	162	239	895	73
Number of Events	36	19	328	243	377	1,302	84
Aortic valve stenosis				1		3	
Arrhythmia	2	4	12	4	17	48	
Arteriosclerosis coronary artery			1	2	5	12	
Atrial fibrillation					9	46	2
Atrial flutter					1	2	
Atrial thrombosis					1	2	
Atrioventricular block						2	2
Atrioventricular block complete				1		2	
Atrioventricular block first degree					1	1	
Atrioventricular block second degree			1				
Bradycardia	1		1	1	3	10	
Bundle branch block left					1		
Bundle branch block right					1	3	
Cardiac aneurysm					2	2	1
Cardiac arrest	9	2	57	49	80	177	10
Cardiac asthma						1	
Cardiac discomfort						2	
Cardiac disorder	2	1	5	5	5	24	4
Cardiac dysfunction			1		2	4	
Cardiac failure		2	7	9	23	152	3
Cardiac failure acute	1	1	5	4	9	42	1
Cardiac failure chronic		1				9	
Cardiac failure congestive			2	4	4	24	
Cardiac fibrillation						1	
Cardiac flutter			1		1	1	
Cardiac hypertrophy			2	2	2	1	
Cardiac perforation					1		
Cardiac steatosis				1			
Cardiac tamponade			2	2	2	7	
Cardiac valve disease						2	
Cardiac valve sclerosis				1			
Cardiac ventricular thrombosis			1		2	1	
Cardiogenic shock	1		5	4	6	17	1
Cardiomegaly	2		5	3	3	17	
Cardiomyopathy			6	1	1	4	
Cardiopulmonary failure	1	1	1		3	11	
Cardiorenal syndrome						2	
Cardio-respiratory arrest	3	1	41	23	30	203	1
Cardiovascular disorder			3	1	6	14	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	25	13	206	162	239	895	73
Number of Events	36	19	328	243	377	1,302	84
Cardiovascular insufficiency				1			
Cardiovascular symptom						1	
Carditis			1				1
Conduction disorder						1	
Congestive cardiomyopathy					1	3	
Coronary artery disease			1	7	4	7	
Coronary artery embolism						1	
Coronary artery occlusion			3	1	2	7	
Coronary artery stenosis			1	3	1	5	
Coronary artery thrombosis			3	1	5	9	
Cor pulmonale						2	1
Cor pulmonale acute						1	
Diastolic dysfunction					1		
Dilatation ventricular			1				
Endocarditis noninfective			1				
Eosinophilic myocarditis				1			
Extrasystoles					1	2	
Hypertensive heart disease				1		3	
Immune-mediated myocarditis					1		
Intracardiac thrombus			3	2	4	2	
Intrapericardial thrombosis					1		
Ischaemic cardiomyopathy					1	2	1
Left ventricular dilatation			1				
Left ventricular dysfunction			1			3	
Left ventricular failure						6	
Left ventricular hypertrophy				1	1	5	
Low cardiac output syndrome					1		
Mitral valve calcification						1	
Mitral valve disease				1			
Mitral valve incompetence			1			5	
Mitral valve stenosis						1	
Myocardial fibrosis			2	4		5	
Myocardial hypoxia					1		
Myocardial infarction	1	1	46	29	44	130	28
Myocardial injury			1	1			
Myocardial ischaemia		1	7	7	6	22	1
Myocardial necrosis				3		3	
Myocardial oedema			1				
Myocardial rupture			1		3	6	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	25	13	206	162	239	895	73
Number of Events	36	19	328	243	377	1,302	84
Myocarditis	6	3	31	6	9	25	12
Palpitations	2		6	4	3	9	4
Papillary muscle disorder						1	
Papillary muscle rupture				1			
Paroxysmal arrhythmia						1	
Pericardial disease						1	
Pericardial effusion	1		3	4	3	11	1
Pericardial haemorrhage			1	2		5	
Pericarditis			2	2	2	7	
Pulmonary valve disease						1	
Pulseless electrical activity			2		1	3	
Right ventricular dilatation						1	
Right ventricular dysfunction					1		
Right ventricular failure			2		3	1	1
Right ventricular hypertrophy					1		
Sinus tachycardia			1			3	
Stress cardiomyopathy			2	1		3	
Supraventricular tachycardia						2	
Tachyarrhythmia						1	
Tachycardia			10	9	8	35	2
Tachycardia paroxysmal						1	
Torsade de pointes						1	
Toxic cardiomyopathy			1				
Tricuspid valve incompetence					1	2	
Ventricle rupture					1		
Ventricular arrhythmia			3		2	2	
Ventricular dysfunction			1	1			
Ventricular extrasystoles	1		1			2	
Ventricular fibrillation	2	1	12	8	9	14	1
Ventricular hypertrophy					1		
Ventricular hypokinesia			1	1	1	1	
Ventricular tachycardia			1	2	4	6	
Congenital, familial and genetic disorders							
Number of Cases	1	2	2		2	4	1
Number of Events	1	2	2		2	4	1
Aberrant aortic arch					1		
Arrhythmogenic right ventricular dysplasia					1		
Branchial cyst						1	
Congenital anomaly							1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Congenital, familial and genetic disorders							
Number of Cases	1	2	2		2	4	1
Number of Events	1	2	2		2	4	1
Fallot's tetralogy						1	
Foramen magnum stenosis						1	
Hereditary spherocytosis		1					
Hypertrophic cardiomyopathy						1	
Hypoplastic left heart syndrome			1				
Myocardial bridging	1						
Myotonic dystrophy			1				
Platybasia		1					
Ear and labyrinth disorders							
Number of Cases			2	1	1	13	2
Number of Events			3	1	2	13	2
Deafness bilateral						1	
Ear disorder					1		
Ear pain			1			1	
External ear pain					1		
Hypoacusis				1			1
Otorrhoea						1	
Sudden hearing loss			1				
Tinnitus						2	1
Vertigo						8	
Vestibular disorder			1				
Endocrine disorders							
Number of Cases			1	2		5	
Number of Events			1	2		5	
Adrenal insufficiency						1	
Cushing's syndrome						1	
Diabetes insipidus			1	1			
Hypopituitarism				1			
Hypothyroidism						2	
Inappropriate antidiuretic hormone secretion						1	
Eye disorders							
Number of Cases	2	2	12	6	13	33	3
Number of Events	2	2	14	7	19	42	3
Blindness						5	2
Blindness cortical					1		
Cataract cortical	1						
Conjunctival haemorrhage						1	
Cystoid macular oedema						1	
Diplopia			3		1	1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Eye disorders							
Number of Cases	2	2	12	6	13	33	3
Number of Events	2	2	14	7	19	42	3
Exfoliation syndrome						1	
Eye disorder						1	
Eye haematoma						1	
Eyelid ptosis						3	
Eye movement disorder			1	2		1	
Eye pain		1			2	1	
Eye pruritus				1		1	
Eye swelling					2		
Gaze palsy			1			3	
Keratic precipitates						1	
Lacrimation increased						1	
Mydriasis			1	2	1	1	
Ocular hyperaemia						1	
Ophthalmoplegia						1	
Photophobia						1	
Pupil fixed						1	
Pupillary disorder						1	
Pupillary reflex impaired			1	1	2	1	
Pupils unequal	1			1	1	2	
Retinal artery occlusion						1	
Retinal degeneration			1				
Retinal detachment			1				
Retinal haemorrhage					1		
Retinal tear			1			1	
Swelling of eyelid					1		
Vision blurred			2		2	1	
Visual impairment		1	2		5	8	1
Gastrointestinal disorders							
Number of Cases	13	6	54	47	79	417	20
Number of Events	22	7	74	67	117	617	36
Abdominal discomfort					1	7	1
Abdominal distension			2	1	1	8	1
Abdominal hernia						1	
Abdominal pain	2	1	8	6	12	42	4
Abdominal pain lower						1	
Abdominal pain upper			5	4	3	18	1
Abdominal tenderness						2	
Abnormal faeces	1						
Acute abdomen				1		4	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	13	6	54	47	79	417	20
Number of Events	22	7	74	67	117	617	36
Anal haemorrhage						1	
Anal incontinence				1		2	
Anal sphincter atony	1						
Aphthous ulcer						1	
Ascites				1	2	7	
Autoimmune pancreatitis						1	
Change of bowel habit						1	
Colitis				1			1
Colitis ischaemic					1	2	
Constipation				1		6	
Defaecation disorder	1					1	
Diarrhoea	2	1	10	7	9	62	5
Diarrhoea haemorrhagic						1	
Discoloured vomit						1	
Diverticulum intestinal					1	1	
Dry mouth				1		3	
Duodenal ulcer haemorrhage						1	
Dyspepsia						5	1
Dysphagia			3	2	4	30	
Enteritis				1		1	1
Enterocolitis						1	
Enterovesical fistula					1		
Faecaloma						1	
Faecal vomiting						1	
Faeces discoloured					3	5	
Flatulence						1	
Functional gastrointestinal disorder					1	1	
Gastric disorder	1			1		1	
Gastric haemorrhage						3	
Gastric ulcer	1					1	
Gastritis							1
Gastritis erosive	1					1	
Gastritis haemorrhagic			1			1	
Gastrointestinal disorder					2	6	
Gastrointestinal haemorrhage			1	2	3	16	3
Gastrointestinal necrosis			1	1		6	
Gastrointestinal obstruction						1	
Gastrointestinal pain						1	1
Gastrointestinal ulcer						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	13	6	54	47	79	417	20
Number of Events	22	7	74	67	117	617	36
Gastrooesophageal reflux disease						3	
Gingival swelling			1				
Glossoptosis			1			1	
Haematemesis	1		1	2	4	15	4
Haematochezia					1	2	
Haemorrhoids							1
Hiatus hernia						1	
Hypoaesthesia oral			1				
Ileus				3	1	4	
Ileus paralytic					1	4	
Inguinal hernia						1	
Intestinal dilatation					1		
Intestinal haemorrhage						1	
Intestinal infarction					1	5	
Intestinal ischaemia	1			1	3	18	
Intestinal obstruction			1			7	
Intestinal perforation						3	
Intestinal ulcer						1	
Intra-abdominal haemorrhage	1						
Large intestinal haemorrhage				1			
Large intestinal obstruction						2	
Large intestine perforation					1	1	
Lip discolouration						1	
Lower gastrointestinal haemorrhage						1	
Melaena			2			5	
Mesenteric arterial occlusion						1	
Mesenteric vein thrombosis				1	1	1	
Mouth haemorrhage			1		1	2	1
Mouth swelling						1	
Mouth ulceration					1		
Nausea	1	3	15	11	16	93	3
Noninfective gingivitis						1	
Oesophageal pain						1	
Oesophageal varices haemorrhage					1	1	
Oral pain						1	
Pancreatic steatosis						2	
Pancreatitis				1		4	1
Pancreatitis acute			1		2	2	1
Pancreatitis chronic					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	13	6	54	47	79	417	20
Number of Events	22	7	74	67	117	617	36
Pancreatitis necrotising						1	
Paraesthesia oral				1		2	
Peptic ulcer						1	
Peritoneal disorder					1		
Peritoneal perforation						1	
Pneumatosis intestinalis					1		
Rectal haemorrhage						3	
Rectal perforation					1		
Rectal ulcer						1	
Regurgitation						1	
Retching			1			4	
Salivary hypersecretion						2	
Small intestinal haemorrhage						1	
Small intestinal obstruction						1	
Stomatitis						1	
Subileus					1	2	
Swollen tongue						1	
Thrombosis mesenteric vessel						1	
Tooth loss						1	
Umbilical hernia						1	
Upper gastrointestinal haemorrhage					1	2	
Volvulus						2	
Vomiting	8	2	18	15	32	144	5
General disorders and administration site conditions							
Number of Cases	53	34	250	242	418	1,847	462
Number of Events	70	42	411	353	651	2,733	526
Adverse event						1	
Adverse reaction						1	
Asthenia	3		18	14	38	170	6
Axillary pain			1				
Brain death	1	1	5	5	4	4	2
Cardiac death			8	4	6	13	
Chest discomfort	1		8	6	6	31	1
Chest pain	1	1	31	19	27	67	2
Chills	1	1	14	5	11	38	
Concomitant disease aggravated				2	2	2	1
Concomitant disease progression						3	
Condition aggravated		1	8	4	4	67	1
Crepitations	1					1	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	53	34	250	242	418	1,847	462
Number of Events	70	42	411	353	651	2,733	526
Critical illness	1						
Crying					1	1	
Cyst			1				
Death	27	13	84	96	137	484	351
Decapitation							1
Decreased activity			1			3	
Discomfort			1	5		13	2
Disease complication					1		
Disease progression					1	5	1
Disease recurrence			4	2	8	21	1
Drowning	2		1	2		11	1
Drug ineffective	2	2	12	12	31	186	77
Drug interaction			1		1	4	1
Effusion				1			
Exercise tolerance decreased			1		1	2	
Extravasation					1		
Face oedema					1	1	
Facial pain			1				
Fatigue	2	2	27	18	38	135	13
Feeling abnormal	1	1	8	1	5	12	1
Feeling cold			3		3	5	
Feeling drunk						1	
Feeling hot	1		1			3	
Feeling jittery				1			
Feeling of body temperature change			3		1	1	
Foaming at mouth	1		2		1	5	
Gait disturbance	1			4	8	25	1
Gait inability			2	1	1	13	1
Generalised oedema			1		2	5	
General physical health deterioration		2	6	4	12	114	6
Gravitational oedema				1		1	
Hernia					1		
Hyperpyrexia				3	2	5	
Hyperthermia		1		1	3	9	
Hypertrophy				1			
Hypothermia			1		1	11	
Illness			3		8	10	7
Inflammation					9	22	
Influenza like illness			4	5	3	12	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	53	34	250	242	418	1,847	462
Number of Events	70	42	411	353	651	2,733	526
Injection site discomfort						1	
Localised oedema						1	
Local reaction					4	4	1
Loss of control of legs						2	
Malaise	4	3	27	18	59	163	3
Mass				1		1	
Moaning						3	
Multi-organ disorder			1			1	
Multiple organ dysfunction syndrome	1		7	9	12	68	4
Necrosis			1	1	1	1	
Oedema			4			11	
Oedema peripheral				5	3	29	2
Organ failure			2	1		3	1
Pain	1		5	7	15	50	4
Performance status decreased						1	
Peripheral swelling			3	2	2	14	3
Physical deconditioning			2	3	3	24	
Prosthetic cardiac valve thrombosis						1	
Puncture site haemorrhage					1		
Pyrexia	8	7	51	32	65	287	16
Secretion discharge					1	1	
Sluggishness			1				
Stenosis						1	
Sudden cardiac death	1	1	5	8	12	13	2
Sudden death	6	1	28	34	41	130	5
Swelling		1	1	2	2	6	
Swelling face		1			1	1	
Systemic inflammatory response syndrome				1		6	
Temperature regulation disorder					1		
Tenderness			1		1		
Terminal state							1
Therapeutic response decreased					1		
Thirst		1				1	
Vaccination failure		2	1	6	32	354	5
Vaccination site erythema					2	3	
Vaccination site haematoma						1	
Vaccination site haemorrhage				1			
Vaccination site inflammation						2	
Vaccination site mass						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	53	34	250	242	418	1,847	462
Number of Events	70	42	411	353	651	2,733	526
Vaccination site nodule						1	
Vaccination site pain	3		7	4	11	22	
Vaccination site pruritus			1		1	1	
Vaccination site rash					1	1	
Vaccination site reaction			1				
Vaccination site scar						1	
Vaccination site swelling			1	1		1	
Vaccination site warmth						2	
Vascular stent stenosis						1	
Hepatobiliary disorders							
Number of Cases	2		10	11	17	69	3
Number of Events	2		14	12	29	108	3
Acute hepatic failure				1	1	1	
Autoimmune cholangitis						1	
Autoimmune hepatitis						1	
Bile duct stone					1		
Cholangitis					1	2	
Cholangitis acute						2	
Cholecystitis					2	2	
Cholecystitis acute						1	
Cholelithiasis				1	1	14	
Chronic hepatic failure					1		
Congestive hepatopathy			2	1			
Drug-induced liver injury					1	2	
Gallbladder cholesterolosis					1		
Gallbladder enlargement						1	
Gallbladder hypofunction						1	
Gallbladder oedema						1	
Gallbladder polyp						1	
Hepatic atrophy						1	
Hepatic cirrhosis					1	2	1
Hepatic cyst						1	
Hepatic cytolysis				1		2	
Hepatic failure	1		3		6	16	
Hepatic function abnormal			1	2	1	9	
Hepatic haemorrhage				1			
Hepatic infarction						1	
Hepatic ischaemia						1	
Hepatic lesion						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Hepatobiliary disorders							
Number of Cases	2		10	11	17	69	3
Number of Events	2		14	12	29	108	3
Hepatic necrosis			1			1	
Hepatic steatosis			1	1		5	
Hepatic vein thrombosis				1			
Hepatitis			1			2	
Hepatitis acute						1	
Hepatocellular injury				1			
Hepatomegaly			1		1	1	
Hepatorenal failure						1	
Hepatorenal syndrome					1	2	
Hepatotoxicity						1	
Hyperbilirubinaemia						1	
Ischaemic hepatitis						1	
Jaundice			1		1	7	
Jaundice cholestatic						1	
Liver disorder	1		1		4	11	
Liver injury			1	1		2	
Ocular icterus			1			2	
Portal hypertension						1	
Portal vein embolism							1
Portal vein thrombosis				1	4	3	1
Portosplenomesenteric venous thrombosis						1	
Subacute hepatic failure					1		
Immune system disorders							
Number of Cases	3	2	8	12	5	34	9
Number of Events	3	2	8	12	5	38	10
Amyloidosis						1	
Anaphylactic reaction	1		2		1	9	4
Anaphylactic shock	2	1	1	3		1	
Anti-neutrophil cytoplasmic antibody positive vasculitis						3	
Autoimmune disorder			1	3		2	
Corneal graft rejection						1	
Cytokine release syndrome				2			
Cytokine storm					1	1	1
Food allergy							1
Haemophagocytic lymphohistiocytosis				1		2	1
Heart transplant rejection			1				
Hypersensitivity		1	1		1	6	1
Immune system disorder			1	1	1	5	1
Immunisation reaction				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Immune system disorders							
Number of Cases	3	2	8	12	5	34	9
Number of Events	3	2	8	12	5	38	10
Immunodeficiency				1			
Immunosuppression						1	
Lung transplant rejection					1		
Multisystem inflammatory syndrome in adults			1				
Sarcoidosis						1	
Serum sickness							1
Type I hypersensitivity						1	
Type IV hypersensitivity reaction						1	
Vaccine associated enhanced disease						3	
Infections and infestations							
Number of Cases	5	8	49	55	151	954	106
Number of Events	9	8	68	69	210	1,217	116
Abdominal sepsis						1	
Abscess					1	2	
Acute hepatitis B					1		
Appendicitis							1
Arteriosclerotic gangrene						1	
Aspergillus infection						1	
Asymptomatic COVID-19						4	
Atypical mycobacterial infection						1	
Atypical pneumonia						2	
Bacteraemia					1	2	
Bacterial infection					2	4	1
Bacterial sepsis					1	1	
Bacteriuria					1		
Bacteroides bacteraemia				1			
Beta haemolytic streptococcal infection			1				
Bronchitis				1	2	6	
Bronchopulmonary aspergillosis						1	
Candida infection						1	
Candida sepsis			1			1	
Cardiac infection			1			1	1
Cardiac valve vegetation						1	
Catheter site infection						1	
Cavernous sinus thrombosis		1					
Cellulitis					2	5	
Clostridium difficile infection						1	2
Colon gangrene						1	
Conjunctivitis					2		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	5	8	49	55	151	954	106
Number of Events	9	8	68	69	210	1,217	116
COVID-19	1	4	13	16	58	444	68
COVID-19 pneumonia			3	6	15	154	1
Creutzfeldt-Jakob disease				1	1	5	
Cystitis				1		1	
Cytomegalovirus infection				1			
Cytomegalovirus infection reactivation					1		
Cytomegalovirus viraemia						1	
Diarrhoea infectious						1	
Diverticulitis						2	1
Dysentery						1	
Eczema herpeticum						1	
Encephalitis			2	1	4	1	1
Encephalitis viral						1	
Endocarditis			1	1	1	4	
Endocarditis staphylococcal						1	
Endotoxic shock						1	
Enteritis infectious					1	1	
Enterobacter sepsis						1	
Enterococcal infection			1				
Enterococcal sepsis				1			
Erysipelas						4	
Escherichia infection			1				
Escherichia pyelonephritis						1	
Escherichia sepsis			1			2	
Escherichia urinary tract infection						2	
Focal peritonitis						1	
Fungal infection			1			1	1
Furuncle						1	
Gangrene					1		
Gastric infection				1			
Gastroenteritis					1	3	
Gingival abscess						1	
Haemorrhagic pneumonia			1				
Hepatitis C						1	
Herpes simplex					1		
Herpes simplex encephalitis						1	
Herpes zoster					4	13	1
Herpes zoster meningoencephalitis						2	
Infected skin ulcer							1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	5	8	49	55	151	954	106
Number of Events	9	8	68	69	210	1,217	116
Infection				1	3	10	1
Infective aneurysm						1	
Infective exacerbation of chronic obstructive airways disease					1		
Influenza				1	3	6	
Intervertebral discitis						2	
Kidney infection							1
Klebsiella bacteraemia					1		
Klebsiella infection			1			2	
Labyrinthitis				1			
Legionella infection						1	
Liver abscess					1		
Localised infection					1		
Lower respiratory tract infection			1	1	3	7	
Lower respiratory tract infection bacterial					1		
Lower respiratory tract infection viral						1	
Mastoiditis						1	
Meningitis						3	
Meningitis aseptic			2				
Meningitis viral			1				
Meningoencephalitis bacterial						1	
Meningoencephalitis herpetic						1	1
Meningoencephalitis viral			1			1	
Mucormycosis					1		
Mycobacterial infection						1	
Myelitis					1	2	
Nasopharyngitis	1	1	5	3	5	16	1
Nosocomial infection			1		1	1	
Ophthalmic herpes zoster							1
Oral candidiasis						1	
Oral fungal infection						1	
Orchitis					1		
Osteomyelitis						2	
Otitis media						1	
Overgrowth bacterial						1	
Parainfluenzae virus infection						1	
Parotitis						1	
Pathogen resistance					1		
Pericarditis tuberculous						1	
Peritonitis				1	1	3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	5	8	49	55	151	954	106
Number of Events	9	8	68	69	210	1,217	116
Pharyngitis		1	1	1		1	
Pleurisy viral	1						
Pneumococcal bacteraemia						1	
Pneumococcal infection						2	
Pneumocystis jirovecii infection						1	
Pneumocystis jirovecii pneumonia						1	
Pneumonia	1	1	7	9	28	172	6
Pneumonia aspiration			3		4	44	2
Pneumonia bacterial			1			13	
Pneumonia klebsiella				1		1	
Pneumonia legionella						1	
Pneumonia pneumococcal						2	
Pneumonia staphylococcal					1		
Pneumonia viral	1					3	
Prion disease			1		1		
Proteus infection			1				
Pseudomonas infection						2	
Pulmonary sepsis	1					2	
Pustule						1	
Pyelonephritis					1		
Pyelonephritis acute						3	
Renal graft infection						1	
Respiratory tract infection						4	
Rhinitis						2	
Salmonella sepsis						1	
Salmonellosis						1	
Sepsis			3	5	18	59	4
Septic arthritis staphylococcal						1	
Septic embolus						1	
Septic encephalopathy						1	
Septic rash					1		
Septic shock	3		4	6	12	40	1
Severe acute respiratory syndrome						1	
Severe fever with thrombocytopenia syndrome						1	
Sinusitis				1	1	3	
Skin bacterial infection						1	
Skin infection						2	
Soft tissue infection						1	
Spinal cord infection				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	5	8	49	55	151	954	106
Number of Events	9	8	68	69	210	1,217	116
Splenic infection						1	
Sputum purulent						1	
Staphylococcal bacteraemia				1		2	
Staphylococcal infection			1			3	
Staphylococcal sepsis						3	
Streptococcal infection						1	
Streptococcal sepsis						1	
Superinfection bacterial						2	
Suspected COVID-19			2	2	5	15	18
Systemic bacterial infection			1				
Systemic infection						1	
Testicular abscess					1		
Tonsillitis					1		
Tooth infection			1				
Toxic shock syndrome				1	1	1	
Tuberculosis						1	
Upper respiratory tract infection					1		
Urinary tract infection			1	1	4	42	1
Urinary tract infection bacterial					1	4	
Urosepsis					1	5	
Vaccination site abscess						1	
Vaccine associated paralytic poliomyelitis						1	
Vaccine breakthrough infection			1			1	
Variant Creutzfeldt-Jakob disease				1			
Varicella					1		
Viral myocarditis					1	1	
Zoonotic bacterial infection			1				
Injury, poisoning and procedural complications							
Number of Cases	10	6	52	60	76	386	53
Number of Events	10	8	58	72	91	477	56
Accident	1						
Accident at home						1	
Adverse event following immunisation	1		4	4	1	1	1
Alcohol poisoning				1		2	
Anaemia postoperative						1	
Anastomotic complication				1			
Ankle fracture						1	
Bone contusion						2	
Brain herniation	1	1	2	3	2	5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	10	6	52	60	76	386	53
Number of Events	10	8	58	72	91	477	56
Central nervous system injury						1	
Chest injury						2	
Contusion			1	1	4	9	
Craniocerebral injury				1			
Expired product administered		1					
Exposure during pregnancy			1				
Exposure to toxic agent			1				
Exposure to vaccinated person				1			
Extra dose administered				2	2	17	1
Extradural haematoma						1	
Eye injury						1	
Face injury						2	
Facial bones fracture				1		1	
Fall			5	12	15	118	3
Femoral neck fracture						4	
Femur fracture						2	
Foetal exposure during pregnancy		1					
Foot fracture					1		
Fracture				1		1	
Head injury	1			2		11	
Heat illness					2	3	
Heat oedema			1				
Hip fracture						4	
Inappropriate schedule of product administration	1	4	18	14	24	84	1
Incomplete course of vaccination				1			
Incorrect route of product administration			2	2	2	7	
Injection related reaction				1			
Injury						2	1
Intentional product use issue						1	
Joint injury						1	
Limb injury					1	2	
Liver contusion			1				
Lower limb fracture						1	
Lumbar vertebral fracture						1	
Maternal exposure during pregnancy		1	3				
Maternal exposure timing unspecified							3
Medication error				1			
Multiple injuries					1		
Muscle rupture						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	10	6	52	60	76	386	53
Number of Events	10	8	58	72	91	477	56
Muscle strain						1	
Near drowning						3	
Neck injury				1			
Nerve injury	1					1	
Off label use	2		14	15	27	122	13
Overdose					1	8	
Periprosthetic fracture						1	
Poisoning						2	
Poor quality product administered			1				1
Post procedural haemorrhage						1	
Procedural pain						1	
Product administered at inappropriate site						2	
Product dose omission issue				1			
Product use issue			1	1		10	
Rib fracture			1	1		2	
Road traffic accident				1	1		
Scratch						1	
Shunt thrombosis						1	
Skin abrasion						3	
Skin injury						1	
Skin laceration				1		2	
Skull fracture					1		
Spinal fracture						3	
Splenic rupture					1		
Subcutaneous haematoma						2	
Subdural haematoma	1				3	4	
Subdural haemorrhage						1	
Tibia fracture						1	
Tissue injury							2
Transfusion related complication					1		
Traumatic haemorrhage						1	
Traumatic haemothorax						1	
Traumatic intracranial haemorrhage						1	
Ulna fracture						1	
Underdose							28
Upper limb fracture						1	
Vaccination complication						3	1
Vaccination error				1		1	
Vascular procedure complication						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	10	6	52	60	76	386	53
Number of Events	10	8	58	72	91	477	56
Vascular pseudoaneurysm			1				
Vasoplegia syndrome						1	
Venous injury	1						
Wound						3	1
Wrong product administered			1	1	1		
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Activated partial thromboplastin time prolonged					1	1	
Activated partial thromboplastin time ratio decreased						1	
Activated partial thromboplastin time shortened						3	
ADAMTS13 activity decreased	1			1			
Alanine aminotransferase increased				1		7	
Albumin globulin ratio decreased						2	
Albumin urine absent						1	
Ammonia increased						1	
Amylase increased						1	
Anion gap increased						1	
Antibody test abnormal						1	
Antimitochondrial antibody positive						1	
Aspartate aminotransferase abnormal						1	
Aspartate aminotransferase increased				1	1	7	
Bacterial test						1	
Bacterial test positive				1	1	3	
Basophil count decreased						1	
Basophil count increased						1	
Bleeding time prolonged						1	
Blood albumin decreased						5	
Blood albumin increased						1	
Blood alkaline phosphatase increased						3	
Blood bicarbonate decreased						3	
Blood bilirubin increased					2	3	
Blood calcium decreased						1	
Blood chloride decreased						1	
Blood chloride increased					1	1	
Blood cholesterol increased				1			
Blood cholinesterase increased						1	
Blood creatine increased				1		3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Blood creatine phosphokinase increased					2	8	
Blood creatine phosphokinase MB increased				1		1	
Blood creatinine increased	1			2		9	
Blood fibrinogen increased						3	
Blood glucose abnormal			1		1	1	
Blood glucose decreased				1	2	1	
Blood glucose fluctuation						1	
Blood glucose increased			1	3	4	10	
Blood immunoglobulin E increased						2	
Blood immunoglobulin G increased						1	
Blood iron increased						1	
Blood lactate dehydrogenase decreased					1		
Blood lactate dehydrogenase increased						9	
Blood lactic acid increased			1	2		1	
Blood magnesium decreased						1	
Blood phosphorus increased				1		1	
Blood potassium decreased				1		2	
Blood potassium increased					1	3	
Blood pressure abnormal				2		2	
Blood pressure decreased			3	2	7	42	1
Blood pressure diastolic increased						1	
Blood pressure immeasurable						3	
Blood pressure increased			5	7	7	16	1
Blood pressure systolic decreased						2	
Blood pressure systolic increased						2	
Blood sodium decreased						3	
Blood test abnormal			1			2	
Blood triglycerides increased				2			
Blood urea decreased						1	
Blood urea increased					1	11	
Blood urea nitrogen/creatinine ratio increased						1	
Blood urine present					1	2	
Blood viscosity increased					1		
Body mass index abnormal		1					
Body temperature decreased						2	
Body temperature fluctuation					1		
Body temperature increased		1	1		3	8	1
Bone marrow myelogram abnormal					1		
Brain natriuretic peptide increased						5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Breath sounds							1
Breath sounds abnormal			1			3	
Capillary nail refill test abnormal						1	
Carbon dioxide decreased						1	
Cardiac murmur						1	
Cardiac output decreased						1	
Cells in urine						1	
Chest X-ray abnormal						3	
Coagulation factor V level decreased						1	
Coma scale abnormal		2			1	6	
Corneal reflex decreased						1	
C-reactive protein increased			1	1	4	37	
Creatinine renal clearance increased						1	
CSF glucose increased						1	
CSF protein increased					1	1	
Culture urine positive						1	
Cytomegalovirus test positive						2	
Drug specific antibody absent						1	
Eastern Cooperative Oncology Group performance status worsened						1	
Ejection fraction decreased			2	1	1	1	
Electrocardiogram repolarisation abnormality						1	
Electrocardiogram ST segment elevation			1				
Electrocardiogram ST-T segment elevation						1	
Enzyme level abnormal						1	
Eosinophil count increased						2	
Escherichia test positive						1	
Fibrin abnormal					1		
Fibrin D dimer decreased						1	
Fibrin D dimer increased	1		4	2	6	15	
Fibrin degradation products increased				1		1	
Fibrinolysis increased					1		
Full blood count abnormal						2	
Fungal test positive						1	
Gamma-glutamyltransferase increased				1		1	
General physical condition abnormal						2	
Glomerular filtration rate decreased						6	
Glycosylated haemoglobin increased				1		1	
Grip strength decreased					1		
Haematocrit decreased			1			8	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Haemoglobin decreased	1		1	1	2	19	
Haptoglobin decreased						1	
Heart rate abnormal						1	
Heart rate decreased				2	2	9	
Heart rate increased			1	2	5	18	1
Heart rate irregular						2	
Heart sounds abnormal						3	
Hepatic enzyme increased					3	2	
Histamine level increased						1	
Immunoglobulins increased						1	
Inflammatory marker increased					3	5	
Interleukin level decreased					1		
Interleukin level increased					1	3	
International normalised ratio increased						8	1
Lactobacillus test positive						1	
Legionella test positive						1	
Lipase decreased					1		
Liver function test abnormal					2		
Liver function test decreased					1		
Lymphocyte count decreased			1			2	
Lymphocyte count increased				1			
Lymphocyte percentage decreased						1	
Mean cell haemoglobin concentration decreased			1			6	
Mean cell haemoglobin decreased						1	
Mean cell volume decreased						1	
Mean cell volume increased						2	
Metamyelocyte count increased			1				
Monocyte count decreased						1	
Monocyte count increased						1	
Myelocyte count increased			1				
Myocardial necrosis marker increased						2	
Myocardial strain imaging						1	
Neutrophil count decreased						1	
Neutrophil count increased				1		4	
Neutrophil percentage increased						1	
NIH stroke scale score decreased						1	
Nitrite urine present						1	
N-terminal prohormone brain natriuretic peptide increased						2	
Osmolar gap increased				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Oxygen saturation						1	
Oxygen saturation abnormal						2	
Oxygen saturation decreased		1	6	6	18	102	2
Oxygen saturation immeasurable	1						
PCO2 decreased						2	
Platelet count abnormal						1	
Platelet count decreased	2		4	4	2	23	7
Platelet count increased		1				2	
Plateletcrit increased						1	
Platelet factor 4			1				
PO2 decreased						2	
Prealbumin decreased						1	
Procalcitonin increased					1	3	
Protein total decreased				1		3	
Protein urine present					1		
Prothrombin time prolonged					2	1	
Prothrombin time ratio increased						1	
Pulse abnormal				1	1		
Pulse absent		1			3	2	
Pyruvate kinase increased						1	
Quality of life decreased						2	
Radial pulse abnormal						1	
Red blood cell count decreased			1			8	
Red blood cell sedimentation rate increased						2	
Red blood cells urine positive						2	
Red cell distribution width increased			1			2	
Respiratory rate decreased			1			1	
Respiratory rate increased			1			5	
Reticulocyte count decreased						1	
Right ventricular systolic pressure increased						1	
SARS-CoV-2 antibody test positive					1		
SARS-CoV-2 test negative		1					
SARS-CoV-2 test positive				1	1	13	
Serratia test positive						1	
Serum ferritin increased					1	1	
Sinus rhythm						1	
Streptococcus test positive						1	
Total lung capacity decreased						1	
Transaminases increased						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	7	30	34	72	337	15
Number of Events	7	8	47	61	114	690	18
Troponin abnormal				1		1	
Troponin I increased						3	
Troponin increased			1			3	
Troponin T increased					1	5	
Tryptase increased						1	
Tumour marker increased						2	
Urine chromium increased						1	
Urine copper						1	
Urine output decreased			1			3	
Weight decreased				1	4	17	3
Weight increased						3	
White blood cell count decreased					1	6	
White blood cell count increased			1	1	1	24	
White blood cells urine positive						1	
Metabolism and nutrition disorders							
Number of Cases	4	3	8	15	44	226	9
Number of Events	4	4	11	15	60	285	9
Acidosis			1		3	2	
Adult failure to thrive						2	
Cachexia					1	10	
Decreased appetite	2	1	3	5	21	93	4
Dehydration		1		2	4	33	
Diabetes mellitus	1	1			2	4	1
Diabetes mellitus inadequate control						2	
Diabetic ketoacidosis	1		1		1	1	
Diet refusal						2	
Dyslipidaemia						1	
Electrolyte imbalance			1		1	4	
Feeding disorder			1	1	2	12	
Fluid intake reduced						2	
Fluid retention					2	4	
Food refusal						1	
Hypercholesterolaemia							1
Hyperglycaemia			1		1	7	
Hyperglycaemic hyperosmolar nonketotic syndrome						3	
Hyperkalaemia			1	1	3	9	1
Hyperlactacidaemia					2	2	
Hypernatraemia					1	5	
Hyperuricaemia					1	3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Metabolism and nutrition disorders							
Number of Cases	4	3	8	15	44	226	9
Number of Events	4	4	11	15	60	285	9
Hypervolaemia					1	1	
Hypoalbuminaemia				1	1	1	
Hypocalcaemia						1	
Hypochloraemia						1	
Hypoglycaemia						7	
Hypokalaemia					2	7	
Hyponatraemia			1	2	3	12	
Hypophagia					1	17	
Hypophosphataemia						1	
Hypoproteinaemia						1	
Ketoacidosis		1			1		
Lactic acidosis				2	2	3	
Malnutrition					1	7	
Marasmus						11	1
Metabolic acidosis			1		3	8	
Metabolic disorder						1	
Obesity				1		2	
Polydipsia						1	
Type 2 diabetes mellitus						1	1
Musculoskeletal and connective tissue disorders							
Number of Cases	5	1	41	33	50	188	7
Number of Events	6	1	52	40	58	253	11
Antisynthetase syndrome					1		
Arthralgia		1	9	8	10	31	3
Arthritis			1			1	
Back disorder				1			
Back pain	1		4	6	5	29	1
Bone disorder						1	
Bone pain			1		1	1	
Bone swelling						1	
Connective tissue disorder					1		
Facial asymmetry			1				
Fibromyalgia						1	
Flank pain			1			1	
Foot deformity						1	
Groin pain				1	1	2	
Haematoma muscle						1	
Immobilisation syndrome						1	
Immune-mediated myositis					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Musculoskeletal and connective tissue disorders							
Number of Cases	5	1	41	33	50	188	7
Number of Events	6	1	52	40	58	253	11
Joint stiffness						1	
Joint swelling				1		5	
Limb discomfort			1		1	9	
Mobility decreased					3	14	1
Muscle atrophy						1	
Muscle rigidity					1	3	
Muscle spasms				1		8	
Muscle twitching			2			2	
Muscular weakness	1		4	3	5	23	
Musculoskeletal chest pain						2	
Musculoskeletal discomfort				1		1	
Musculoskeletal disorder						1	
Musculoskeletal pain				1	1	2	1
Musculoskeletal stiffness			2	3		3	
Myalgia	1		10	1	13	29	3
Myopathy						2	
Myositis						1	
Neck pain			3	3		6	
Nuchal rigidity						1	
Oligoarthritis						1	
Osteitis						1	
Osteoarthritis						1	
Pain in extremity	3		13	8	10	49	1
Pain in jaw						1	
Polymyositis						2	
Rhabdomyolysis					3	6	
Sarcopenia						1	
Scoliosis						1	
Slipping rib syndrome						1	
Soft tissue haemorrhage				1			
Spinal disorder						1	
Spinal pain						1	
Spinal stenosis						1	
Systemic lupus erythematosus							1
Tendonitis				1			
Torticollis						1	
Trismus					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1		6	18	27	100	14
Number of Events	1		6	19	29	122	15
Abdominal neoplasm						2	
Acute leukaemia					4	3	
Acute lymphocytic leukaemia			1				
Acute megakaryocytic leukaemia					1		
Acute myeloid leukaemia					1	6	
Acute myeloid leukaemia recurrent						1	
Adenocarcinoma of colon						1	
Anaplastic thyroid cancer			1				
B-cell lymphoma						3	
Bile duct cancer						2	
Bladder cancer						1	
Bone cancer						1	
Brain cancer metastatic						1	
Breast cancer							1
Breast cancer metastatic						1	
Breast cancer recurrent						1	
Breast cancer stage IV			1				
Carcinoid tumour pulmonary						1	
Castleman's disease				1	1		
Cholangiosarcoma						1	
Chronic leukaemia						1	
Chronic lymphocytic leukaemia						2	
Chronic myeloid leukaemia						1	
Diffuse large B-cell lymphoma						1	
Endocrine neoplasm malignant						1	
Essential thrombocythaemia						1	
Follicular lymphoma stage IV					1		
Gastric cancer						2	
Glioblastoma			1			2	
Haemangioma				1			
Haematopoietic neoplasm						1	
Hepatic cancer						1	3
Hepatic cancer metastatic						1	
Hepatic neoplasm						3	
Invasive ductal breast carcinoma				1			
Leiomyosarcoma				1			
Leukaemia	1				1	4	1
Lip and/or oral cavity cancer				1			
Lung adenocarcinoma						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1		6	18	27	100	14
Number of Events	1		6	19	29	122	15
Lung cancer metastatic				2	2	1	1
Lung carcinoma cell type unspecified stage 0						1	
Lung neoplasm malignant				2		10	1
Lymphangioma				1			
Lymphoma					3	3	
Lymphoproliferative disorder						2	
Malignant ascites						1	
Malignant neoplasm of renal pelvis						1	
Malignant neoplasm progression					1	2	
Malignant pleural effusion						1	
Malignant splenic neoplasm				1			
Marrow hyperplasia					1		
Metastases to bone						2	
Metastases to central nervous system						2	
Metastases to liver					1	3	
Metastases to lung					1	1	
Metastases to lymph nodes						1	
Metastases to pituitary gland				1			
Metastases to the mediastinum						1	
Metastasis			1			1	
Metastatic bronchial carcinoma						1	
Metastatic lymphoma					1		
Myelodysplastic syndrome						3	1
Myeloid leukaemia						1	
Myeloproliferative neoplasm						3	
Neoplasm malignant			1	2		3	6
Neoplasm progression				3	4	12	1
Neoplasm recurrence						2	
Non-Hodgkin's lymphoma						1	
Ovarian cancer						1	
Pancreatic carcinoma					2	4	
Pancreatic neoplasm					1	1	
Papilloma						1	
Paraneoplastic syndrome					1		
Plasmacytoma						1	
Pleural mesothelioma						1	
Prostate cancer						2	
Renal cancer						1	
Renal neoplasm						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1		6	18	27	100	14
Number of Events	1		6	19	29	122	15
Small cell lung cancer					1		
Squamous cell carcinoma of the tongue						1	
Testis cancer						1	
Thymoma				1			
Transitional cell carcinoma					1		
Tumour rupture				1			
Uterine leiomyoma						1	
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Acute disseminated encephalomyelitis			3	1	1	1	
Ageusia						1	1
Alexia						1	
Altered state of consciousness			4	5	5	49	
Amnesia						2	
Anosmia						2	1
Aphasia			1		2	17	
Apraxia				1			
Areflexia			1		1	1	
Ataxia						2	
Autoimmune encephalopathy						1	
Autonomic nervous system imbalance					1	1	
Balance disorder				1	1	9	1
Basal ganglia haemorrhage			1				
Basilar artery occlusion					1	1	
Basilar artery thrombosis			1		3	2	
Bradykinesia						2	
Brain compression		1	1			1	
Brain hypoxia	1				1	1	
Brain injury		2	4	3	3	4	2
Brain oedema	2	3	7	10	4	4	
Brain stem haemorrhage		1	1	1	2	5	
Brain stem infarction			1		1	3	
Brain stem ischaemia						1	
Brain stem stroke			1			1	
Brain stem thrombosis					1		
Burning sensation					1		
Carotid arteriosclerosis						2	
Carotid artery disease				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Carotid artery dissection			1				
Carotid artery occlusion					3	2	
Carotid artery stenosis					1	1	
Carotid artery thrombosis		1			1		
Cataplexy						1	
Central nervous system lesion					2		
Central nervous system vasculitis				1			
Cerebellar ataxia					1		
Cerebellar atrophy						1	
Cerebellar haemorrhage	1				2	2	
Cerebellar infarction			1	2		2	
Cerebellar stroke						1	
Cerebellar tonsillar ectopia		1					
Cerebral arteriosclerosis				1		4	
Cerebral artery embolism						7	
Cerebral artery occlusion				1		1	
Cerebral artery thrombosis			1		1	1	
Cerebral atrophy						6	
Cerebral circulatory failure						1	
Cerebral disorder				1	1	3	
Cerebral haematoma			1		4	9	
Cerebral haemorrhage	1	1	10	12	25	86	4
Cerebral infarction			2	4	11	50	3
Cerebral ischaemia			1	1		7	
Cerebral thrombosis		1	3	2	2	6	3
Cerebral vascular occlusion						1	
Cerebral venous sinus thrombosis	1	3	11	1	1	2	
Cerebral venous thrombosis			2	4	1	1	
Cerebral ventricular rupture					3	3	
Cerebrovascular accident			9	6	20	99	17
Cerebrovascular disorder				1		5	
Cerebrovascular stenosis					1		
Clumsiness						1	
Cognitive disorder					3	9	1
Coma	1		5	10	9	48	2
Coma hepatic					1		
Consciousness fluctuating						2	
Coordination abnormal						2	
Cranial nerve disorder						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Decerebrate posture						1	
Dementia						10	2
Dementia Alzheimer's type						1	
Demyelinating polyneuropathy					1		
Demyelination			1	1			
Depressed level of consciousness	1	1	5	7	3	50	
Diplegia					1	1	
Disturbance in attention				1	2	8	
Dizziness	4	1	12	9	16	55	4
Dysarthria			5	2	6	16	
Dysgeusia					2		
Dyskinesia	1		1			3	
Dyslalia						1	
Dyslexia			1			1	
Dysstasia				1	2	11	
Embolic cerebral infarction						1	
Embolic stroke						3	
Encephalitis autoimmune			1		1	3	
Encephalopathy			1	1	3	5	
Epilepsy			1	2	2	12	
Facial paralysis				2	2	6	
Facial paresis			1			1	
Febrile convulsion						2	
Frontotemporal dementia						1	
Generalised tonic-clonic seizure			1	2		1	
Guillain-Barre syndrome			2		2	11	1
Haemorrhage intracranial		1	4	1	2	4	
Haemorrhagic cerebral infarction					1	3	
Haemorrhagic stroke			3		6	22	1
Haemorrhagic transformation stroke				1	2	2	
Headache	6	9	48	33	29	73	6
Head discomfort						2	
Hemiparaesthesia			1				
Hemiparesis	2		4	1	3	22	
Hemiplegia			2	1	2	12	
Hepatic encephalopathy			1		1	2	
Hydrocephalus		1		1	2	3	
Hyperammonaemic encephalopathy						1	
Hypercapnic coma						2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Hyperkinesia						1	
Hypersomnia					1	4	
Hypoaesthesia	1		2	2	6	11	
Hypogeusia						1	
Hypokinesia						4	1
Hyporeflexia			1				
Hyporesponsive to stimuli						2	
Hyposmia						1	
Hypotonia		1	1	1	3	1	
Hypotonic-hyporesponsive episode					2		
Hypoxic-ischaemic encephalopathy				2	1	3	
IIIrd nerve disorder					1		
IIIrd nerve paralysis			1				
Incoherent					1		
Intellectual disability			1				
Intracranial aneurysm			2	3	1	4	
Intracranial pressure increased	1		3		2	1	
Intraventricular haemorrhage				1		4	
Ischaemic cerebral infarction			1			2	
Ischaemic stroke			6	4	5	20	
Lacunar infarction						1	
Language disorder					1	3	
Lethargy			2	1	7	20	
Leukoencephalopathy			1			2	
Locked-in syndrome						1	
Loss of consciousness	3		20	16	30	107	6
Memory impairment					3	5	
Meningoradiculitis			1				
Meningorrhagia				1		2	
Mental impairment						3	1
Metabolic encephalopathy						1	
Migraine			3		1	2	
Miller Fisher syndrome							1
Monoparesis					1		
Monoplegia			1			6	
Motor dysfunction					1	5	
Motor neurone disease				1			
Movement disorder			1		1	12	1
Multiple sclerosis						1	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Multiple sclerosis relapse					1		
Multiple system atrophy						1	
Muscle contractions involuntary						1	
Myasthenia gravis						4	
Myelitis transverse							1
Myoclonus				1	1	1	
Narcolepsy						2	
Nervous system disorder	1		2	1	2	6	1
Neuralgia					1	2	
Neuritis cranial						1	
Neuroleptic malignant syndrome					2		
Neurological decompensation	1			1		1	
Neurological symptom						2	
Neuromyelitis optica spectrum disorder						1	
Neuropathy peripheral						2	
Nystagmus						1	
Pachymeningitis						1	
Paraesthesia	1		3	2	1	6	
Paralysis			2	1		9	
Paraplegia						2	
Paresis						2	
Parkinson's disease			1			1	
Peroneal nerve palsy				1			
Petit mal epilepsy			1				
Pleocytosis					1	1	
Polyneuropathy					1	5	
Post cardiac arrest syndrome				1		1	
Posterior reversible encephalopathy syndrome				1			
Postictal paralysis						1	
Postictal state	1						
Precerebral artery occlusion					1		
Presyncope			1			2	
Psychomotor hyperactivity			1			1	
Psychomotor skills impaired			2		1		
Pyramidal tract syndrome			1				
Quadriparesis					1	1	
Quadriplegia						2	
Ruptured cerebral aneurysm			2	4	3	5	
Sciatica						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	19	21	159	122	193	781	60
Number of Events	42	36	289	224	347	1,338	74
Sedation			2			1	
Seizure	4	5	13	7	7	19	2
Sensory disturbance			1				
Sensory loss						3	
Slow response to stimuli			1				
Slow speech						2	
Somnolence	1		4	3	6	46	2
Speech disorder			3	1	1	18	1
Spinal stroke						1	
Status epilepticus	1			2		4	
Stupor						1	
Subarachnoid haemorrhage	1		10	15	11	23	1
Superior sagittal sinus thrombosis		1					
Syncope	3	2	14	9	15	36	4
Taste disorder				1		2	
Thalamic infarction						1	
Thalamus haemorrhage			1				
Thrombotic cerebral infarction						3	
Thrombotic stroke					2	2	
Tonic convulsion			1	1			
Toxic encephalopathy					1		
Transient aphasia						1	
Transient ischaemic attack			1			6	
Transverse sinus thrombosis						1	
Tremor			3	1	4	16	2
Unresponsive to stimuli	2		2	2	4	19	
Vascular dementia						2	
Vertebral artery dissection			1	1			
Vertebrobasilar stroke						1	
Visual agnosia						1	
VIth nerve paralysis			1			1	
Vocal cord paralysis						1	
Pregnancy, puerperium and perinatal conditions							
Number of Cases			4	1			
Number of Events			4	1			
Cranial nerve injury secondary to birth trauma				1			
Hyperemesis gravidarum			1				
Pre-eclampsia			1				
Stillbirth			2				

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Product issues							
Number of Cases			1		1	1	2
Number of Events			2		1	1	2
Device breakage						1	
Product contamination chemical			1				
Product contamination microbial			1				
Product temperature excursion issue							1
Suspected counterfeit product					1		1
Psychiatric disorders							
Number of Cases	1	1	26	12	32	159	3
Number of Events	1	1	33	15	48	202	4
Abnormal behaviour					1	6	
Abnormal dreams						1	
Affect lability					1	1	
Aggression						2	
Agitation			1		1	10	
Anger			1		1		
Anxiety			5	3	3	12	
Apathy					1	5	
Behaviour disorder					1	2	
Bipolar disorder			1				
Communication disorder			1		2	3	
Completed suicide	1		5		2	5	1
Confusional state		1	5	2	8	47	
Delirium				1	5	9	1
Delusion						2	
Delusional perception							1
Depressed mood						2	
Depression			1			2	
Disinhibition						1	
Disorganised speech						1	
Disorientation					1	15	
Dissociative amnesia						1	
Dysphoria				1			
Eating disorder						7	
Emotional distress			1		1		
Fear						1	
Fear of falling						2	
Gastrointestinal somatic symptom disorder						1	
Hallucination			1		2	6	
Hallucination, auditory						1	
Hallucination, visual						3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Psychiatric disorders							
Number of Cases	1	1	26	12	32	159	3
Number of Events	1	1	33	15	48	202	4
Hostility			1				
Insomnia				2	6	7	
Irritability					1	1	
Lack of spontaneous speech						2	
Listless						2	
Logorrhoea			1				
Major depression						1	
Mental disorder			1	1	1	1	
Mental fatigue						1	
Mental status changes					1		
Mutism				1			
Near death experience						1	
Neurosis				1	1		
Nightmare						1	
Panic attack			1		1		
Panic disorder			1				
Paranoia			1		1		
Personality change			1	1		1	
Poor quality sleep						2	
Psychiatric symptom						1	
Psychomotor retardation						2	
Restlessness			1		5	16	
Schizophrenia			1				
Sleep disorder						6	
Soliloquy						1	
Sopor			1	1		6	
Stress					1		
Suicidal ideation						2	
Suicide attempt			1	1			
Suspected suicide							1
Renal and urinary disorders							
Number of Cases	3		18	15	37	191	7
Number of Events	4		22	21	41	229	7
Acute kidney injury			3	6	7	57	3
Anuria	1		1		2	10	
Azotaemia						4	
Bladder dilatation						1	
Bladder disorder					1	1	
Bladder necrosis						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Renal and urinary disorders							
Number of Cases	3		18	15	37	191	7
Number of Events	4		22	21	41	229	7
Bladder sphincter atony	1						
Calculus bladder					1		
Chromaturia						1	
Chronic kidney disease			1		4	6	
Crush syndrome			1				
Cystitis noninfective						1	
Diabetic nephropathy						1	
Dysuria			1		2	3	
End stage renal disease						1	
Glomerulonephritis						1	
Haematuria				2	1	3	
Haemoglobinuria			1				
Haemorrhage urinary tract						1	1
Hydronephrosis						1	
Hypertensive nephropathy					1		
Incontinence					1	8	
Kidney congestion			1	1			
Mesangioproliferative glomerulonephritis				1			
Micturition urgency			1			2	
Nephritis			1				
Nephrolithiasis						1	
Nephrosclerosis					2	2	
Nephrotic syndrome						2	
Oliguria						2	
Pollakiuria			1	1		4	
Polyuria			1			3	
Proteinuria			1	1			
Renal atrophy						1	
Renal cyst			1			3	
Renal cyst haemorrhage						1	
Renal disorder	1				2	4	
Renal failure			5	3	8	64	3
Renal haemorrhage				1			
Renal hypertrophy						1	
Renal impairment			1		6	20	
Renal infarct				1			
Renal mass						1	
Renal pain						2	
Renal tubular necrosis				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Renal and urinary disorders							
Number of Cases	3		18	15	37	191	7
Number of Events	4		22	21	41	229	7
Renal vein thrombosis						1	
Ureteral disorder					1		
Ureteric obstruction						1	
Urinary bladder haemorrhage	1			1			
Urinary incontinence				2	1	6	
Urinary retention			1		1	4	
Urinary tract inflammation						1	
Urinary tract obstruction						1	
Urine abnormality						1	
Reproductive system and breast disorders							
Number of Cases	1		2			8	2
Number of Events	1		2			9	2
Amenorrhoea			1				
Benign prostatic hyperplasia							1
Breast hyperplasia						1	
Breast mass						1	
Breast pain						2	
Nipple pain							1
Ovarian cyst						1	
Ovarian enlargement	1						
Pelvic pain						1	
Prostatitis			1				
Testicular oedema						2	
Uterine mass						1	
Respiratory, thoracic and mediastinal disorders							
Number of Cases	23	13	140	116	186	868	36
Number of Events	34	14	205	172	274	1,308	44
Acute chest syndrome			1				
Acute pulmonary oedema			1	2	1	13	
Acute respiratory distress syndrome				3	8	39	
Acute respiratory failure				4	6	29	1
Agonal respiration			1	1	2	1	
Alveolar lung disease						1	
Alveolitis						1	
Anoxia			1				
Apnoea			1	1	2	13	
Apnoeic attack						1	
Asphyxia		1	1	1	4	11	
Aspiration			1		3	8	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	23	13	140	116	186	868	36
Number of Events	34	14	205	172	274	1,308	44
Asthma				1	2	4	
Atelectasis						1	
Autoimmune lung disease			1				
Bradypnoea					1		
Bronchial wall thickening					1	1	
Bronchiectasis						4	
Bronchitis chronic			1				
Bronchopneumopathy						3	
Bronchospasm	1		1	1	3	1	
Cheyne-Stokes respiration						2	
Choking			1		2	2	
Choking sensation			1		1		
Chronic hyperplastic eosinophilic sinusitis					1		
Chronic obstructive pulmonary disease					4	19	
Chronic respiratory failure						1	
Cough			21	12	24	76	5
Cyanosis central				1		1	
Diffuse alveolar damage					2	1	
Dysphonia					1	5	
Dyspnoea	8	2	50	46	70	322	18
Dyspnoea at rest						1	
Dyspnoea exertional		1	5		1	13	
Emphysema				1	1	3	
Eosinophilic pneumonia acute						1	
Epistaxis	1			1	1	5	
Haemoptysis			3	3	3	13	
Haemothorax						1	
Hiccups			1	1			
Hydrothorax						2	
Hypercapnia					1	3	
Hyperventilation			2		1	2	
Hypocapnia						2	
Hypopnoea		1	1			5	
Hypoventilation	1				1		
Hypoxia	1		4	2	8	44	
Idiopathic pulmonary fibrosis						3	
Increased bronchial secretion						2	
Increased upper airway secretion					1	2	
Interstitial lung disease				3	2	39	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	23	13	140	116	186	868	36
Number of Events	34	14	205	172	274	1,308	44
Irregular breathing						2	
Laryngeal oedema			1			1	
Laryngospasm						1	
Lower respiratory tract congestion			2			5	
Lung consolidation				1		2	
Lung disorder	2		1	1	3	14	3
Lung infiltration					3	3	1
Lung opacity						3	
Mediastinal haemorrhage					1		
Mouth breathing					1	3	
Nasal congestion	1				1	1	
Nasal disorder						1	
Obstructive airways disorder	1			1	1		
Organising pneumonia					1	3	
Oropharyngeal discomfort						2	
Oropharyngeal pain		1	4	4	4	10	
Orthopnoea				1		1	
Painful respiration			1			1	
Pharyngeal swelling					1		
Pleural effusion			4	1	2	29	
Pleural fibrosis						1	
Pleurisy						1	
Pleuritic pain						1	
Pneumomediastinum					1		
Pneumonitis						10	
Pneumothorax					1	4	
Productive cough					4	14	1
Pulmonary alveolar haemorrhage					2	9	
Pulmonary artery thrombosis				1	1	1	
Pulmonary congestion	1		3	3	3	6	
Pulmonary embolism	3	4	36	42	34	110	10
Pulmonary fibrosis					1	6	
Pulmonary haemorrhage	1		2	1		3	
Pulmonary hypertension		1			2	3	
Pulmonary infarction			1	1		1	
Pulmonary mass			1	1		2	1
Pulmonary necrosis						1	
Pulmonary oedema	4	1	8	9	8	31	1
Pulmonary thrombosis			7	3	2	3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	23	13	140	116	186	868	36
Number of Events	34	14	205	172	274	1,308	44
Rales						11	
Respiration abnormal					2	3	
Respiratory acidosis			1	1		6	
Respiratory alkalosis						3	
Respiratory arrest	2		11	4	10	64	
Respiratory depression			2			1	
Respiratory disorder		1	2	1	2	34	1
Respiratory distress	1		4	1	3	29	
Respiratory failure	5	1	7	5	9	96	
Respiratory fatigue					1	2	
Respiratory tract congestion			1				
Respiratory tract haemorrhage						1	
Rhinorrhoea			1	1		3	
Rhonchi						1	
Sneezing					1		
Snoring						2	
Sputum discoloured						3	
Sputum increased			1			1	
Sputum retention						1	
Stertor			1	1		1	
Stridor						1	
Suffocation feeling				1		1	
Tachypnoea			3	1	6	36	
Thoracic haemorrhage	1					2	
Throat irritation			1		1		
Throat tightness						1	
Tonsillar inflammation				1			
Upper airway obstruction						1	
Upper respiratory tract congestion						1	
Use of accessory respiratory muscles						2	
Wheezing				1	4	11	1
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	12	21	31	95	8
Number of Events	1	2	13	25	42	129	9
Acantholysis						1	
Acute generalised exanthematous pustulosis						1	
Angioedema		1			2	1	
Blister					1	3	
Cold sweat			3	2	2	7	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	12	21	31	95	8
Number of Events	1	2	13	25	42	129	9
Cutaneous vasculitis						2	
Decubitus ulcer					1	2	
Dermatitis					1		
Dermatitis allergic						2	
Dermatitis bullous					1	1	
Dermatomyositis						1	
Drug eruption						1	
Drug reaction with eosinophilia and systemic symptoms						1	
Dry skin						2	
Ecchymosis						1	
Eczema				1			
Erythema				2		7	
Haemorrhage subcutaneous				2		4	
Henoch-Schonlein purpura				1		1	
Hyperhidrosis			3	6	10	16	1
Livedo reticularis				1		1	
Lividity						1	
Nail discolouration						1	
Night sweats					1		
Pain of skin						2	
Pemphigoid						4	
Petechiae			2	3	2	7	1
Pruritus			1	1	3	6	2
Psoriasis					1		
Purpura				1		5	1
Rash	1	1	1	1	7	10	1
Rash erythematous						1	
Rash macular						7	
Rash maculo-papular						1	
Rash pruritic					1	1	
Scab							1
Skin burning sensation						2	
Skin discolouration			1		3	3	
Skin disorder					1	3	
Skin exfoliation						2	
Skin haemorrhage				1		1	
Skin lesion					3	2	
Skin plaque			1				
Skin reaction				1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	12	21	31	95	8
Number of Events	1	2	13	25	42	129	9
Skin ulcer					1	5	1
Skin warm						1	
Skin weeping						1	
Stevens-Johnson syndrome						1	1
Subcutaneous emphysema						1	
Toxic epidermal necrolysis						1	
Toxic skin eruption				1			
Urticaria				1	1	2	
Vascular purpura						1	
Xeroderma						1	
Yellow skin			1			1	
Social circumstances							
Number of Cases				2	5	27	1
Number of Events				2	5	29	1
Anal sex							1
Bedridden					2	6	
Blood product transfusion dependent				1			
Dependence on oxygen therapy						1	
Disability						1	
Immobile				1	1	5	
Impaired quality of life						3	
Loss of personal independence in daily activities						7	
Refusal of treatment by patient						2	
Walking disability					2	4	
Surgical and medical procedures							
Number of Cases	1		22	28	52	290	19
Number of Events	1		25	32	59	321	21
Abortion induced			1				
Aneurysm repair						1	
Bladder catheter permanent						1	
COVID-19 immunisation				1		1	
Craniectomy				1			
Dermabrasion						1	
Endotracheal intubation						2	1
Haemodialysis						1	
Immunisation			14	16	32	266	10
Interchange of vaccine products	1		10	13	22	42	8
Mechanical ventilation					1		
Medical induction of coma				1	1		1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Surgical and medical procedures							
Number of Cases	1		22	28	52	290	19
Number of Events	1		25	32	59	321	21
Oxygen therapy					1	1	
Palliative care					1	1	
Resuscitation						2	
Thrombectomy					1	1	
Tracheostomy						1	
Transfusion							1
Vascular disorders							
Number of Cases	10	3	65	60	106	398	21
Number of Events	11	3	77	80	134	510	25
Acute aortic syndrome				1			
Aneurysm	1			1		5	1
Aneurysm ruptured			3	1	2	3	
Angiodysplasia						1	
Angiopathy			1		1	1	
Aortic aneurysm						3	
Aortic aneurysm rupture					3	13	1
Aortic arteriosclerosis				2		3	
Aortic dilatation						2	
Aortic dissection			1	5	8	26	
Aortic dissection rupture			1		2	1	
Aortic embolus						1	
Aortic intramural haematoma						1	
Aortic rupture					3	1	
Aortic stenosis				1		6	
Aortic thrombosis			1		1	5	
Arterial disorder					1		
Arterial haemorrhage						1	
Arterial occlusive disease			2		1	2	
Arterial rupture				1	2	2	
Arterial thrombosis						2	
Arteriosclerosis			2	3	2	16	2
Arteriovenous fistula						1	
Artery dissection					1	1	
Atherosclerotic plaque rupture				1	1		
Axillary vein thrombosis				1			
Blood pressure fluctuation					1	4	1
Bloody discharge						2	
Capillary leak syndrome						1	
Circulatory collapse	1	1	10	9	13	39	3

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Vascular disorders							
Number of Cases	10	3	65	60	106	398	21
Number of Events	11	3	77	80	134	510	25
Cyanosis	1		5	1	4	29	1
Deep vein thrombosis	1		6	7	12	19	2
Embolism			2	1	4	11	1
Embolism arterial						1	
False lumen dilatation of aortic dissection				1			
Femoral artery embolism					1		
Giant cell arteritis					1	2	
Haematoma			3	1	1	8	
Haemodynamic instability				1		2	
Haemorrhage			1	2	5	6	1
Haemorrhagic infarction				1			
Hot flush				1	2	3	
Hyperaemia			1			1	
Hypertension			4	4	9	32	1
Hypertensive crisis			2	2		6	
Hypertensive emergency						1	
Hypoperfusion					1	1	
Hypotension	2	1	5	5	13	48	1
Hypotensive crisis						1	
Hypovolaemic shock			1			1	
Infarction	2			1	2	10	
Intermittent claudication					1		
Internal haemorrhage			1			9	
Ischaemia						8	
Jugular vein distension						1	
Jugular vein embolism						1	
Jugular vein thrombosis			1				
Labile hypertension						1	
Leriche syndrome						1	
Lymphoedema				1			
Macroangiopathy						1	
Malignant hypertension				2			
Necrosis ischaemic				1			
Orthostatic hypotension						1	
Pallor			2	1	4	26	
Pelvic venous thrombosis						1	
Peripheral arterial occlusive disease			1			3	
Peripheral artery occlusion						2	
Peripheral artery thrombosis					1	1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Vascular disorders							
Number of Cases	10	3	65	60	106	398	21
Number of Events	11	3	77	80	134	510	25
Peripheral circulatory failure						1	
Peripheral coldness				1	2	4	
Peripheral ischaemia					1	8	
Peripheral vascular disorder					2	1	1
Peripheral venous disease						1	
Phlebitis				1			
Phlebolith						1	
Shock	2		4	5	3	28	
Shock haemorrhagic			1	1	2	8	
Subclavian artery dissection					1		
Subclavian artery occlusion					1		
Subclavian artery thrombosis					1		
Subclavian vein thrombosis				1		1	
Superior vena cava syndrome						1	
Thrombophlebitis						2	
Thrombosis	1	1	11	9	15	60	8
Varicose vein						1	
Vascular pain						1	1
Vasculitis			3	3	1	5	
Vasodilatation						1	
Vena cava thrombosis						1	
Venoocclusive disease						1	
Venous thrombosis			2		1	2	
Venous thrombosis limb					1	1	

*Only post birth cases included

Summary Tabulation of Fatal Cases and Adverse Events by System Organ Class (SOC) and Preferred Terms (PT) by Age Group

BNT162B2;BNT162B2S01 - ALL

Reporting Period: 01-JAN-1900 Through 18-DEC-2021

Total Number of Cases: 10424 (100%) (ALL) / 10424 (OVERALL)

Total Number of Adverse Events (PT): 38564 (ALL)

MedDRA Version: v.24.1.

CT

Total Number of Cases: 111

Total Number of Adverse Events (PT): 159

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Cardiac disorders					
Number of Cases		1	8	10	11
Number of Events		1	8	11	11
Acute myocardial infarction				1	1
Atrial fibrillation					1
Cardiac arrest		1	2	3	3
Cardiac failure congestive			1		
Cardiogenic shock					1
Cardio-respiratory arrest			3	2	3
Coronary artery disease				2	
Hypertensive heart disease					1
Myocardial infarction			2	2	1
Pericardial haemorrhage				1	
Eye disorders					
Number of Cases			1		1
Number of Events			1		1
Blindness unilateral			1		
Optic ischaemic neuropathy					1
Gastrointestinal disorders					
Number of Cases			1	5	2
Number of Events			1	5	2
Acute abdomen					1
Duodenal perforation					1
Gastrointestinal haemorrhage			1	1	
Intestinal ischaemia				1	
Intestinal obstruction				1	
Large intestine perforation				1	
Pancreatitis				1	
General disorders and administration site conditions					
Number of Cases		2	5	6	4
Number of Events		2	5	6	4
Condition aggravated		1	2		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
General disorders and administration site conditions					
Number of Cases		2	5	6	4
Number of Events		2	5	6	4
Death		1	3	3	2
Disease progression					1
Multiple organ dysfunction syndrome				1	1
Sudden cardiac death				1	
Sudden death				1	
Hepatobiliary disorders					
Number of Cases				1	
Number of Events				1	
Biliary cyst				1	
Infections and infestations					
Number of Cases		2	8	11	7
Number of Events		5	10	11	8
Acquired immunodeficiency syndrome		2			
COVID-19			2	3	
COVID-19 pneumonia			1	3	1
Emphysematous cholecystitis					1
HIV infection		1			
Infection					1
Kidney infection					1
Lower respiratory tract infection		1			
Pneumocystis jirovecii pneumonia		1			
Pneumonia			1	1	1
Pneumonia aspiration			1	1	
Pneumonia bacterial				1	
Postoperative wound infection			1		
Sepsis			2	1	1
Septic shock			1	1	1
Shigella sepsis					1
Staphylococcal sepsis			1		
Injury, poisoning and procedural complications					
Number of Cases	1	4	1	2	1
Number of Events	1	5	1	3	1
Accidental overdose		1			
Gun shot wound	1				
Injury		1		1	
Overdose		1	1		
Road traffic accident		1		2	1
Toxicity to various agents		1			

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Metabolism and nutrition disorders					
Number of Cases		1	1		
Number of Events		1	1		
Hypoglycaemia		1			
Type 2 diabetes mellitus			1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Number of Cases			2	4	4
Number of Events			2	5	6
Angiosarcoma				1	
Biliary cancer metastatic				1	
Bladder cancer					1
Gastric cancer				1	
Glioblastoma			1		
Lung cancer metastatic			1		
Metastases to liver				1	
Metastases to lung					1
Neoplasm progression					1
Pancreatic carcinoma metastatic					2
Pancreatic neoplasm				1	
Penis carcinoma metastatic					1
Nervous system disorders					
Number of Cases			3	2	4
Number of Events			3	2	4
Amyotrophic lateral sclerosis			1		
Basal ganglia haemorrhage			1		
Cerebrovascular accident			1		1
Dementia Alzheimer's type					2
Haemorrhagic stroke				1	1
Ischaemic stroke				1	
Psychiatric disorders					
Number of Cases	1	5		2	
Number of Events	1	5		2	
Alcohol abuse		1			
Completed suicide	1	3		2	
Drug abuse		1			
Renal and urinary disorders					
Number of Cases				1	1
Number of Events				1	1
Acute kidney injury					1
Oliguria				1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years
Respiratory, thoracic and mediastinal disorders					
Number of Cases		1	3	7	1
Number of Events		1	3	7	1
Acute respiratory distress syndrome				1	
Acute respiratory failure		1	1	1	
Chronic obstructive pulmonary disease				2	
Pulmonary embolism				3	1
Pulmonary fibrosis			1		
Respiratory arrest			1		
Vascular disorders					
Number of Cases		1	2	3	3
Number of Events		1	2	3	3
Aortic dissection				1	
Arteriosclerosis			1	1	1
Deep vein thrombosis					1
Embolism		1			
Hypertensive emergency			1		
Hypovolaemic shock				1	
Shock haemorrhagic					1

*Only post birth cases included

Non CT

Total Number of Cases: 10313

Total Number of Adverse Events (PT): 38405

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Blood and lymphatic system disorders							
Number of Cases	6	4	22	31	49	277	17
Number of Events	11	6	31	39	64	369	19
Acquired haemophilia					1	3	
Agranulocytosis		1				1	
Anaemia	2			1	12	49	1
Anaemia folate deficiency						1	
Anaemia macrocytic						2	
Anaemia megaloblastic						1	
Anaemia vitamin B12 deficiency						1	
Antiphospholipid syndrome						2	
Aplastic anaemia				1	1		
Autoimmune haemolytic anaemia					1	4	
Autoimmune pancytopenia						1	
Bicytopenia						1	
Blood disorder						2	
Blood loss anaemia					1		
Bone marrow failure	1					2	
Coagulation factor deficiency					1		
Coagulopathy	2	1	6	4	1	13	2
Coombs negative haemolytic anaemia						1	
Cytopenia						1	
Disseminated intravascular coagulation	1		1	3	7	24	
Elephantiasis						1	
Febrile neutropenia				1			1
Haemolysis				1	2	3	
Haemolytic anaemia					1	2	
Haemolytic uraemic syndrome						1	
Haemorrhagic diathesis		1			2	2	
Haemorrhagic disorder					1		
Hilar lymphadenopathy						2	
Hyperchromic anaemia						1	
Hypercoagulation				1		3	
Hypereosinophilic syndrome						1	
Hyperleukocytosis					1	6	
Hypochromasia						1	
Hypocoagulable state						1	
Immune thrombocytopenia			1	1	2	11	1
Increased tendency to bruise					1	1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Blood and lymphatic system disorders							
Number of Cases	6	4	22	31	49	277	17
Number of Events	11	6	31	39	64	369	19
Iron deficiency anaemia					1		
Leukocytosis				2		18	
Leukopenia					2	6	
Lymphadenitis						2	
Lymphadenopathy			5	2	3	20	3
Lymphadenopathy mediastinal				1		1	
Lymph node pain			1			1	
Lymphocytic infiltration				1		1	
Lymphocytosis				1		1	
Lymphopenia						16	
Microangiopathic haemolytic anaemia			1				
Microcytic anaemia						3	
Monocytosis						2	
Myelocytosis						1	
Myelosuppression						1	
Neutropenia				1	1	5	
Neutrophilia					1	6	
Normochromic anaemia						1	
Normochromic normocytic anaemia						1	
Normocytic anaemia						5	
Nucleated red cells						1	
Pancytopenia		1	2		2	11	1
Paratracheal lymphadenopathy						1	
Platelet anisocytosis						1	
Platelet disorder						1	
Polycythaemia						2	
Red blood cell abnormality	1						
Retroperitoneal lymphadenopathy						1	
Sickle cell anaemia with crisis			1				
Spleen disorder						1	
Spleen ischaemia						1	
Splenic artery thrombosis					1		
Splenic haemorrhage						1	
Splenic infarction					1	7	
Splenic thrombosis						1	
Splenic vein thrombosis			1			1	
Splenitis						1	
Splenomegaly				1	1	3	
Spontaneous haematoma					1	1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Blood and lymphatic system disorders							
Number of Cases	6	4	22	31	49	277	17
Number of Events	11	6	31	39	64	369	19
Thrombocytopenia	2	2	8	14	14	75	7
Thrombocytopenic purpura						5	1
Thrombocytosis			1			3	
Thrombosis with thrombocytopenia syndrome			2	1		8	
Thrombotic microangiopathy			1	1		2	
Thrombotic thrombocytopenic purpura	2			1		5	2
White blood cell disorder					1		
Cardiac disorders							
Number of Cases	26	18	273	237	379	2,028	110
Number of Events	37	28	426	355	587	2,911	129
Acute cardiac event						3	
Acute coronary syndrome			3	3	3	28	2
Acute left ventricular failure			2	1		4	
Acute myocardial infarction	1		8	23	42	122	5
Acute right ventricular failure						1	
Angina pectoris			3	3	6	8	
Angina unstable						1	
Aortic valve calcification						1	
Aortic valve disease				1			
Aortic valve incompetence			1			5	
Aortic valve sclerosis						1	
Aortic valve stenosis				1		8	
Arrhythmia	2	4	16	10	23	93	1
Arrhythmia supraventricular						1	
Arteriosclerosis coronary artery			2	3	6	23	1
Arteriospasm coronary				1			
Atrial fibrillation			1	2	15	112	2
Atrial flutter					1	11	
Atrial tachycardia						1	
Atrial thrombosis					1	3	
Atrioventricular block						4	2
Atrioventricular block complete				1		7	
Atrioventricular block first degree					1	1	
Atrioventricular block second degree			1				
Atrioventricular dissociation		1					
Bradyarrhythmia						1	
Bradycardia	1		2	1	7	37	1
Bundle branch block bilateral							1
Bundle branch block left					1	2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	26	18	273	237	379	2,028	110
Number of Events	37	28	426	355	587	2,911	129
Bundle branch block right					1	7	
Cardiac amyloidosis						1	
Cardiac aneurysm					2	2	1
Cardiac arrest	10	4	86	80	131	451	20
Cardiac asthma						8	
Cardiac discomfort						3	
Cardiac disorder	2	1	6	5	7	47	6
Cardiac dysfunction			1		2	5	
Cardiac failure		2	10	13	32	369	5
Cardiac failure acute	1	1	8	4	13	80	2
Cardiac failure chronic		1				17	
Cardiac failure congestive			2	4	7	45	3
Cardiac fibrillation						3	
Cardiac flutter			1		1	3	
Cardiac hypertrophy			2	4	3	10	1
Cardiac perforation					1		
Cardiac steatosis				1			
Cardiac tamponade			3	2	4	16	
Cardiac valve disease					1	4	
Cardiac valve sclerosis				1			
Cardiac ventricular thrombosis			1		2	3	
Cardiogenic shock	1	1	5	5	10	52	1
Cardiomegaly	2		5	5	6	33	1
Cardiomyopathy			7	1	2	9	
Cardiopulmonary failure	1	1	2		6	39	
Cardiorenal syndrome						2	
Cardio-respiratory arrest	3	2	56	28	51	374	3
Cardio-respiratory distress						3	
Cardiovascular disorder			3	2	8	40	1
Cardiovascular insufficiency				1		2	
Cardiovascular symptom						1	
Carditis			1				1
Conduction disorder						1	
Congestive cardiomyopathy			1		2	4	
Coronary artery disease			3	10	6	16	2
Coronary artery embolism						1	
Coronary artery insufficiency						2	
Coronary artery occlusion			4	2	3	13	
Coronary artery stenosis			1	5	2	12	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	26	18	273	237	379	2,028	110
Number of Events	37	28	426	355	587	2,911	129
Coronary artery thrombosis			4	2	6	12	1
Cor pulmonale						5	1
Cor pulmonale acute				1		1	
Diastolic dysfunction					1		
Dilatation ventricular			1			1	
Endocarditis noninfective			1				
Eosinophilic myocarditis				1			
Extrasystoles					1	3	
Hypertensive heart disease			2	1	2	9	
Immune-mediated myocarditis					1		
Intracardiac thrombus			3	3	6	7	
Intrapericardial thrombosis					1		
Ischaemic cardiomyopathy					1	6	1
Kounis syndrome						1	
Left atrial enlargement			1				
Left ventricular dilatation			1				
Left ventricular dysfunction			1			6	
Left ventricular failure				1	1	13	1
Left ventricular hypertrophy			1	1	1	8	
Low cardiac output syndrome					1		
Mitral valve calcification						1	
Mitral valve disease				1			
Mitral valve incompetence			1			6	
Mitral valve stenosis						1	
Myocardial fibrosis			2	5	2	9	
Myocardial haemorrhage						1	
Myocardial hypoxia				1	1		
Myocardial infarction	1	1	53	45	70	293	38
Myocardial injury			1	1		1	
Myocardial ischaemia		1	9	9	11	62	2
Myocardial necrosis				3		5	
Myocardial oedema			1				
Myocardial rupture			1		4	11	
Myocarditis	6	5	33	9	10	37	13
Nodal rhythm		1			1		
Palpitations	2		7	4	4	13	4
Papillary muscle disorder						1	
Papillary muscle rupture				1			
Paroxysmal arrhythmia						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Cardiac disorders							
Number of Cases	26	18	273	237	379	2,028	110
Number of Events	37	28	426	355	587	2,911	129
Pericardial disease						1	
Pericardial effusion	1		4	4	4	22	1
Pericardial haemorrhage			1	2		12	
Pericarditis			3	2	2	13	
Pulmonary valve disease						1	
Pulseless electrical activity			3	1	4	7	
Rhythm idioventricular						1	
Right atrial enlargement						1	
Right ventricular dilatation						2	
Right ventricular dysfunction					2		
Right ventricular enlargement			1			1	
Right ventricular failure			2		5	6	1
Right ventricular hypertrophy					1		
Sinus bradycardia						1	
Sinus tachycardia			2			5	
Stress cardiomyopathy			2	1	1	5	
Supraventricular extrasystoles						1	
Supraventricular tachyarrhythmia						1	
Supraventricular tachycardia						4	
Tachyarrhythmia				1		3	
Tachycardia		1	12	13	9	87	3
Tachycardia induced cardiomyopathy			1				
Tachycardia paroxysmal						1	
Torsade de pointes						2	
Toxic cardiomyopathy			1				
Tricuspid valve incompetence					1	2	
Ventricle rupture					1	1	
Ventricular arrhythmia			5		2	4	
Ventricular dysfunction			1	1			
Ventricular extrasystoles	1		1			3	
Ventricular failure					1		
Ventricular fibrillation	2	1	15	14	14	36	1
Ventricular hypertrophy					1		
Ventricular hypokinesia			1	1	1	3	
Ventricular tachycardia			1	3	4	15	
Congenital, familial and genetic disorders							
Number of Cases	1	2	2	2	3	9	1
Number of Events	1	2	2	2	3	9	1
Aberrant aortic arch					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Congenital, familial and genetic disorders							
Number of Cases	1	2	2	2	3	9	1
Number of Events	1	2	2	2	3	9	1
Aplasia						1	
Arrhythmogenic right ventricular dysplasia					1		
Branchial cyst						1	
Congenital anomaly							1
Congenital cystic kidney disease						1	
Factor V deficiency						1	
Fallot's tetralogy						1	
Foramen magnum stenosis						1	
Hereditary spherocytosis		1					
Huntington's disease				1			
Hypertrophic cardiomyopathy				1	1	3	
Hypoplastic left heart syndrome			1				
Myocardial bridging	1						
Myotonic dystrophy			1				
Platybasia		1					
Ear and labyrinth disorders							
Number of Cases			2	1	2	26	4
Number of Events			3	1	3	29	4
Auditory disorder						1	
Deafness bilateral						1	
Ear disorder					1		
Ear pain			1			3	1
External ear pain					1		
Hypoacusis				1		2	1
Otolithiasis						1	
Otorrhoea						1	
Sudden hearing loss			1			1	
Tinnitus						3	2
Vertigo					1	16	
Vestibular disorder			1				
Endocrine disorders							
Number of Cases			1	2	1	13	
Number of Events			1	2	1	13	
Adrenal disorder						1	
Adrenal insufficiency						2	
Adrenal mass					1		
Cushing's syndrome						1	
Diabetes insipidus			1	1			
Goitre						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Endocrine disorders							
Number of Cases			1	2	1	13	
Number of Events			1	2	1	13	
Hypercalcaemia of malignancy						1	
Hyperthyroidism						3	
Hypopituitarism				1			
Hypothyroidism						2	
Inappropriate antidiuretic hormone secretion						1	
Thyroid mass						1	
Eye disorders							
Number of Cases	2	3	14	8	16	86	3
Number of Events	2	3	16	10	22	104	3
Blindness					1	8	2
Blindness cortical				1	1		
Blindness unilateral						1	
Cataract cortical	1						
Conjunctival haemorrhage						2	
Conjunctival oedema						1	
Cystoid macular oedema						1	
Diplopia			3		1	2	
Exfoliation syndrome						1	
Eye discharge						1	
Eye disorder						2	
Eye haematoma						1	
Eyelid haematoma						1	
Eyelid oedema						2	
Eyelid ptosis						7	
Eye movement disorder			1	2		5	
Eye pain		1			3	2	
Eye pruritus				1		1	
Eye swelling					2	1	
Gaze palsy			1			8	
Keratic precipitates						1	
Lacrimation increased						3	
Lens disorder						1	
Miosis		1				1	
Mydriasis			1	2	2	4	
Ocular discomfort						1	
Ocular hyperaemia						3	
Ophthalmic vein thrombosis						1	
Ophthalmoplegia						1	
Orbital haematoma						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Eye disorders							
Number of Cases	2	3	14	8	16	86	3
Number of Events	2	3	16	10	22	104	3
Orbital swelling						1	
Photophobia						1	
Pupil fixed			1			4	
Pupillary disorder						1	
Pupillary reflex impaired			1	2	2	3	
Pupils unequal	1			2	1	7	
Retinal artery embolism						1	
Retinal artery occlusion						1	
Retinal degeneration			1				
Retinal detachment			1				
Retinal haemorrhage					1		
Retinal tear			1			1	
Strabismus			1				
Swelling of eyelid					1		
Vision blurred			2		2	4	
Visual acuity reduced						1	
Visual impairment		1	2		5	15	1
Gastrointestinal disorders							
Number of Cases	14	9	74	75	126	1,052	40
Number of Events	23	11	100	103	186	1,577	58
Abdominal adhesions						1	
Abdominal discomfort				1	4	20	1
Abdominal distension			3	1	2	15	1
Abdominal hernia						1	
Abdominal pain	2	1	12	10	16	97	6
Abdominal pain lower			1		1	3	
Abdominal pain upper			5	5	7	39	3
Abdominal symptom						1	
Abdominal tenderness						4	
Abdominal wall haematoma					1	2	
Abdominal wall haemorrhage						1	
Abnormal faeces	1					2	
Acute abdomen				1		7	
Anal haemorrhage						2	
Anal incontinence				1		9	
Anal sphincter atony	1				1		
Aphthous ulcer						2	
Ascites			1	1	2	11	
Autoimmune pancreatitis						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	14	9	74	75	126	1,052	40
Number of Events	23	11	100	103	186	1,577	58
Change of bowel habit						1	
Coeliac artery stenosis						1	
Colitis				1		1	1
Colitis ischaemic					1	3	
Constipation		1		1		26	
Defaecation disorder	1					2	
Diarrhoea	3	1	12	9	19	179	8
Diarrhoea haemorrhagic						1	
Discoloured vomit						1	
Diverticular perforation						1	
Diverticulum						1	
Diverticulum intestinal					1	2	
Dry mouth				1		4	
Duodenal ulcer						1	
Duodenal ulcer haemorrhage						1	
Duodenal ulcer perforation				1			
Dyschezia						1	
Dyspepsia					1	9	1
Dysphagia			3	2	6	86	2
Enteritis				1		1	1
Enterocolitis						2	
Enterovesical fistula					1	1	
Epigastric discomfort					1		
Eructation						1	
Faecaloma						3	
Faecal vomiting						7	
Faeces discoloured					3	8	
Flatulence						2	
Functional gastrointestinal disorder					1	2	
Gastric dilatation						1	
Gastric disorder	1			1		2	
Gastric haemorrhage						7	1
Gastric ulcer	1					2	
Gastric volvulus						1	
Gastritis						2	1
Gastritis erosive	1					3	
Gastritis haemorrhagic			1			1	
Gastrointestinal disorder					2	9	
Gastrointestinal haemorrhage			1	3	4	35	4

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	14	9	74	75	126	1,052	40
Number of Events	23	11	100	103	186	1,577	58
Gastrointestinal inflammation						2	
Gastrointestinal necrosis			1	2	1	12	
Gastrointestinal obstruction						2	
Gastrointestinal pain						2	1
Gastrointestinal ulcer						1	
Gastrooesophageal reflux disease						3	
Gingival pain						1	
Gingival swelling			1				
Glossoptosis			1			1	
Haematemesis	1	1	2	4	5	36	6
Haematochezia					1	10	1
Haemoperitoneum						1	
Haemorrhoids						1	1
Hiatus hernia					1	2	
Hypoaesthesia oral			1			2	
Ileus				3	1	7	
Ileus paralytic					1	11	
Inguinal hernia						1	
Intestinal dilatation					1	1	
Intestinal haemorrhage						4	
Intestinal infarction					1	9	
Intestinal ischaemia	1			2	5	41	
Intestinal obstruction			1			13	
Intestinal perforation						6	
Intestinal pseudo-obstruction			1				
Intestinal ulcer						1	
Intra-abdominal haemorrhage	1					1	
Large intestinal haemorrhage				1			
Large intestinal obstruction						2	
Large intestine perforation					2	3	
Lip discolouration						2	
Lip haemorrhage			1				
Lip oedema						2	
Lip pain						1	
Lip swelling			1		1	2	
Lower gastrointestinal haemorrhage						2	
Megacolon						1	
Melaena			2		1	16	
Mesenteric arterial occlusion						3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	14	9	74	75	126	1,052	40
Number of Events	23	11	100	103	186	1,577	58
Mesenteric artery embolism						2	
Mesenteric artery thrombosis						5	
Mesenteric vascular insufficiency						1	
Mesenteric vascular occlusion						1	
Mesenteric vein thrombosis			1	2	1	4	
Mouth haemorrhage			1	1	1	6	1
Mouth swelling						2	1
Mouth ulceration					1		
Nausea	1	3	20	17	25	232	6
Noninfective gingivitis						2	
Obturator hernia						1	
Odynophagia						1	
Oesophageal haemorrhage				1			
Oesophageal pain						1	
Oesophageal varices haemorrhage				1	1	3	
Oral discharge						1	
Oral disorder						2	
Oral mucosal blistering					1		
Oral mucosal exfoliation						1	
Oral pain						1	
Overflow diarrhoea						1	
Pancreatic infarction						1	
Pancreatic steatosis						2	
Pancreatitis				1		4	1
Pancreatitis acute			1		4	8	1
Pancreatitis chronic					1		
Pancreatitis necrotising						2	
Pancreatitis relapsing						1	
Paraesthesia oral				1		2	
Peptic ulcer						1	
Peritoneal disorder					1		
Peritoneal perforation						1	
Pneumatosis intestinalis					1		
Pneumoperitoneum						1	
Poor dental condition						1	
Rectal haemorrhage						10	
Rectal perforation					1		
Rectal ulcer						1	
Regurgitation						3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Gastrointestinal disorders							
Number of Cases	14	9	74	75	126	1,052	40
Number of Events	23	11	100	103	186	1,577	58
Retching			1			10	1
Retroperitoneal haematoma						1	
Retroperitoneal haemorrhage						1	
Salivary hypersecretion				2		3	
Small intestinal haemorrhage						3	
Small intestinal obstruction						3	
Stomatitis						1	
Subileus					1	6	
Swollen tongue					1	3	
Thrombosis mesenteric vessel						2	
Tongue erythema		1					
Tongue oedema						1	
Toothache						1	
Tooth loss						1	
Truncus coeliacus thrombosis						2	
Umbilical hernia						1	
Upper gastrointestinal haemorrhage					2	7	
Varices oesophageal							1
Visceral venous thrombosis				1			
Volvulus						3	
Vomiting	8	3	25	24	49	389	7
General disorders and administration site conditions							
Number of Cases	55	40	353	359	650	4,287	726
Number of Events	76	54	551	527	1,012	6,461	840
Adverse event						1	
Adverse reaction						1	
Apparent death					1		
Asthenia	3	2	22	21	51	374	10
Atrophy						1	
Axillary pain			1			2	
Brain death	1	1	6	8	6	9	3
Cardiac death			8	4	7	34	1
Chest discomfort	1		8	8	9	44	2
Chest pain	1	3	37	24	43	135	5
Chills	2	2	17	7	21	109	4
Concomitant disease aggravated				2	4	5	1
Concomitant disease progression					2	9	
Condition aggravated		1	9	7	10	145	4
Crepitations	1					6	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	55	40	353	359	650	4,287	726
Number of Events	76	54	551	527	1,012	6,461	840
Critical illness	1					1	
Crying					1	1	
Cyst			1				
Death	28	14	137	147	222	1,340	516
Decapitation							1
Decreased activity			1			5	
Discomfort			1	6	2	30	2
Disease complication					1		
Disease progression					1	13	1
Disease recurrence			4	3	11	52	2
Drowning	2		2	2	2	14	1
Drug ineffective	3	2	14	16	46	386	144
Drug interaction			1		1	5	1
Drug resistance						1	
Effusion				1		1	
Exercise tolerance decreased			1		1	2	
Extensive swelling of vaccinated limb			1				
Extravasation					1		
Face oedema					1	4	
Facial pain			1				
Fatigue	3	3	37	26	52	370	17
Feeling abnormal	2	1	10	1	7	31	3
Feeling cold			3		5	18	4
Feeling drunk						2	
Feeling hot	1		1		1	11	
Feeling jittery				1			
Feeling of body temperature change			3		1	1	
Fibrosis					1		
Foaming at mouth	1		2	1	2	6	
Gait disturbance	1			5	12	52	2
Gait inability			2	1	1	24	2
Generalised oedema			1		2	7	
General physical health deterioration		2	8	8	19	373	9
General symptom				1		1	
Glassy eyes						1	
Gravitational oedema				1		1	
Hernia					1	1	
Hernia pain						1	
Hyperpyrexia			1	3	3	14	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	55	40	353	359	650	4,287	726
Number of Events	76	54	551	527	1,012	6,461	840
Hyperthermia		1		1	4	25	
Hypertrophy				1	2		
Hypothermia			1		2	27	
Ill-defined disorder						1	
Illness	1		5	2	13	23	9
Inflammation				1	11	38	
Influenza like illness			6	9	3	38	1
Injection site discomfort						1	
Localised oedema						1	
Local reaction					4	5	1
Loss of control of legs						2	
Malaise	4	4	38	37	94	454	20
Mass				1		2	
Moaning						5	
Multimorbidity				1		1	
Multi-organ disorder			1			2	
Multiple organ dysfunction syndrome	1	1	8	11	19	123	5
Necrosis			1	2	1	2	
Nodule						1	
Oedema			4			19	1
Oedema peripheral			1	5	5	67	3
Organ failure			2	1	1	7	2
Pain	1		7	12	22	117	6
Perforation					2		
Performance status decreased						2	
Peripheral swelling			3	3	4	34	7
Physical deconditioning			3	3	6	27	
Pneumatosis						1	
Prolapse						2	
Prosthetic cardiac valve thrombosis						2	
Puncture site haematoma					1		
Puncture site haemorrhage					1		
Pyrexia	8	10	62	45	103	714	24
Secretion discharge				2	1	4	
Sensation of foreign body						1	
Sense of oppression					1	1	
Sluggishness			1			1	
Stenosis					1	2	
Sudden cardiac death	1	1	7	9	16	35	3

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
General disorders and administration site conditions							
Number of Cases	55	40	353	359	650	4,287	726
Number of Events	76	54	551	527	1,012	6,461	840
Sudden death	6	1	40	47	72	393	10
Sudden unexplained death in epilepsy			1				
Suprapubic pain						1	
Swelling		1	1	2	3	15	
Swelling face		1			2	11	
Systemic inflammatory response syndrome				1		10	1
Temperature regulation disorder					1		
Tenderness			1		1	1	
Terminal state				1		5	1
Therapeutic response decreased					1		
Therapeutic response unexpected						1	
Thirst		1		1		3	
Vaccination failure		2	3	10	43	492	6
Vaccination site bruising						1	
Vaccination site dermatitis				1			
Vaccination site discolouration					1		
Vaccination site erythema			1		2	11	1
Vaccination site haematoma						2	
Vaccination site haemorrhage				1		1	
Vaccination site inflammation				2		5	
Vaccination site joint discomfort						1	
Vaccination site mass						1	
Vaccination site nodule						1	
Vaccination site oedema						1	
Vaccination site pain	3		10	10	15	55	2
Vaccination site paraesthesia						1	
Vaccination site pruritus			1		1	2	
Vaccination site rash					1	1	
Vaccination site reaction			2		1	1	1
Vaccination site scar						1	
Vaccination site swelling			1	1		7	
Vaccination site warmth						4	
Vascular stent stenosis						1	
Vascular stent thrombosis						1	
Hepatobiliary disorders							
Number of Cases	2		15	20	25	111	7
Number of Events	2		22	23	40	156	8
Acute hepatic failure				1	1	1	
Autoimmune cholangitis						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Hepatobiliary disorders							
Number of Cases	2		15	20	25	111	7
Number of Events	2		22	23	40	156	8
Autoimmune hepatitis						1	
Bile duct stone					1		
Biliary colic						1	
Cholangitis					2	3	
Cholangitis acute						2	
Cholecystitis					2	6	
Cholecystitis acute						1	
Cholelithiasis				1	1	16	
Cholestasis			1			1	
Chronic hepatic failure					1		
Congestive hepatopathy			2	1		3	1
Drug-induced liver injury					1	2	
Fatty liver alcoholic					1		
Gallbladder cholesterolosis					1		
Gallbladder disorder						1	
Gallbladder enlargement						1	
Gallbladder hypofunction						1	
Gallbladder oedema						1	
Gallbladder polyp						1	
Hepatic atrophy						1	
Hepatic cirrhosis					1	5	1
Hepatic cyst				1		1	
Hepatic cytolysis				1		4	
Hepatic failure	1		4	3	6	21	
Hepatic fibrosis				1			
Hepatic function abnormal			1	3	2	12	
Hepatic haemorrhage			1	2	1		
Hepatic infarction					2	2	
Hepatic ischaemia						1	
Hepatic lesion						2	
Hepatic necrosis			1			1	
Hepatic steatosis			1	2	2	5	1
Hepatic vein thrombosis				1			
Hepatitis			1			3	1
Hepatitis acute			1			3	
Hepatocellular injury				1			
Hepatomegaly			1		1	1	
Hepatorenal failure						1	
Hepatorenal syndrome					1	3	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Hepatobiliary disorders							
Number of Cases	2		15	20	25	111	7
Number of Events	2		22	23	40	156	8
Hepatotoxicity						1	
Hyperbilirubinaemia			1			3	
Hypertransaminasaemia							1
Ischaemic hepatitis						1	
Jaundice			2		2	17	
Jaundice cholestatic						2	
Liver disorder	1		2		4	12	
Liver injury			1	1		2	
Ocular icterus			1		1	2	
Portal hypertension						1	
Portal vein embolism							1
Portal vein phlebitis						1	
Portal vein thrombosis			1	4	5	4	1
Portosplenomesenteric venous thrombosis						1	
Subacute hepatic failure					1		
Immune system disorders							
Number of Cases	3	2	11	19	11	76	13
Number of Events	3	2	11	20	11	83	14
Allergy to vaccine						1	
Amyloidosis						1	
Anamnestic reaction						2	
Anaphylactic reaction	1		3	3	5	28	5
Anaphylactic shock	2	1	1	3		7	
Anaphylactoid reaction						1	
Anti-neutrophil cytoplasmic antibody positive vasculitis						4	
Autoimmune disorder			1	3		3	1
Corneal graft rejection						1	
Cytokine release syndrome				3			
Cytokine storm				1	1	1	1
Drug hypersensitivity							1
Food allergy							1
Haemophagocytic lymphohistiocytosis			1	2		5	1
Heart transplant rejection			1				
Hypersensitivity		1	1		2	11	2
Immune reconstitution inflammatory syndrome				1			
Immune system disorder			1	1	2	6	1
Immunisation reaction				1			
Immunodeficiency				1		1	
Immunosuppression						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Immune system disorders							
Number of Cases	3	2	11	19	11	76	13
Number of Events	3	2	11	20	11	83	14
Lung transplant rejection			1		1		
Multisystem inflammatory syndrome in adults			1				
Primary amyloidosis						1	
Reaction to excipient						1	
Sarcoidosis						1	
Serum sickness							1
Systemic immune activation						2	
Transplant rejection				1			
Type I hypersensitivity						1	
Type IV hypersensitivity reaction						1	
Vaccine associated enhanced disease						3	
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Abdominal infection						1	
Abdominal sepsis					1	1	
Abscess					1	2	
Acute hepatitis B					1		
Aerococcus urinae infection						1	
Appendicitis							1
Arteriosclerotic gangrene						1	
Aspergillus infection						1	
Asymptomatic bacteriuria						2	
Asymptomatic COVID-19					1	15	1
Atypical mycobacterial infection						1	
Atypical pneumonia						4	
Bacteraemia					1	3	
Bacterial infection					2	6	1
Bacterial pyelonephritis						1	
Bacterial sepsis					1	7	
Bacteriuria					1	1	
Bacteroides bacteraemia				1			
Beta haemolytic streptococcal infection			1				
Blister infected							1
Bone abscess						1	
Brain abscess						1	
Bronchiolitis							1
Bronchitis				1	2	21	1
Bronchitis bacterial					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Bronchopulmonary aspergillosis						1	
Candida infection						1	
Candida sepsis			1			2	
Cardiac infection			1			3	1
Cardiac valve vegetation						1	
Catheter site infection						1	
Cavernous sinus thrombosis		1					
Cellulitis					2	8	
Central nervous system infection						1	
Clostridium difficile colitis						2	
Clostridium difficile infection						2	2
Colon gangrene						1	
Conjunctivitis					2	2	
Conjunctivitis bacterial						1	
Coronavirus infection						4	
COVID-19	2	4	18	25	94	851	213
COVID-19 pneumonia			3	9	31	273	1
Creutzfeldt-Jakob disease				1	2	6	
Cystitis				1		4	
Cytomegalovirus infection				1			
Cytomegalovirus infection reactivation					1		
Cytomegalovirus viraemia						1	
Dermo-hypodermitis						1	
Device related infection						1	
Diarrhoea infectious						1	
Disseminated Bacillus Calmette-Guerin infection						1	
Diverticulitis						2	1
Dysentery						1	
Ear infection						1	
Eczema herpeticum						1	
Encephalitis			3	2	4	6	1
Encephalitis brain stem						1	
Encephalitis viral						2	
Endocarditis			1	1	2	7	
Endocarditis staphylococcal						1	
Endotoxic shock						1	
Enteritis infectious					1	1	
Enterobacter infection						1	
Enterobacter sepsis						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Enterococcal infection			1			1	
Enterococcal sepsis				1			
Erysipelas						10	
Escherichia infection			1			3	
Escherichia pyelonephritis						1	
Escherichia sepsis			1		1	5	
Escherichia urinary tract infection						5	
Febrile infection						3	
Focal peritonitis						1	
Fungal infection			1			1	1
Fungal skin infection						1	
Furuncle						1	
Gangrene					1		
Gastric infection				1			
Gastroenteritis		1			1	5	
Gastrointestinal infection						1	
Genital herpes						1	
Gingival abscess						1	
Haemorrhagic pneumonia			2				
Hepatitis C						2	1
Herpes simplex					1		
Herpes simplex encephalitis						3	
Herpes zoster				1	4	19	1
Herpes zoster meningitis						1	
Herpes zoster meningoencephalitis						2	
Infected skin ulcer							1
Infection		1	1	2	4	42	1
Infection susceptibility increased						1	
Infective aneurysm						1	
Infective exacerbation of chronic obstructive airways disease				1	1		
Infective myositis						1	
Infective spondylitis						1	
Influenza				1	3	13	1
Infusion site infection		1					
Intervertebral discitis						3	
Intestinal gangrene				1			
Kidney infection						1	1
Klebsiella bacteraemia					1		
Klebsiella infection		1	1			6	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Labyrinthitis				1			
Laryngitis						1	
Legionella infection						1	
Listeriosis						1	
Liver abscess					1		
Localised infection					1	1	
Lower respiratory tract infection			1	2	5	20	2
Lower respiratory tract infection bacterial					1		
Lower respiratory tract infection viral						1	
Lung abscess						3	
Mastoiditis						1	
Meningitis						6	
Meningitis aseptic			2				
Meningitis bacterial						2	
Meningitis herpes						1	
Meningitis pneumococcal						1	
Meningitis viral			1				
Meningoencephalitis bacterial						1	
Meningoencephalitis herpetic						1	1
Meningoencephalitis viral			1			2	
Mucormycosis					1		
Mycobacterial infection						1	
Myelitis					1	2	
Myocarditis infectious						1	
Myocarditis septic						1	
Nasopharyngitis	1	1	5	3	5	31	1
Necrotising fasciitis						2	
Neutropenic sepsis					1	1	
Nosocomial infection			1		1	1	
Ophthalmic herpes zoster						1	1
Oral candidiasis						3	
Oral fungal infection						3	
Orchitis					1		
Osteomyelitis						3	
Otitis media						1	
Overgrowth bacterial						1	
Parainfluenzae virus infection						1	
Parotitis						1	
Pathogen resistance					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Pericarditis tuberculous						1	
Periorbital infection						1	
Peritonitis				2	2	4	
Peritonitis bacterial							1
Pharyngitis		1	1	1		2	
Pharyngotonsillitis			1				
Pleurisy viral	1						
Pneumococcal bacteraemia						1	
Pneumococcal infection						2	
Pneumocystis jirovecii infection						1	
Pneumocystis jirovecii pneumonia						2	
Pneumonia	1	1	8	12	43	392	11
Pneumonia aspiration			3	5	6	120	5
Pneumonia bacterial			1		3	24	1
Pneumonia klebsiella				1		2	
Pneumonia legionella						1	
Pneumonia moraxella						1	
Pneumonia pneumococcal					1	2	
Pneumonia staphylococcal					1	1	
Pneumonia viral	1				1	4	1
Prion disease			1		1		
Progressive multifocal leukoencephalopathy				1			
Proteus infection			1				
Pseudomonal bacteraemia						1	
Pseudomonas infection						3	
Pulmonary sepsis	1				1	8	
Pulmonary tuberculosis					1		
Purulent discharge						1	
Pustule						1	
Pyelonephritis					2	9	
Pyelonephritis acute						4	
Renal graft infection						1	
Respiratory tract infection				2		19	
Respiratory tract infection bacterial						2	
Respiratory tract infection viral						1	
Rhinitis			1			2	
Salmonella sepsis						1	
Salmonellosis						1	
SARS-CoV-2 sepsis					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Sepsis		1	5	9	25	124	10
Sepsis syndrome						2	
Septic arthritis staphylococcal						1	
Septic embolus						1	
Septic encephalopathy						1	
Septic rash					1		
Septic shock	3	1	4	7	23	70	1
Serratia infection					1	1	
Severe acute respiratory syndrome						4	
Severe fever with thrombocytopenia syndrome						2	
Severe invasive streptococcal infection						1	
Sinusitis				1	1	4	
Skin bacterial infection						1	
Skin infection						2	
Soft tissue infection						3	
Spinal cord infection				1			
Splenic infection						2	
Sputum purulent						1	
Staphylococcal bacteraemia				1		4	
Staphylococcal infection			1			3	
Staphylococcal sepsis						7	
Streptococcal infection						1	
Streptococcal sepsis						1	
Superinfection						2	
Superinfection bacterial					1	4	
Suspected COVID-19			2	3	8	32	20
Systemic bacterial infection			1				
Systemic infection						1	
Testicular abscess					1		
Tonsillitis					1		
Tooth abscess						2	
Tooth infection			1				
Toxic shock syndrome				1	1	1	
Tuberculosis						1	
Upper respiratory tract infection					1	5	
Urinary tract infection			1	1	5	80	3
Urinary tract infection bacterial					1	10	
Urinary tract infection enterococcal						1	
Urinary tract infection fungal						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Infections and infestations							
Number of Cases	6	10	61	85	230	1,953	274
Number of Events	10	15	81	105	325	2,525	290
Urosepsis					2	25	
Vaccination site abscess					1	1	
Vaccine associated paralytic poliomyelitis						1	
Vaccine breakthrough infection			1			3	
Variant Creutzfeldt-Jakob disease				1			
Varicella					1		
Vascular device infection						1	
Viral infection		1				2	
Viral myocarditis					1	1	
Viral sepsis						1	
Virologic failure						1	
Zoonotic bacterial infection			1				
Injury, poisoning and procedural complications							
Number of Cases	11	6	63	73	101	692	64
Number of Events	11	8	71	87	121	877	70
Accident	1						
Accident at home						1	
Adverse event following immunisation	1		4	4	3	6	1
Alcohol poisoning			1	1		3	
Anaemia postoperative						1	
Anastomotic complication				1			
Ankle fracture						1	
Arthropod bite						1	
Bone contusion						2	
Brain contusion						1	
Brain herniation	1	1	2	5	3	10	
Burn oral cavity							1
Carbon monoxide poisoning						1	
Cardiac procedure complication				1			
Central nervous system injury						1	
Cerebral ventricle collapse				1			
Chest injury						5	
Complications of transplanted kidney					1		
Contusion			1	3	6	26	1
Craniocerebral injury				1		4	
Eschar						1	
Expired product administered		1					
Exposure during pregnancy			1				
Exposure to SARS-CoV-2						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	11	6	63	73	101	692	64
Number of Events	11	8	71	87	121	877	70
Exposure to toxic agent			1				
Exposure to vaccinated person				1			
Extra dose administered				2	2	17	1
Extradural haematoma						3	
Eye injury						1	
Face crushing					1		
Face injury						3	
Facial bones fracture				1		2	
Fall			7	14	21	280	4
Femoral neck fracture						7	
Femur fracture						3	
Foetal exposure during pregnancy		1					
Foot fracture					1		
Foreign body aspiration			1				
Fracture				1		2	
Gun shot wound							1
Hand fracture						1	
Head injury	1			2	2	27	
Heat illness					2	5	
Heat oedema			1				
Hip fracture						5	
Humerus fracture						1	
Inappropriate schedule of product administration	1	4	19	15	27	122	2
Incomplete course of vaccination				1		1	
Incorrect route of product administration			4	3	5	34	1
Injection related reaction				1			
Injury						3	2
Intentional product use issue						1	
Joint injury						2	
Limb injury					1	2	
Liver contusion			1				1
Lower limb fracture						1	
Lumbar vertebral fracture						1	
Maternal exposure during pregnancy		1	3				
Maternal exposure timing unspecified							3
Medication error				1			
Multiple fractures						1	
Multiple injuries					1		
Muscle rupture						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	11	6	63	73	101	692	64
Number of Events	11	8	71	87	121	877	70
Muscle strain						1	
Near drowning						4	
Neck injury				1			
Nerve injury	1					1	
Off label use	2		15	16	30	142	15
Overdose				1	1	10	
Pelvic fracture						3	
Periprosthetic fracture						1	
Pneumoconiosis						3	
Poisoning						2	
Poor quality product administered			2				1
Postoperative ileus						1	
Post procedural haemorrhage						1	
Post vaccination syndrome			1				
Procedural pain						1	
Product administered at inappropriate site						5	
Product administered to patient of inappropriate age	1						
Product dose omission issue				1			
Product use in unapproved indication						1	
Product use issue			1	2	1	15	1
Radius fracture						1	
Recalled product administered						1	
Rib fracture			1	1	1	8	
Road traffic accident				1	3	1	
Scapula fracture						1	
Scar					1	1	
Scratch						1	
Scrotal injury						1	
Shunt stenosis						1	
Shunt thrombosis						1	
Skin abrasion						4	
Skin injury						1	
Skin laceration				1		4	
Skin wound						1	
Skull fracture					1	1	
Spinal fracture						3	
Splenic rupture					1		
Sternal fracture					1		
Subcutaneous haematoma						2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Injury, poisoning and procedural complications							
Number of Cases	11	6	63	73	101	692	64
Number of Events	11	8	71	87	121	877	70
Subdural haematoma	1				3	12	
Subdural haemorrhage						4	
Thermal burn							1
Tibia fracture						1	
Tissue injury							2
Toxicity to various agents						4	1
Tracheal haemorrhage						1	
Tracheal obstruction				1			
Transfusion related complication					1		
Transplant failure			1				
Traumatic haemorrhage						3	
Traumatic haemothorax						1	
Traumatic intracranial haemorrhage						3	
Ulna fracture						1	
Underdose						1	28
Upper limb fracture						3	
Vaccination complication			1	1		10	2
Vaccination error				1		1	
Vascular procedure complication						1	
Vascular pseudoaneurysm			1				
Vasoplegia syndrome						3	
Venous injury	1						
Wound						7	1
Wound complication						1	
Wound necrosis						1	
Wrist fracture						1	
Wrong patient received product						1	
Wrong product administered			1	1	1	2	
Wrong technique in product usage process			1				
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Activated partial thromboplastin time abnormal						1	
Activated partial thromboplastin time prolonged				1	3	4	
Activated partial thromboplastin time ratio decreased						1	
Activated partial thromboplastin time ratio increased						1	
Activated partial thromboplastin time shortened					1	5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
ADAMTS13 activity decreased	1			1			
Alanine aminotransferase decreased						2	
Alanine aminotransferase increased			1	1	2	8	
Albumin globulin ratio decreased						3	
Albumin urine absent						1	
Ammonia increased						1	
Amylase decreased				1			
Amylase increased						3	
Anion gap increased						1	
Antibody test abnormal						1	
Anticoagulation drug level below therapeutic						1	
Anti factor VIII antibody positive						1	
Antimitochondrial antibody positive						1	
Antinuclear antibody positive						1	
Aspartate aminotransferase abnormal						1	
Aspartate aminotransferase increased			1	1	2	10	
AST/ALT ratio abnormal						1	
Auscultation						1	
Bacterial test						1	
Bacterial test positive				1	1	5	
Band neutrophil count increased						1	
Base excess increased						1	
Basophil count decreased						2	
Basophil count increased						2	
Blast cell count increased						1	
Bleeding time prolonged						1	
Blood albumin decreased						7	
Blood albumin increased						1	
Blood alcohol decreased						1	
Blood alkaline phosphatase decreased					1		
Blood alkaline phosphatase increased						7	
Blood bicarbonate decreased						6	
Blood bilirubin increased					2	6	
Blood calcium decreased						6	
Blood chloride decreased						1	
Blood chloride increased					1	3	
Blood cholesterol increased				1			
Blood cholinesterase increased						1	
Blood creatine increased				1		3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Blood creatine phosphokinase increased				1	2	12	
Blood creatine phosphokinase MB increased				2		1	
Blood creatinine decreased				1	1	1	
Blood creatinine increased	1	1		3	1	17	
Blood fibrinogen decreased						1	
Blood fibrinogen increased				1		5	
Blood folate decreased						1	
Blood glucose abnormal		1	1		1	2	
Blood glucose decreased		1	1	1	3	3	
Blood glucose fluctuation						2	
Blood glucose increased			1	4	6	25	
Blood immunoglobulin E increased						2	
Blood immunoglobulin G increased						1	
Blood iron decreased		1				2	
Blood iron increased						1	
Blood lactate dehydrogenase decreased					1		
Blood lactate dehydrogenase increased				1		14	
Blood lactic acid increased			1	3		9	
Blood magnesium decreased						2	
Blood magnesium increased				1			
Blood methaemoglobin present						1	
Blood osmolarity increased						1	
Blood pH decreased			1				
Blood phosphorus decreased				1		1	
Blood phosphorus increased				1		2	
Blood potassium decreased				2		5	
Blood potassium increased		1			1	5	
Blood pressure abnormal			1	2	1	4	
Blood pressure decreased			4	3	12	83	3
Blood pressure diastolic decreased						3	
Blood pressure diastolic increased						2	
Blood pressure immeasurable						8	
Blood pressure increased			6	10	7	40	2
Blood pressure systolic decreased				1		5	
Blood pressure systolic increased						6	
Blood sodium decreased						8	
Blood sodium increased				1		4	
Blood test abnormal			1			2	
Blood thrombin						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Blood thyroid stimulating hormone decreased					1		
Blood triglycerides increased				2			
Blood urea decreased						1	
Blood urea increased					2	22	
Blood urea nitrogen/creatinine ratio increased						1	
Blood uric acid increased					1	4	
Blood urine present					1	3	
Blood viscosity increased					1		
Body mass index abnormal		1					
Body temperature abnormal						1	
Body temperature decreased					1	12	
Body temperature fluctuation					1		
Body temperature increased		1	2		4	30	1
Bone marrow myelogram abnormal					1		
Brain natriuretic peptide increased						6	
Breath sounds						1	1
Breath sounds abnormal			1	1		11	
Capillary nail refill test abnormal						1	
Carbohydrate antigen 19-9 increased				1			
Carbon dioxide decreased						1	
Carbon dioxide increased			1				
Carboxyhaemoglobin increased						1	
Carcinoembryonic antigen increased				1			
Cardiac murmur						1	
Cardiac output decreased						1	
Cardiothoracic ratio increased					1		
Cells in urine						1	
Chest X-ray abnormal					1	5	
Clot retraction						1	
Coagulation factor V level decreased						1	
Coma scale abnormal		2			1	15	
Corneal reflex decreased						1	
Coronavirus test positive						1	1
C-reactive protein abnormal						2	
C-reactive protein increased		1	3	2	6	89	1
Creatinine renal clearance decreased						1	
Creatinine renal clearance increased						1	
CSF glucose increased			1			1	
CSF protein increased					1	2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Culture urine positive						2	
Cytomegalovirus test positive						2	
Drug specific antibody absent						1	
Eastern Cooperative Oncology Group performance status worsened						2	
Ejection fraction decreased			2	1	2	2	
Electrocardiogram abnormal						2	
Electrocardiogram repolarisation abnormality						1	
Electrocardiogram ST segment abnormal						1	
Electrocardiogram ST segment elevation			1			3	
Electrocardiogram ST-T segment elevation						1	
Electrocardiogram T wave inversion						1	
Electroencephalogram abnormal					1	2	
Enzyme level abnormal						1	
Eosinophil count decreased				1		4	
Eosinophil count increased						2	
Escherichia test positive					1	2	
Fibrin abnormal					1		
Fibrin D dimer decreased						1	
Fibrin D dimer increased	1		5	3	6	34	
Fibrin degradation products increased				1		1	
Fibrinolysis increased					1		
Full blood count abnormal						3	
Fungal test positive					1	1	
Gamma-glutamyltransferase increased				1		3	
General physical condition abnormal						12	
Glomerular filtration rate decreased						16	
Glycosylated haemoglobin increased				1		2	
Grip strength decreased					1	2	
Haematocrit decreased			1	1	1	14	
Haemoglobin abnormal						1	
Haemoglobin decreased	1	1	1	2	3	35	
Haptoglobin decreased						1	
Haptoglobin increased					1		
Heart rate abnormal						2	
Heart rate decreased				2	4	21	
Heart rate increased		2	2	2	5	42	3
Heart rate irregular						5	
Heart sounds abnormal						3	
Hepatic enzyme increased					3	5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Histamine level increased						1	
Immature granulocyte count increased						3	
Immunoglobulins increased						1	
Inflammatory marker increased				1	3	10	
Interleukin level decreased					1		
Interleukin level increased					1	4	
International normalised ratio abnormal						1	
International normalised ratio decreased				1		1	
International normalised ratio increased						20	1
Laboratory test abnormal						1	
Lactobacillus test positive						1	
Legionella test positive						1	
Lipase decreased					1		
Lipase increased						1	
Lipids increased						1	
Liver function test abnormal					2	3	
Liver function test decreased					1		
Liver function test increased						1	
Low density lipoprotein increased						2	
Lymphocyte count decreased			1	1	1	10	
Lymphocyte count increased				1			
Lymphocyte percentage decreased						1	
Magnetic resonance imaging head abnormal						1	
Mean cell haemoglobin concentration decreased			1		1	7	
Mean cell haemoglobin concentration increased						1	
Mean cell haemoglobin decreased						1	
Mean cell haemoglobin increased						1	
Mean cell volume decreased					1	1	
Mean cell volume increased						3	
Mean platelet volume decreased						1	
Metamyelocyte count increased			1			1	
Monocyte count decreased						2	
Monocyte count increased						4	
Myelocyte count increased			1			1	
Myocardial necrosis marker increased						2	
Myocardial strain imaging						1	
Neutrophil count decreased						3	
Neutrophil count increased				1		15	
Neutrophil percentage increased						2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
NIH stroke scale score decreased						1	
Nitrite urine present						1	
N-terminal prohormone brain natriuretic peptide increased						5	
Osmolar gap increased				1			
Oxygen saturation						2	
Oxygen saturation abnormal						8	
Oxygen saturation decreased		2	8	9	30	261	5
Oxygen saturation immeasurable	1					1	
PCO2 abnormal						1	
PCO2 decreased						2	
PCO2 increased		1				4	
pH body fluid decreased						1	
Platelet count abnormal						2	
Platelet count decreased	2	1	4	5	4	45	9
Platelet count increased		1		1		4	
Plateletcrit increased						1	
Platelet factor 4			1				
PO2 decreased						2	
PO2 increased						1	
Prealbumin decreased						1	
Procalcitonin increased					1	6	
Prohormone brain natriuretic peptide increased						1	
Prostatic specific antigen increased					1		
Protein C increased		1					
Protein total decreased				2		4	
Protein urine present					1		
Prothrombin level abnormal						1	
Prothrombin level increased						1	
Prothrombin time prolonged				1	2	3	
Prothrombin time ratio increased						2	
Prothrombin time shortened						1	
Pulmonary arterial pressure increased						2	
Pulse abnormal				1	1	7	
Pulse absent		1			5	7	
Pulse pressure decreased						1	
Pyruvate kinase increased						1	
Quality of life decreased						2	
Radial pulse abnormal						1	
Red blood cell count decreased			1	1	1	14	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
Red blood cell sedimentation rate increased			1			4	
Red blood cells urine positive						2	
Red cell distribution width increased			1			5	
Renal function test abnormal						1	
Respiratory rate decreased			1			7	
Respiratory rate increased			1	1		21	
Reticulocyte count decreased					1	1	
Reticulocyte count increased						1	
Right ventricular systolic pressure increased						1	
SARS-CoV-2 antibody test positive					1		
SARS-CoV-2 test negative		1				1	
SARS-CoV-2 test positive				3	2	46	2
Serratia test positive						2	
Serum ferritin abnormal						1	
Serum ferritin increased			1		1	2	
Sinus rhythm						1	
Sputum abnormal						1	
Stenotrophomonas test positive						1	
Streptococcus test positive						1	
Thyroid function test abnormal						1	
Tidal volume decreased			1				
Total lung capacity decreased						1	
Transaminases increased		1	1			3	
Troponin abnormal				1		1	
Troponin I increased						4	
Troponin increased		1	1	2	1	7	
Troponin T increased					1	6	
Tryptase increased						1	
Tumour marker increased						2	
Urine chromium increased						1	
Urine copper						1	
Urine output decreased			1			8	
Venous oxygen saturation decreased						2	
Vitamin B12 abnormal						1	
Vitamin B12 decreased		1					
Weight decreased				1	5	27	3
Weight increased						5	1
White blood cell count abnormal						1	
White blood cell count decreased		2			2	9	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Investigations							
Number of Cases	6	12	40	50	113	824	29
Number of Events	7	26	67	106	176	1,568	33
White blood cell count increased			1	3	1	41	
White blood cells urine positive						2	
Metabolism and nutrition disorders							
Number of Cases	5	4	14	22	67	556	15
Number of Events	5	6	17	23	87	687	15
Abnormal weight gain						1	
Acetonaemia						1	
Acidosis			1		5	7	
Adult failure to thrive						4	
Cachexia					2	21	
Cell death					1	1	
Decreased appetite	3	1	4	6	28	211	7
Dehydration		2		3	5	103	1
Diabetes mellitus	1	1		1	5	9	1
Diabetes mellitus inadequate control						4	
Diabetic complication					1	2	
Diabetic ketoacidosis	1		2		2	3	
Diabetic metabolic decompensation						1	
Diet refusal					1	7	
Dyslipidaemia						1	
Electrolyte depletion						1	
Electrolyte imbalance		1	1		1	7	
Failure to thrive						1	
Feeding disorder			1	2	2	27	
Fluid imbalance						1	
Fluid intake reduced						8	
Fluid retention					2	8	
Food refusal			1			5	
Gout						2	
Hypercalcaemia						6	
Hyperchloraemia						1	
Hypercholesterolaemia						1	1
Hyperglycaemia			1		1	16	
Hyperglycaemic hyperosmolar nonketotic syndrome						4	
Hyperkalaemia			2	1	5	17	1
Hyperlactacidaemia					3	5	
Hypernatraemia					1	19	
Hyperphagia						1	
Hypertriglyceridaemia						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Metabolism and nutrition disorders							
Number of Cases	5	4	14	22	67	556	15
Number of Events	5	6	17	23	87	687	15
Hyperuricaemia					1	4	1
Hypervitaminosis B12						1	
Hypervolaemia					1	2	
Hypoalbuminaemia				1	1	3	
Hypocalcaemia						1	
Hypochloraemia						1	
Hypoglycaemia						14	
Hypokalaemia				1	2	16	
Hyponatraemia			1	2	3	22	
Hypophagia				1	2	40	
Hypophosphataemia						1	
Hypoproteinaemia						1	
Ketoacidosis		1		1	1		
Lactic acidosis				3	2	10	
Lipid metabolism disorder			1				
Lipomatosis					1		
Malnutrition					1	10	1
Marasmus						28	1
Metabolic acidosis			1		7	14	
Metabolic disorder						2	
Obesity				1		2	
Polydipsia						1	
Starvation						2	
Tetany			1				
Type 1 diabetes mellitus						1	
Type 2 diabetes mellitus						3	1
Vitamin D deficiency						1	
Musculoskeletal and connective tissue disorders							
Number of Cases	6	3	55	53	76	413	15
Number of Events	7	3	73	62	94	525	20
Antisynthetase syndrome					1		
Arthralgia		1	12	9	15	64	3
Arthritis			1			1	
Back disorder				1	1	1	
Back pain	1		7	6	7	57	2
Bone disorder						2	
Bone pain			2		1	1	
Bone swelling						1	
Cervical spinal stenosis					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Musculoskeletal and connective tissue disorders							
Number of Cases	6	3	55	53	76	413	15
Number of Events	7	3	73	62	94	525	20
Connective tissue disorder					1		
Costochondritis						1	
Facial asymmetry			1				
Fibromyalgia				1		1	
Flank pain			1			3	
Foot deformity						1	
Groin pain				2	1	3	
Haemarthrosis						1	
Haematoma muscle						2	
Hand deformity						1	
Immobilisation syndrome						2	
Immune-mediated myositis					1		
Intervertebral disc protrusion					1		
Joint range of motion decreased				1			
Joint stiffness						1	
Joint swelling				1	1	6	
Limb discomfort			1	1	2	12	
Mobility decreased				1	3	32	1
Muscle atrophy						1	
Muscle disorder						2	
Muscle fatigue					1		
Muscle rigidity					1	6	
Muscle spasms				1	1	14	
Muscle tightness						2	
Muscle twitching			2	1		6	
Muscular weakness	1		5	4	9	48	2
Musculoskeletal chest pain						3	1
Musculoskeletal discomfort				1		2	
Musculoskeletal disorder						1	
Musculoskeletal pain				1	1	8	1
Musculoskeletal stiffness			3	5	1	6	
Myalgia	1		16	5	18	84	5
Myopathy				2		2	
Myositis						1	
Neck pain			4	4	1	14	
Nuchal rigidity						1	
Oligoarthritis						1	
Osteitis						1	
Osteoarthritis						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Musculoskeletal and connective tissue disorders							
Number of Cases	6	3	55	53	76	413	15
Number of Events	7	3	73	62	94	525	20
Osteopenia						1	
Pain in extremity	4	1	17	13	19	99	4
Pain in jaw						3	
Polymyositis						2	
Posture abnormal						1	
Rhabdomyolysis		1			4	9	
Rheumatoid arthritis					1	1	
Sarcopenia						1	
Scoliosis						1	
Slipping rib syndrome						2	
Soft tissue haemorrhage				1			
Spinal disorder						3	
Spinal osteoarthritis						1	
Spinal pain			1			2	
Spinal stenosis						1	
Systemic lupus erythematosus							1
Tendonitis				1			
Torticollis						1	
Trismus					1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1	1	8	23	36	150	15
Number of Events	1	1	11	25	43	180	16
Abdominal neoplasm						2	
Acute leukaemia					5	3	
Acute lymphocytic leukaemia			1	1		1	
Acute megakaryocytic leukaemia					1		
Acute myeloid leukaemia					1	8	
Acute myeloid leukaemia recurrent						1	
Adenocarcinoma metastatic						1	
Adenocarcinoma of colon						1	
Adenoma benign						1	
Anaplastic thyroid cancer			1				
B-cell lymphoma						4	
Benign breast neoplasm						1	
Bile duct cancer						2	
Bladder adenocarcinoma stage unspecified						1	
Bladder cancer						1	
Bone cancer						1	
Bone cancer metastatic						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1	1	8	23	36	150	15
Number of Events	1	1	11	25	43	180	16
Brain cancer metastatic						1	
Brain neoplasm			1				
Breast cancer						2	1
Breast cancer metastatic						1	
Breast cancer recurrent						1	
Breast cancer stage IV			1				
Bronchial neoplasm					1		
Carcinoid tumour pulmonary						1	
Castleman's disease				1	1		
Cerebral haemangioma			1				
Cholangiosarcoma						1	
Chronic leukaemia						1	
Chronic lymphocytic leukaemia						3	
Chronic myeloid leukaemia						1	
Colon neoplasm						2	
Diffuse large B-cell lymphoma						1	
Endocrine neoplasm malignant						1	
Essential thrombocythaemia						1	
Fallopian tube neoplasm						1	
Follicular lymphoma stage IV					1		
Gastric cancer						4	
Gastric cancer recurrent						1	
Glioblastoma			1			2	
Haemangioma				1			
Haematopoietic neoplasm						1	
Hepatic cancer						1	3
Hepatic cancer metastatic						1	
Hepatic neoplasm						3	
Invasive ductal breast carcinoma				1			
Kaposi's sarcoma AIDS related						1	
Leiomyosarcoma				1			
Leukaemia	1				1	8	1
Lip and/or oral cavity cancer				1			
Lip and/or oral cavity cancer recurrent						1	
Lung adenocarcinoma						1	
Lung cancer metastatic				2	2	2	1
Lung carcinoma cell type unspecified stage 0						1	
Lung neoplasm					1		
Lung neoplasm malignant				2		12	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1	1	8	23	36	150	15
Number of Events	1	1	11	25	43	180	16
Lymphangioma				1			
Lymphoma					3	3	1
Lymphoproliferative disorder						2	
Malignant ascites						1	
Malignant neoplasm of renal pelvis						1	
Malignant neoplasm progression					1	2	
Malignant peritoneal neoplasm				1			
Malignant pleural effusion						2	
Malignant splenic neoplasm				1			
Marrow hyperplasia					1		
Meningioma			1			1	
Metastases to adrenals						1	
Metastases to bone						2	
Metastases to central nervous system						2	
Metastases to liver					2	4	
Metastases to lung					2	2	
Metastases to lymph nodes						1	
Metastases to peritoneum						2	
Metastases to pituitary gland				1			
Metastases to the mediastinum						1	
Metastasis			1			1	
Metastatic bronchial carcinoma						1	
Metastatic lymphoma					1		
Myelodysplastic syndrome					1	5	1
Myelofibrosis						1	
Myeloid leukaemia						1	
Myeloproliferative neoplasm						3	
Neoplasm						2	
Neoplasm malignant			1	2	2	5	6
Neoplasm progression				5	6	20	1
Neoplasm recurrence					1	2	
Neuroendocrine carcinoma of the skin						1	
Non-Hodgkin's lymphoma		1				2	
Oesophageal carcinoma						2	
Ovarian cancer				1		1	
Pancreatic carcinoma				1	2	4	
Pancreatic neoplasm					1	1	
Papilloma						1	
Paraneoplastic syndrome					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Number of Cases	1	1	8	23	36	150	15
Number of Events	1	1	11	25	43	180	16
Plasma cell leukaemia						1	
Plasmacytoma						1	
Pleural mesothelioma						1	
Polycythaemia vera					1		
Prostate cancer						3	
Renal cancer						1	
Renal neoplasm					1	1	
Small cell lung cancer					1		
Squamous cell carcinoma of the tongue						1	
T-cell lymphoma			1				
Testis cancer						1	
Thymoma				1			
Transitional cell carcinoma					1		
Tumour haemorrhage			1				
Tumour perforation						1	
Tumour rupture				1			
Tumour thrombosis						1	
Uterine leiomyoma					1	2	
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Acute disseminated encephalomyelitis			4	1	1	1	
Ageusia					1	6	1
Alexia						1	
Altered state of consciousness			4	6	6	94	
Amnesia					1	5	1
Anosmia					1	4	1
Anosognosia						1	
Apallic syndrome						4	
Aphasia			3	1	5	48	1
Apraxia				1		1	
Areflexia			1		1	3	
Ataxia					1	4	
Autoimmune encephalopathy						1	
Autonomic nervous system imbalance					1	1	
Balance disorder				1	2	21	1
Ballismus						1	
Basal ganglia haemorrhage			1			2	
Basal ganglia infarction					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Basilar artery occlusion					1	3	
Basilar artery thrombosis			1	1	3	3	1
Bell's palsy			1				
Bradykinesia						5	
Brain compression		1	2			3	
Brain hypoxia	1				1	5	
Brain injury		2	4	4	8	12	2
Brain oedema	2	3	8	12	9	14	1
Brain stem haemorrhage		1	1	1	4	11	
Brain stem infarction			2		1	4	
Brain stem ischaemia						1	
Brain stem stroke			1			3	
Brain stem syndrome					1		
Brain stem thrombosis					1		
Burning sensation					1	2	
Carotid arteriosclerosis						3	
Carotid artery disease				1			
Carotid artery dissection			2				
Carotid artery occlusion					3	4	
Carotid artery stenosis					1	3	
Carotid artery thrombosis		1			1	2	
Cataplexy						1	
Central nervous system lesion					2	1	
Central nervous system vasculitis				1			
Cerebellar ataxia					1		
Cerebellar atrophy						2	
Cerebellar haematoma						1	
Cerebellar haemorrhage	1		1	1	3	5	
Cerebellar infarction			1	2		3	
Cerebellar stroke						2	
Cerebellar tonsillar ectopia		1					
Cerebral amyloid angiopathy						3	
Cerebral arteriosclerosis				1		4	
Cerebral artery embolism					1	9	1
Cerebral artery occlusion				1		2	1
Cerebral artery perforation			1				
Cerebral artery stenosis				1			
Cerebral artery thrombosis			1		1	4	
Cerebral atrophy						11	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Cerebral circulatory failure						1	
Cerebral congestion					1		
Cerebral cyst							1
Cerebral disorder				1	2	5	
Cerebral haematoma			1		5	17	
Cerebral haemorrhage	1	1	13	23	38	205	13
Cerebral infarction			2	4	13	106	4
Cerebral ischaemia			1	2		17	
Cerebral mass effect					1		
Cerebral thrombosis		1	3	3	3	21	3
Cerebral vascular occlusion						1	
Cerebral venous sinus thrombosis	1	3	12	3	3	8	
Cerebral venous thrombosis			3	4	2	2	
Cerebral ventricular rupture					4	4	
Cerebrovascular accident			12	11	28	258	28
Cerebrovascular disorder				2		14	
Cerebrovascular stenosis					1		
Clumsiness						1	
Cognitive disorder			1		3	21	1
Coma	1		7	16	16	82	3
Coma hepatic					2	1	1
Consciousness fluctuating						2	
Coordination abnormal				1		5	
Cranial nerve disorder						1	
Decerebrate posture						1	
Delayed ischaemic neurological deficit						1	
Dementia						24	3
Dementia Alzheimer's type						10	
Dementia of the Alzheimer's type, with delirium						1	
Demyelinating polyneuropathy					1		
Demyelination			1	2			
Depressed level of consciousness	1	1	5	10	7	120	
Diabetic coma					1	2	
Diabetic hyperosmolar coma					1	1	
Diplegia					2	2	
Disturbance in attention				2	2	23	1
Dizziness	4	3	16	16	27	106	5
Dizziness postural			1				
Drooling						3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Dropped head syndrome						1	
Dysarthria			5	2	7	39	
Dysgeusia					2	1	
Dyskinesia	1		1	1		6	
Dyslalia						3	
Dyslexia			1			1	
Dysstasia			1	1	3	22	
Embolic cerebral infarction						2	
Embolic stroke						5	
Encephalitis autoimmune			1		1	3	
Encephalopathy			1	1	3	9	
Epilepsy			3	4	4	30	
Extensor plantar response						1	
Extrapyramidal disorder						1	
Facial nerve disorder			1				
Facial paralysis				2	2	14	
Facial paresis			1		2	3	
Febrile convulsion						2	
Fine motor skill dysfunction						1	
Frontotemporal dementia						1	
Fumbling						1	
Generalised onset non-motor seizure						1	
Generalised tonic-clonic seizure			1	4		8	
Guillain-Barre syndrome			2		3	19	1
Haemorrhage intracranial		1	4	2	3	16	1
Haemorrhagic cerebral infarction					1	4	
Haemorrhagic stroke			4	3	10	49	3
Haemorrhagic transformation stroke				1	4	4	
Headache	7	10	58	45	42	148	11
Head discomfort						3	
Hemianaesthesia						1	
Hemianopia					1	1	
Hemianopia homonymous					1		
Hemiapraxia						1	
Hemiparaesthesia			1				
Hemiparesis	2		4	2	6	56	
Hemiplegia			4	1	3	42	
Hepatic encephalopathy			1		1	2	
Hydrocephalus		1		1	3	5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Hyperaesthesia						1	
Hyperammonaemic encephalopathy						1	
Hypercapnic coma						3	
Hyperkinesia						1	
Hypersomnia	1				3	14	
Hypertensive encephalopathy						2	
Hypertonia						1	
Hypoaesthesia	1		3	3	7	16	
Hypogeusia						2	
Hypoglycaemic coma						1	
Hypokinesia						9	1
Hyporeflexia			1			2	
Hyporesponsive to stimuli						6	
Hyposmia						1	
Hypotonia		1	1	1	5	14	
Hypotonic-hyporesponsive episode					2	3	
Hypoxic-ischaemic encephalopathy				2	1	8	
IIIrd nerve disorder					1		
IIIrd nerve paralysis			1				
Incoherent					1	6	
Intellectual disability			1				
Intracranial aneurysm			4	4	2	5	
Intracranial haematoma						1	
Intracranial pressure increased	1		3		2	2	
Intraventricular haemorrhage				3		6	
Ischaemic cerebral infarction			1		1	10	
Ischaemic stroke			6	6	9	69	
Lacunar infarction						2	
Language disorder				1	1	6	
Lethargy	1		2	2	7	37	
Leukoencephalopathy			1			3	
Locked-in syndrome						1	
Loss of consciousness	3		29	34	52	252	9
Memory impairment					3	8	1
Meningism						1	
Meningoradiculitis			1				
Meningorrhagia				1		2	
Mental impairment						10	1
Metabolic encephalopathy						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Migraine			3		2	2	
Miller Fisher syndrome							1
Monoparesis					1	1	
Monoplegia			1		1	8	
Motor dysfunction					2	9	
Motor neurone disease				1			
Movement disorder			1		1	15	1
Multiple sclerosis				1		1	1
Multiple sclerosis relapse					1		
Multiple system atrophy						1	
Muscle contractions involuntary						1	
Muscle spasticity						1	
Myasthenia gravis						4	
Myelitis transverse							1
Myelopathy						1	
Myoclonus				1	1	2	
Narcolepsy						2	
Nerve compression						1	
Nervous system disorder	1		3	1	4	21	1
Neuralgia					2	5	1
Neuritis cranial						1	
Neuroleptic malignant syndrome					2		
Neurological decompensation	1			1		1	
Neurological symptom						5	
Neurologic neglect syndrome						1	
Neuromyelitis optica spectrum disorder						1	
Neuromyotonia						1	
Neuropathy peripheral						2	
Normal pressure hydrocephalus						1	
Nystagmus						4	
Opisthotonus						1	
Optic neuritis					1		
Pachymeningitis						1	
Paraesthesia	1		3	2	1	13	1
Paralysis			2	2	1	14	2
Paraparesis					1		
Paraplegia					1	2	
Paresis						8	
Parkinsonism						2	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Parkinson's disease			1		1	4	
Partial seizures						1	
Patient elopement						1	
Peroneal nerve palsy				1			
Petit mal epilepsy			1			1	
Pleocytosis					1	1	
Polyneuropathy					1	5	
Post cardiac arrest syndrome				1		1	
Posterior reversible encephalopathy syndrome				1			
Postictal paralysis						1	
Postictal state	1						
Post stroke epilepsy						1	
Precerebral artery occlusion					1		
Presyncope			1	1	3	12	
Progressive supranuclear palsy						1	
Psychomotor hyperactivity			1	1		3	
Psychomotor skills impaired			2		1	1	
Pyramidal tract syndrome			1				
Quadriparesis					1	4	
Quadriplegia				1		4	
Restless legs syndrome					1		
Ruptured cerebral aneurysm			4	4	3	6	
Sciatica						2	
Secondary cerebellar degeneration						1	
Sedation			2			4	
Seizure	4	7	17	10	15	57	3
Seizure like phenomena						1	
Sensorimotor disorder						1	
Sensory disturbance			2	1		1	
Sensory loss						4	1
Slow response to stimuli			1			3	
Slow speech						4	
Somnolence	1		4	4	12	126	2
Speech disorder			3	2	3	37	1
Spinal cord compression					1	1	
Spinal epidural haemorrhage						1	
Spinal meningeal cyst						1	
Spinal stroke						1	
Status epilepticus	1			2		14	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Nervous system disorders							
Number of Cases	20	25	203	187	308	1,845	102
Number of Events	45	42	364	343	554	3,136	131
Stroke in evolution						1	
Stupor						3	
Subarachnoid haemorrhage	1		16	18	17	46	2
Superior sagittal sinus thrombosis		1		1			
Syncope	3	2	16	13	25	84	5
Taste disorder		1		1		3	
Thalamic infarction						3	
Thalamus haemorrhage			1		1	2	
Thrombotic cerebral infarction						6	
Thrombotic stroke				1	2	4	
Tongue biting						1	
Tonic convulsion			1	1			
Toxic encephalopathy					1		
Transient aphasia						1	
Transient ischaemic attack			1			19	1
Transverse sinus thrombosis						1	
Tremor			4	2	4	35	3
Tumefactive multiple sclerosis			1				
Unresponsive to stimuli	2		3	4	11	67	2
Upper motor neurone lesion					1		
Vascular dementia						9	
Vascular parkinsonism						1	
Vertebral artery aneurysm			1				
Vertebral artery dissection			1	1			
Vertebral artery stenosis						2	
Vertebrobasilar insufficiency						1	
Vertebrobasilar stroke						1	
Visual agnosia						1	
VIth nerve paralysis			1			1	
Vocal cord paralysis						1	
White matter lesion						1	
Pregnancy, puerperium and perinatal conditions							
Number of Cases			5	1		1	1
Number of Events			5	1		1	1
Cephalhaematoma						1	
Cranial nerve injury secondary to birth trauma				1			
Hyperemesis gravidarum			1				
Pre-eclampsia			1				
Stillbirth			3				1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Product issues							
Number of Cases			1		1	1	2
Number of Events			2		1	1	2
Device breakage						1	
Product contamination chemical			1				
Product contamination microbial			1				
Product temperature excursion issue							1
Suspected counterfeit product					1		1
Psychiatric disorders							
Number of Cases	2	2	33	19	44	403	11
Number of Events	2	5	43	29	61	504	15
Abnormal behaviour					1	10	2
Abnormal dreams						1	
Affect lability					1	1	
Aggression						5	
Agitation		1	1	1	1	26	
Alcoholism					1		
Anger			2		1		
Anxiety		1	5	4	3	27	
Apathy			1		1	13	
Autism spectrum disorder							1
Autoscopy						1	
Behaviour disorder					1	5	
Bipolar disorder			1				
Bradyphrenia						3	
Communication disorder			1		3	8	1
Completed suicide	2		6	1	2	6	3
Confusional state		2	6	4	13	130	2
Delirium				1	5	33	1
Delusion						6	
Delusional perception							1
Depressed mood						6	
Depression			1			3	
Disinhibition						1	
Disorganised speech						1	
Disorientation		1	1		1	38	
Dissociative amnesia						1	
Dysphoria				1		2	
Eating disorder				1		16	
Emotional distress			1		1		
Enuresis						1	
Fear						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Psychiatric disorders							
Number of Cases	2	2	33	19	44	403	11
Number of Events	2	5	43	29	61	504	15
Fear of falling						2	
Gastrointestinal somatic symptom disorder						1	
Hallucination			1	1	2	14	
Hallucination, auditory						2	
Hallucinations, mixed						1	
Hallucination, visual						5	
Head banging						1	
Hostility			1				
Indifference							1
Insomnia			1	5	8	18	
Intrusive thoughts				1			
Irritability				1	1	3	
Lack of spontaneous speech						3	
Listless						2	
Logorrhoea			1				
Major depression						1	
Mental disorder			2	1	1	2	
Mental fatigue						1	
Mental status changes					1	1	
Mood altered						2	
Mood swings			1				
Mutism				1		3	
Near death experience						1	
Nervousness					1	1	
Neuropsychiatric symptoms						1	
Neurosis				1	1		
Nightmare						1	
Organic brain syndrome					1	1	1
Panic attack			2		1	1	
Panic disorder			1				
Panic reaction						1	
Paranoia			1		1	1	
Persistent depressive disorder						1	
Personality change			1	1		5	
Poor quality sleep					1	4	
Post-traumatic stress disorder						1	
Posturing					1		
Psychiatric symptom						2	
Psychomotor retardation						3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Psychiatric disorders							
Number of Cases	2	2	33	19	44	403	11
Number of Events	2	5	43	29	61	504	15
Restlessness			1	1	5	40	
Schizophrenia			1				
Sleep disorder						7	
Sleep talking						1	
Social avoidant behaviour							1
Soliloquy						1	
Sopor			2	1		14	
Staring						1	
Stress					1	1	
Suicidal ideation						2	
Suicide attempt			1	1			
Suspected suicide							1
Suspiciousness						1	
Tachyphrenia				1			
Tension						4	
Tic						1	
Renal and urinary disorders							
Number of Cases	3	1	19	19	56	406	19
Number of Events	4	1	23	25	64	471	21
Acute kidney injury		1	3	6	16	127	4
Albuminuria							1
Anuria	1		1		3	20	
Azotaemia						7	
Bladder dilatation						2	
Bladder disorder					1	2	
Bladder necrosis						1	
Bladder sphincter atony	1						
Calculus bladder					1		
Chromaturia						2	
Chronic kidney disease			1		4	20	
Crush syndrome			1				
Cystitis noninfective						2	
Diabetic nephropathy						1	
Dysuria			1		2	8	2
End stage renal disease						2	
Glomerulonephritis						1	
Glomerulonephritis chronic						1	
Glomerulosclerosis					1		
Haematuria				3	1	6	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Renal and urinary disorders							
Number of Cases	3	1	19	19	56	406	19
Number of Events	4	1	23	25	64	471	21
Haemoglobinuria			1			1	
Haemorrhage urinary tract						1	1
Hydronephrosis						1	
Hypertensive nephropathy					1		
Incontinence			1		1	15	1
Kidney congestion			1	1			
Kidney fibrosis						1	
Leukocyturia						2	
Mesangioproliferative glomerulonephritis				1			
Micturition urgency			1			2	
Nephritis			1				
Nephrolithiasis						2	
Nephropathy						1	
Nephrosclerosis					3	4	
Nephrotic syndrome						3	
Oliguria					2	3	
Pollakiuria			1	1		4	
Polyuria			1			4	
Prerenal failure						1	
Proteinuria			1	1		1	
Renal atrophy						3	
Renal cyst			1			6	
Renal cyst haemorrhage						1	
Renal disorder	1				2	10	4
Renal failure			5	6	14	124	4
Renal haemorrhage				1			1
Renal hypertrophy						1	
Renal impairment			1		8	33	
Renal infarct				1	1	2	
Renal mass						1	
Renal pain						3	
Renal tubular necrosis				1			
Renal vasculitis							1
Renal vein thrombosis						1	
Ureteral disorder					1		
Ureteric obstruction						1	
Urinary bladder haemorrhage	1			1			1
Urinary incontinence				2	1	19	
Urinary retention			1		1	15	1

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Renal and urinary disorders							
Number of Cases	3	1	19	19	56	406	19
Number of Events	4	1	23	25	64	471	21
Urinary tract inflammation						1	
Urinary tract obstruction						1	
Urine abnormality						1	
Reproductive system and breast disorders							
Number of Cases	1		4	1		17	3
Number of Events	1		5	1		18	3
Amenorrhoea			1				
Benign prostatic hyperplasia							1
Breast haematoma						1	
Breast hyperplasia						1	
Breast mass						1	
Breast pain			1			3	
Breast swelling						1	
Genital haemorrhage			1				
Genital rash							1
Nipple pain							1
Ovarian cyst						1	
Ovarian enlargement	1						
Pelvic haematoma						1	
Pelvic pain						1	
Prostatic disorder						1	
Prostatitis			1			1	
Prostatomegaly						2	
Testicular oedema						2	
Testicular pain				1			
Uterine haemorrhage			1				
Uterine mass						1	
Vaginal discharge						1	
Respiratory, thoracic and mediastinal disorders							
Number of Cases	24	16	185	168	305	1,993	70
Number of Events	35	23	275	267	467	3,036	90
Acute chest syndrome			1				
Acute pulmonary oedema			2	3	2	32	
Acute respiratory distress syndrome			1	4	17	64	
Acute respiratory failure				7	11	75	1
Agonal respiration			1	1	2	1	
Alveolar lung disease						2	
Alveolitis						1	
Anoxia			1				

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	24	16	185	168	305	1,993	70
Number of Events	35	23	275	267	467	3,036	90
Aphonia						3	
Apnoea			1	3	5	31	
Apnoeic attack					1	1	
Asphyxia		1	1	2	4	23	
Aspiration			3	2	5	34	
Asthma				1	3	10	1
Atelectasis				1		7	
Autoimmune lung disease			1				
Bradypnoea					2		
Bronchial haemorrhage						1	
Bronchial hyperreactivity						1	
Bronchial obstruction						1	
Bronchial wall thickening					1	1	
Bronchiectasis						6	
Bronchitis chronic			1			1	
Bronchopneumopathy						6	
Bronchospasm	1		1	2	4	7	
Cheyne-Stokes respiration						2	
Choking			4	2	2	12	
Choking sensation			1		1		
Chronic hyperplastic eosinophilic sinusitis					1		
Chronic obstructive pulmonary disease				1	6	54	
Chronic respiratory failure						4	
Cough			25	17	34	170	8
Cyanosis central				1		1	
Cystic lung disease						1	
Diaphragmalgia						1	
Diaphragm muscle weakness						1	
Diffuse alveolar damage				1	2	2	
Dysphonia					1	12	1
Dyspnoea	8	4	66	70	119	749	33
Dyspnoea at rest						2	
Dyspnoea exertional		1	5	1	2	21	
Emphysema			1	1	1	9	1
Eosinophilic pneumonia acute						1	
Epistaxis	1	1		2	2	16	2
Grunting						1	
Haemoptysis			3	4	4	22	2
Haemothorax			1			3	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	24	16	185	168	305	1,993	70
Number of Events	35	23	275	267	467	3,036	90
Hiccups			1	1			
Hydrothorax					1	4	
Hypercapnia					1	5	
Hypersensitivity pneumonitis						2	
Hyperventilation			3		1	11	
Hypocapnia						3	
Hypopnoea		1	1	1		15	
Hypoventilation	1				1	3	
Hypoxia	1	1	4	2	9	95	4
Idiopathic pulmonary fibrosis					2	3	
Increased bronchial secretion			1			6	
Increased upper airway secretion					1	7	
Interstitial lung disease			2	3	3	49	1
Irregular breathing						3	
Laryngeal dyspnoea						1	
Laryngeal obstruction						1	
Laryngeal oedema			1			4	
Laryngospasm						1	
Lower respiratory tract congestion			2			13	
Lung consolidation				1	1	5	
Lung disorder	2		1	2	4	37	4
Lung infiltration					3	9	1
Lung opacity			1			4	
Mediastinal haemorrhage					1	1	
Mouth breathing					1	4	
Nasal congestion	1				2	3	
Nasal disorder						1	
Nasal mucosal disorder						1	
Nasal oedema		1					
Obstructive airways disorder	1		1	1	2	4	
Organising pneumonia					2	4	
Oropharyngeal discomfort						3	
Oropharyngeal pain		2	5	6	5	20	1
Orthopnoea				1	1	2	
Painful respiration			1		1	1	
Paranasal sinus haemorrhage		1					
Pharyngeal oedema			1			1	
Pharyngeal swelling					2	3	
Pleural effusion			6	2	3	63	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	24	16	185	168	305	1,993	70
Number of Events	35	23	275	267	467	3,036	90
Pleural fibrosis						1	
Pleurisy						2	
Pleuritic pain						1	
Pneumomediastinum					1		
Pneumonitis					1	25	
Pneumonitis aspiration						2	
Pneumothorax			1	1	1	8	1
Productive cough					4	34	1
Prolonged expiration						1	
Pulmonary alveolar haemorrhage					2	13	
Pulmonary arterial hypertension						3	
Pulmonary artery occlusion						1	
Pulmonary artery thrombosis			1	1	1	5	
Pulmonary congestion	1		4	3	4	22	1
Pulmonary embolism	4	5	50	58	58	253	12
Pulmonary fibrosis					1	9	
Pulmonary haemorrhage	1		2	1	1	8	1
Pulmonary hypertension		1		1	3	8	
Pulmonary infarction			1	2	1	5	
Pulmonary mass			1	1		3	1
Pulmonary necrosis						1	
Pulmonary oedema	4	1	11	10	19	91	5
Pulmonary pain							1
Pulmonary thrombosis			7	4	5	11	
Pulmonary vasculitis						1	
Rales				1		21	
Respiration abnormal					2	12	
Respiratory acidosis			1	1	1	19	
Respiratory alkalosis						5	
Respiratory arrest	2		13	8	20	127	1
Respiratory depression			2			4	
Respiratory disorder		2	3	2	3	61	2
Respiratory distress	1		4	7	11	93	1
Respiratory failure	5	1	14	9	33	226	1
Respiratory fatigue					1	3	
Respiratory muscle weakness						1	
Respiratory paralysis						1	
Respiratory symptom						1	
Respiratory tract congestion			1			1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Respiratory, thoracic and mediastinal disorders							
Number of Cases	24	16	185	168	305	1,993	70
Number of Events	35	23	275	267	467	3,036	90
Respiratory tract haemorrhage						1	1
Respiratory tract inflammation						1	
Respiratory tract oedema						1	
Rhinorrhoea			1	3	1	5	
Rhonchi						5	
Sinus disorder						1	
Sleep apnoea syndrome						1	
Sneezing					1	3	
Snoring						5	
Sputum discoloured						4	
Sputum increased			1			2	
Sputum retention						3	
Stertor			1	1		2	
Stridor						5	
Suffocation feeling				1		1	
Tachypnoea			3	3	8	69	
Thoracic haemorrhage	1					2	
Throat irritation			1		1	1	
Throat tightness						3	
Tonsillar hypertrophy			1				
Tonsillar inflammation				1			
Upper airway obstruction						1	
Upper respiratory tract congestion						1	
Use of accessory respiratory muscles						4	
Wheezing				2	4	48	1
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	21	28	44	234	16
Number of Events	1	2	23	34	58	299	23
Acantholysis						1	
Acute generalised exanthematous pustulosis						1	
Angioedema		1			2	2	
Blister					1	4	1
Cold sweat			3	2	3	19	1
Cutaneous vasculitis						3	
Decubitus ulcer				1	1	6	
Dermatitis					1		
Dermatitis allergic						2	
Dermatitis bullous					1	2	
Dermatitis exfoliative generalised						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	21	28	44	234	16
Number of Events	1	2	23	34	58	299	23
Dermatomyositis						1	
Dermatosis						1	
Drug eruption						1	
Drug reaction with eosinophilia and systemic symptoms						1	
Dry skin			1			2	
Ecchymosis						5	
Eczema				1		1	
Erythema			1	3	1	21	
Erythema multiforme					1		
Haemorrhage subcutaneous				2		7	
Henoch-Schonlein purpura				1		1	
Hirsutism							1
Hyperhidrosis			6	6	15	48	4
Livedo reticularis			1	2	2	14	
Lividity					1	3	
Nail discolouration						2	
Night sweats			1		1		1
Pain of skin						2	
Peau d'orange						1	
Pemphigoid						7	
Petechiae			2	5	3	16	1
Pigmentation disorder						1	
Pruritus			1	1	4	9	2
Psoriasis					1	1	
Purpura				1		8	2
Rash	1	1	2	2	8	23	3
Rash erythematous				1		2	
Rash macular						10	1
Rash maculo-papular						2	
Rash pruritic					1	2	
Rash vesicular						1	
Scab							1
Sensitive skin				1		1	
Skin burning sensation						2	
Skin discolouration			1		4	10	1
Skin disorder					1	6	
Skin erosion						1	
Skin exfoliation						3	
Skin haemorrhage				1		4	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Skin and subcutaneous tissue disorders							
Number of Cases	1	2	21	28	44	234	16
Number of Events	1	2	23	34	58	299	23
Skin hypertrophy						1	
Skin lesion					3	3	
Skin plaque			1				
Skin reaction				1			
Skin striae							1
Skin ulcer					1	9	1
Skin warm						2	
Skin weeping						1	
Solar dermatitis						1	
Stevens-Johnson syndrome			1		1	3	1
Subcutaneous emphysema						2	
Toxic epidermal necrolysis						5	1
Toxic skin eruption				1			
Urticaria			1	2	1	7	
Vascular purpura						1	
Xeroderma						1	
Yellow skin			1			2	
Social circumstances							
Number of Cases				4	7	52	1
Number of Events				5	7	55	1
Alcohol use				1			
Anal sex							1
Bedridden				1	3	19	
Blood product transfusion dependent				1			
Dependence on oxygen therapy						1	
Disability						1	
Immobile				1	1	6	
Impaired quality of life						4	
Loss of personal independence in daily activities				1	1	15	
Patient uncooperative						1	
Refusal of treatment by patient						2	
Sitting disability						1	
Social problem						1	
Walking disability					2	4	
Surgical and medical procedures							
Number of Cases	1		23	32	53	293	19
Number of Events	1		26	36	60	324	21
Abortion induced			1				
Aneurysm repair						1	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Surgical and medical procedures							
Number of Cases	1		23	32	53	293	19
Number of Events	1		26	36	60	324	21
Bed rest						1	
Bladder catheter permanent						1	
COVID-19 immunisation				1	1	1	
Cranial nerve decompression						1	
Craniectomy				1			
Dermabrasion						1	
Endotracheal intubation						2	1
Haemodialysis						1	
Immunisation			14	16	32	266	10
Interchange of vaccine products	1		10	13	22	42	8
Mechanical ventilation					1		
Medical induction of coma				1	1		1
Oxygen therapy					1	1	
Palliative care					1	1	
Resuscitation			1	3		3	
Thrombectomy					1	1	
Tracheostomy						1	
Transfusion							1
Vascular anastomosis				1			
Vascular disorders							
Number of Cases	10	4	83	94	170	880	48
Number of Events	11	5	98	126	209	1,105	54
Acute aortic syndrome				1		2	
Air embolism					1		
Aneurysm	1			2		7	2
Aneurysm ruptured			3	2	3	6	1
Angiodysplasia						1	
Angiopathy			1		1	3	
Aortic aneurysm						13	
Aortic aneurysm rupture				1	3	24	1
Aortic arteriosclerosis				2	1	9	
Aortic dilatation						2	
Aortic dissection			2	6	10	43	
Aortic dissection rupture			1		2	1	
Aortic embolus						1	
Aortic intramural haematoma						1	
Aortic rupture					3	3	
Aortic stenosis				2		10	
Aortic thrombosis			1		1	5	

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Vascular disorders							
Number of Cases	10	4	83	94	170	880	48
Number of Events	11	5	98	126	209	1,105	54
Arterial disorder					1		
Arterial haemorrhage			1			2	
Arterial occlusive disease			2		1	4	
Arterial rupture				1	2	4	
Arterial stenosis						1	
Arterial thrombosis				1		7	
Arteriosclerosis			4	4	7	38	3
Arteriovenous fistula						1	
Artery dissection					1	1	
Atherosclerotic plaque rupture				1	1		
Axillary vein thrombosis				1		1	
Blood pressure fluctuation					1	7	1
Blood pressure inadequately controlled						2	
Bloody discharge						2	
Blue toe syndrome							1
Brachiocephalic artery stenosis						1	
Capillary fragility						1	
Capillary leak syndrome						1	
Circulatory collapse	1	1	12	14	28	104	4
Cyanosis	1		9	6	7	62	1
Deep vein thrombosis	1		8	10	21	48	2
Dependent rubor						1	
Embolism			2	2	5	19	2
Embolism arterial						2	
Embolism venous						2	
Essential hypertension						2	
Exsanguination						1	
Extremity necrosis						1	
False lumen dilatation of aortic dissection				1			
Femoral artery embolism					1	1	
Flushing				1		2	
Giant cell arteritis					1	2	
Haematoma			3	1	4	21	1
Haemodynamic instability				1	1	7	
Haemorrhage		1	1	6	6	21	3
Haemorrhagic infarction				1		1	
Hot flush				1	3	5	1
Hyperaemia			1			1	
Hypertension			7	6	14	77	2

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Vascular disorders							
Number of Cases	10	4	83	94	170	880	48
Number of Events	11	5	98	126	209	1,105	54
Hypertensive crisis			2	2		13	
Hypertensive emergency						2	
Hypoperfusion					1	3	
Hypotension	2	2	5	9	18	144	5
Hypotensive crisis						2	
Hypovolaemic shock			1	1		8	
Infarction	2			1	3	16	2
Intermittent claudication					1		
Internal haemorrhage			1			12	1
Ischaemia						13	1
Jugular vein distension						2	
Jugular vein embolism						1	
Jugular vein thrombosis			1			1	
Labile blood pressure					1		
Labile hypertension						1	
Leriche syndrome						1	
Lymphoedema				1		2	
Macroangiopathy						1	
Malignant hypertension				2			
Necrosis ischaemic				1			
Orthostatic hypotension						1	
Pallor			5	3	7	58	
Paraneoplastic thrombosis					1		
Pelvic venous thrombosis						2	
Peripheral arterial occlusive disease			1			4	
Peripheral artery occlusion						2	
Peripheral artery thrombosis					1	2	
Peripheral circulatory failure					1	4	
Peripheral coldness				1	3	11	
Peripheral embolism						1	
Peripheral ischaemia					1	18	
Peripheral vascular disorder					2	7	1
Peripheral venous disease				1		4	
Phlebitis				1			
Phlebolith						1	
Poor peripheral circulation							1
Shock	2		5	7	6	49	
Shock haemorrhagic			1	1	5	13	
Subclavian artery dissection					1		

*Only post birth cases included

MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PTs)	less or equal to 17 years	18 - 24 years	25 - 49 years	50 - 59 years	60 - 69 years	70+ years	Unknown
Vascular disorders							
Number of Cases	10	4	83	94	170	880	48
Number of Events	11	5	98	126	209	1,105	54
Subclavian artery occlusion					1		
Subclavian artery thrombosis					1		
Subclavian vein thrombosis				1		2	
Superficial vein thrombosis						1	
Superior vena cava syndrome						2	
Systolic hypertension						1	
Thrombophlebitis						6	
Thrombosis	1	1	12	17	22	88	15
Varicose ulceration						1	
Varicose vein						1	
Vascular occlusion						1	1
Vascular pain						1	1
Vascular shunt							1
Vasculitis			3	3	1	7	
Vasodilatation						1	
Vena cava thrombosis			1			2	
Venoocclusive disease						1	
Venous thrombosis			2		1	3	
Venous thrombosis limb					1	4	

*Only post birth cases included